UNITED STATES
NUCLEAR REGULATORY COMMISSION

MEETING WITH THE ADVISORY COMMITTEE ON THE MEDICAL USES
OF ISOTOPES

TUESDAY,
OCTOBER 5, 2021

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
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: 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.
So today's agenda will be as follows.

Next slide.

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

Next slide.

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

Next slide.

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

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

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

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

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

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

Next slide.

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

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

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The topics addressed by the ACMUI during our meetings in 2021 are the following. We had an excellent presentation from the Netherlands on extravasations in nuclear medicine by Dr. Jan van der Pol from Maastricht University Medical Center. We also had a topic that was presented that was very interesting by Dr. DeWard from the University of
Wisconsin on calibration procedures for brachytherapy sources.

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

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

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

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

Our new Committees are Emerging Radiopharmaceutical Knowledge Requirements and Theranostics, Radionuclide Generator Knowledge and Practice Requirements, and our newest Committee is Diffusing Alpha-emitter Radiation Therapy, or DART Manual Brachytherapy Sources Licensing Guidance.
So what about the future? The ACMUI will continue to provide advice and technical assistance to the NRC staff and NRC, will comment on NRC regulations and guidance as requested, and the ACMUI will continue to evaluate issues, uses of the radioactive material, and bring key issues to the attention of the Commission.

And these are my acronyms.

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

CHAIR HANSON: Thank you, Dr. Metter.

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

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

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

First slide, please.

Okay. There we go. Okay. So medical events for the last year -- so the Subcommittee on Medical Events reviews medical events on an every-one-to-two-year basis with a goal of developing perspective and advice for the NRC about the regulation of medical events.
Our Subcommittee includes the people listed here -- next slide, please -- it includes myself, Richard Green, Dr. Metter, Mr. Ouhib, Dr. O’Hara, Mr. Sheetz -- who was the Radiation Safety Officer; his term just concluded -- and Dr. Wolkov.

Next slide, please.

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

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

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

In previous years, we really focused more on our thinking that it had to do with frequency of performance, but in this year's Subcommittee discussion, it was suggested appropriately that many of those may actually be more about the issue of inattention as opposed to a lack of
frequency of performance, and really hard to go beyond that in terms of attribution based on information that we have in front of us.

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

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

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

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

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For this year, our main message is that the number of medical events of Y90 administrations continue to be the most common medical event. Important to note that it is still an extremely small fraction of the number of Y90 administrations across the country. For all medical events across the board, they represent a tiny fraction of all administrations, both on diagnostic and therapeutic side.
Nevertheless, of course, we do want to try and decrease these two as well as possible. And Y90 administrations continue to be stubbornly high and stable, as you will see. Therefore, the Subcommittee is recommending to the wider ACMUI that we create a subcommittee to go and look into this in more depth in connection with users and vendors and propose solutions for starting to make an impact on the number of Y90 medical events.

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

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

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

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In § 35.300, Unsealed Byproduct Material Needing a
Written Directive, there were only two events in the past year.

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

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

Next slide.

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

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By disease, the bulk of them are in GYN. And our sense
is that's proportional to the use of HDR. The brain is obviously about to (inaudible). But the rest are essentially HDR treatments, and overwhelmingly, those procedures are gynecological.

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

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

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

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

Next slide.

In cardiac brachytherapy, two events. One may be what
would be considered a patient intervention issue, which is, again, a topic of
other Subcommittees in the last few years. So I won't go into that further.

Next slide.

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

Next slide, please.

For Y90 -- so we present by both of the Y90 producers.

So the Therasphere product had 15 events, about the same as it's had the
last four years, with the exact issues below, again residual activity of the
device being the number one. And some thought that infrequent or
inattention may be a significant contributing factor.

Next slide, please.

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

Next slide, please.

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

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

CHAIR HANSON: Thank you, Dr. Ennis. I understand
now we'll hear from you about the Abnormal Occurrence Subcommittee report.

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

Next slide, please.

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

Next slide, please.

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

Next slide, please.

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

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So, just by way of a little bit of background, I guess -- so the AO criteria, abnormal occurrence is a level of occurrence of an event, of a radiation exposure, to which the NRC is required to report to Congress an annual report. And as written in the regulations, this is supposed to be
something that is important to public health and safety that Congress should be made aware of.

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

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

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

Next slide, please.

In our Subcommittee, we looked over abnormal occurrences that have been reported to Congress over the years and have a strong feeling that this definition is over-conservative and captures events that are not of significance from the standpoint of public health and safety. They certainly are medical events, but they just don't rise to that level of
needing Congressional reporting. There will be no impact on public health and safety, they don't represent that type of event.

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

Next slide, please.

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

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

Next slide.

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

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So, as I said, we also feel that the NRC's definition would improve medical event criteria -- medical abnormal occurrence criteria,
So, as I stated, we fully support the NRC proposed changes to the abnormal occurrence definition, and we recommend that communication be prepared and distributed to all the NRC agreement state medical licensees to inform them of the best practices for reporting medical events so that important information is provided, root cause analysis on why that occurred, and medical effect on the individual.

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

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

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

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

Next slide.

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

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

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

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

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

Can I have my slides, please?

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

May I have the next slide, please?

This is the membership. I chaired the Subcommittee. The other members included Dr. Vasken Dilsizian, Dr. Ennis, Dr. O'Hara, Mr. Zoubir Ouhib, Mr. Mailman, and our NRC Staff Resource was Maryann Ayoade. I want to thank all of them for contributing to this effort. Also want
to acknowledge Ms. Lisa Dimmick, who was very helpful from NRC as we discussed and deliberated on this particular issue.

May I have the next slide, please?

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

May I have the next slide, please?

So just on to the definition, what is theranostics?

Theranostics is essentially a systemic integration of diagnostic tools which could include imaging. Does not have to be imaging per se, but in this case, we focus on nuclear imaging, and it's paired with therapeutic agents.

And again, this does not have to be radioactive, but again, in this particular topic here, we are focusing on radiopharmaceuticals.

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

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

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

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

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

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

And finally, there's gallium-68 or copper-64 dotatate. The gallium-68 dotatate is commercialized as Netspot, which was approved in 2016. The copper-64 version of it is called Detectnet, and that was approved in 2020. These are for imaging of patients with neuroendocrine tumors who express somatostatin receptors. Gallium-68 dotatoc is also a similar agent for imaging, and that was approved in 2019. And finally, the
therapy pair is lutetium-177 dotatate, which is commercialized as Lutathera, and that was published -- I'm sorry, that was FDA approved in 2018.

Next slide, please.

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

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

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

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

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

Next slide, please.

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

Next slide, please.

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

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

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

Biomedical challenges may be -- can I have the next slide, please? In the biomedical challenges, we always need to identify new biological targets and then, of course, perform the preclinical animal studies, first in-human studies, and large perspective or randomized studies to decipher the place of these new emerging theranostics in the clinic.
And then, of course, after those are being approved or available, then a number of other clinical trials need to be done to see what is the best approach to treatment of patients under the banner of precision medicine. Is it single treatment with theranostics, or should it be in tandem? Should it be modified or adapted depending upon some imaging or other diagnostic tool and how it can be combined with other available treatment? And, of course, we focus on cancer, but theranostics is not only related to cancer and can be applied to other non-oncologic diseases.

Can I have the next slide, please?

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

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

Next slide, please.

Therapy should be done in a dedicated and regulatory approved room appropriate for radioisotope administration. I'll show you an example of that. If in this interdisciplinary team there may be non-radiation workers, for example a nurse, oncology nurse, which may be participating in
preparation of the patient, they may need to wear a radiation badge, and this can be determined by the RSO.

Next slide, please.

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

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

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

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

Next slide, please.

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

Patient dosimetry is an important topic, and this is related to patient-specific dose versus fixed activity, although patient-specific dosimetry plays a relatively minor role at this time. But this is anticipated to be more prevalent in the future. There are a number of challenges in this area. We still don't have a randomized clinical trial that compares dosimetry patients, dosimetry-based versus (inaudible) activity-based treatment to see
if there is an outcome benefit for the patient with, of course, minimization of toxic effects to the normal tissue.

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

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

And next slide, please.

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

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

And thank you again for your time.

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

MR. MAILMAN: The thing is remembering to take yourself off mute before you talk. Thank you very much, Commissioner
Hanson. And thank you to the fellow Commissioners as well for inviting me
to give this talk on patient advocacy and how we bring about change for
patients.

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

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

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

Next slide. So as I said, how can I help. So, as well as
talking to my oncologist, I ended up talking to my, next slide please, I ended
up talking to my nuclear medicine physician. And this was before Lutathera or Lu-177 dotatate was approved in the U.S., when I needed therapy. And I ended up in Europe for my first steps of therapies, and imaging, with gallium-68. And I ended up invited to the First World Congress of gallium-68 and receptor radionuclide therapy.

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

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

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

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

Next slide please. And these are the typical advocate activities. We have patient rights, as we’re talking about here in many
different forms. Both rights in the hospital when we’re under care, matters
of privacy, informed consent and patient representation, awareness building
and support of education survivors and their caregivers.

Next slide. And we do help bring voice to the patients.

But what I really want to like go is to the next slide as well.

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

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

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

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

Next slide please. So as I said, there’s many multi-facets.

When I started writing this particular presentation, I had just come off a
week of one of the things that I do, which is being teaching staff at the Vail
workshop which is a workshop to teach young investigators about how to
manage or run a clinical trial.

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

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

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

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

Next slide please. On the research side, I do sit on the GI
steering committee for the National Cancer Institute. I was also recently
appointed to the scientific research community, or ASCO. And as I
mentioned, I'm the member of the faculty for ASCO-AACR.

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

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

And with that, I want to thank you. Next slide please.

This is my group. We usually use a running person for a running festival,
but as we all are doing now, was virtual this year and so we took virtual
shots and put them altogether.

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

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

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

We'll start with questions this morning with Commissioner
Baran.
COMMISSIONER BARAN: Well, thank you all for your presentations and for your work on the Committee. I'd like to continue the conversation about whether extravasation should be reported as medical events.

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

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

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

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

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

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

MS. MARTIN: Thank you, very much, Commissioner Hanson, for the opportunity to present to you guys today.
We spent a lot of time, and I want to make a couple of points, and then I'm going to have Dr. Dilsizian give the medical view from this. I am the physicist on this committee.

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

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

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

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

COMMISSIONER BARAN: So it sounds like --

MS. MARTIN: And --

COMMISSIONER BARAN: Sorry, I didn't want to interrupt.
MS. MARTIN: No, go ahead.

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

MS. MARTIN: That would be correct, sir.

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

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

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

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

And so, extravasation was excluded, as you know, from
the medical event reporting. And the question is, why not just have it back in to determine what is the current prevalence of this problem.

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

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

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

Once we get that data, then obviously we'd come up with some objective indices, which would be some dose-based approach to
assess and solve the problem. Thank you very much for your attention.

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

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

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

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

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

Is it something that's seen right away? You would look at
it, or the patient would look at it and know, well, this is a case where medical attention is needed or is it less obvious than that?

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

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

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

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

DR. DILSIZIAN: Sure. Thank you.

CHAIRMAN HANSON: Thank you, Commissioner Baran.

Commissioner Wright.

COMMISSIONER WRIGHT: Thank you very much and good morning.

I really appreciate the presentations, as well as the important work that you, all of you, do on the committee. And I think I'll just echo what I said last year, giving you the same thanks that I gave you last
year which is, really thank you for the work that you do outside of the committee as medical professionals.

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

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

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

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

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

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

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

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

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

But the whole point of the AO is a subjective thing as well. It's what rises to the level of meeting Congress and public's awareness. So
that inherently is subjective. And while it would be wonderful if it was
something very nice and objective. I mean, we're all scientist, doctors,
physicists, people, we're very quantitative people. And we all like those
solutions and they're always a lot easier when we can add them. But
sometimes it's quantitative and objective are less good, and in this situation I
think that that's the case.

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

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

COMMISSIONER WRIGHT: Sure. You're on mute.

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

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

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

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

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

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

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

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

I think that at this point we don’t have the data, the
prevalence. And I can tell you that in my 30 years of experience, both as a cardiologist and nuclear medicine physician, while I've had patients come back for repeat studies because of the poor quality images from extravasation, I have not had a patient being harmed from the extravasation at the site of the injection.

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

CHAIRMAN HANSON: Please go ahead.

COMMISSIONER WRIGHT: -- if that's okay?

CHAIRMAN HANSON: Yes.

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

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

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

If you can expand a little bit on that in treating
extravasations of radio, of preventing the extravasations of radiopharmaceuticals?

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

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

COMMISSIONER WRIGHT: Right.

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

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

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

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

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

And at the ACMUI's recommendation, the NRC put out an
information notice to inform licensees about the subcommittee's findings. And I guess I have kind of a two-part question for you.

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

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

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

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

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

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

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

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

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

Then the question is, do you maintain that throughout your career. And I think that's where the infrequency type of issues may come
Is infrequency another way of saying a lack of knowledge, current knowledge of radiation safety? Perhaps that's what it is. I think that's complex. Is it related to a procedure itself, is it related to radiation safety aspect, I don't think I can say. And I sense in our view that we can really dissect that difference.

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

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

I was really interested in your discussion about Y90 microspheres. You know, they represent a significant portion, at least it appeared to me, of medical event reportings. And it seems like they have gone up, or at least the absolute number has gone up over the last few years, but I was wondering if you could kind of provide some context for that. I wasn't sure if Y90 microsphere administrations had also gone up so that maybe there was an increase in both the numerator or the denominator there. And I just was kind of wondering also, given that the absolute number does go up, if you have some insights about what might be attributed in terms of the causes for that increase?

DR. ENNIS: So, with respect, I don't think the numbers over the last few years have gone up. I don't know if we have the slides
available. But I believe the numbers are pretty stable. They are larger than any other of our groups. But I don't see an upward trend beyond random fluctuations. Oh, great, thank you.

CHAIRMAN HANSON: Ah.

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

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

DR. ENNIS: Ah, yes.

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

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

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

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

I'm interested in this idea of kind of a medical consequence, a shift to focus on medical consequences for abnormal
events. And I guess, do you see that as a paradigm shift for how the NRC would regard events of public health and safety significance reported to Congress?

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

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

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

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

CHAIRMAN HANSON: Thank you. Yes, I really appreciate that clarification. As we wrap-up today, Mr. Mailman, I kind of just wanted to give you the last word. And particularly as the patient rights advocate. I know you're new to the committee, but you've been in this space for a long time. And of course, you've been, I'm sure, exposed to the activities of the NRC.
I just wanted to ask you if there are additional areas where
the NRC should be focusing activities or tasks that you think we should be
undertaking or expanding upon, or if you think there are areas where maybe
we're focusing and you don't think that those are necessarily productive?

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

MR. MAILMAN: The unmute thing. I will unmute myself.

Thank you for the opportunity to address the Commission as well.

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

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

One thing that we didn't talk about here, but the release
criteria. I spend tons of time probably second to where patients want to
make sure their physicians are trained, or those who care for them are
trained. I spend a lot of time going over release criteria and understanding
that in laymen's terms so that people who, I feel for when patients are
separated from their families are doing things that aren't necessarily required
for the isotope that they have administered to them. And so, that obviously
dovetails into patient education where it, the more that we can educate patients about the uses and benefits, and even some of the challenges that, knowing what to report and when to report it. These things are important to patients.

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

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

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

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

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

Dr. Metter, thank you for your leadership on the ACMUI.

Thank you to all the members who are on today. We've got a set of
complex, but not intractable issues in front of us. We appreciate your advice and your thoughtfulness in advising the Commission.

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

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