Official Transcript of Proceedings

NUCLEAR REGULATORY COMMISSION

Title: Meeting of the Advisory Committee on the Medical Uses of Isotopes

Docket Number: (n/a)

Location: Teleconference

Date: Monday, October 4, 2021

Work Order No.: NRC-1700 Pages 1-175

QHDO#U1#JURVV#DQG#FR1/#LQF1#
Frxuw#Uhsruwhuv#dqg#Wudqvfulehuv#
4:49#47wk#Vwuhhw/#Q1Z1/#Vxlwh#533#
Zdvklqjwrq/#G1F1##5333<#
+535,#6707766

UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

+ + + + +

ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

+ + + + +

MEETING

+ + + + +

MONDAY,

OCTOBER 4, 2021

The meeting was convened via Video Teleconference, at 10:00 a.m. EDT, Darlene F. Metter, ACMUI Chairman, presiding.

MEMBERS PRESENT:

DARLENE F. METTER, M.D., Chairman

VASKEN DILSIZIAN, M.D., Vice Chairman

REBECCA ALLEN, Member

RONALD D. ENNIS, M.D., Member

RICHARD L. GREEN, Member

HOSSEIN JADVAR, Member

JOSH MAILMAN, Member

MELISSA C. MARTIN, Member

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

ZOUBIR OUHIB, Member

MEGAN L. SHOBER, Member

HARVEY B. WOLKOV, M.D., Member

NRC STAFF PRESENT:

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

MARYANN AYOADE, NMSS/MSST/MSEB/MRST

THERESA CLARK, NMSS/MSST

DANIEL DIMARCO, NMSS/MSST/MSEB

DONNA-BETH HOWE, NMSS/MSST/MSEB/MRST

KELLEE JAMERSON, NMSS/MSST/MSEB

ROBERT LEWIS, NMSS

SARAH LOPAS, NMSS/MSST/MSEB

CELIMAR VALENTIN-RODRIGUEZ, NMSS/MSST

ALSO PRESENT:

THOMAS EIDEN, Public Participant

CALVIN HAN, Public Participant

ROBERT HOBBS, AAPM

MICHAEL SHEETZ, Public Participant

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

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

10:02 a.m.

MR. EINBERG: Good morning. I'm the designated federal officer for this meeting. I am pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes.

My name is Chris Einberg. I'm the Chief of the Medical Safety and Events Assessment Branch and I have been designated as the federal officer for this advisory committee in accordance with 10 CFR Part 7.11.

Participating today we have Celimar Valentin-Rodriguez, who is currently acting as the Medical Radiation Safety Team leader until mid-December, and Mr. Don Lowman, who will serve as the acting ACMUI coordinator for the next six months.

This is an announced meeting of the committee. It is being held in accordance with the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission.

This meeting is being transcribed by the NRC and may be also transcribed or recorded by others.

The meeting was announced in the August 27th, 2021 edition of the *Federal Register*, volume 86, page 48452.

The function of the ACMUI is to advise the

staff on issues and questions that arise on the medical use of byproduct material. The Committee provides counsel for the staff but does not determine or direct the actual decisions of the staff or the Commission. The NRC solicits the views of the Committee and values their opinions.

I request that whenever possible we try to reach consensus on the various issues that we will discuss today, but I also recognize that there may be minority or dissenting opinions. If you have such opinions, please allow them to be read into the record.

At this point I would like to perform a roll call of the ACMUI members participating today.

Dr. Darlene Metter, ACMUI Chair, diagnostic radiologist?

CHAIRMAN METTER: Present.

MR. EINBERG: Dr. Vasken Dilsizian, ACMUI Vice Chair, nuclear cardiologist?

VICE CHAIR DILSIZIAN: Present.

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

MEMBER ENNIS: Present.

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

MEMBER GREEN: Present.

MR. EINBERG: Dr. Hossein Jadvar, nuclear medicine physician?

MEMBER JADVAR: Present.

MR. EINBERG: Ms. Melissa Martin, nuclear medicine physicist?

MEMBER MARTIN: Present.

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

(No audible response.)

MR. EINBERG: Mr. Zoubir Ouhib, radiation therapy physicist?

(No audible response.)

MR. EINBERG: Mr. Ouhib, you're on mute.

MEMBER OUHIB: Present. I apologize.

MR. EINBERG: No problem.

Radiation safety officer position is vacant right now. Mr. Sheetz' term ended at the end of September and we're in the present of backfilling for that.

Next is Ms. Megan Shober, state government representative.

MEMBER SHOBER: Present.

MR. EINBERG: Dr. Harvey Wolkov, radiation oncologist?

MEMBER WOLKOV: Present.

MR. EINBERG: Ms. Rebecca Allen, health care administrator?

MEMBER ALLEN: Present.

MR. EINBERG: Mr. Josh Mailman, patients rights advocate?

(No audible response.)

MR. EINBERG: I confirm that we do have a quorum of at least six present at this time.

I'd like to also welcome Ms. Rebecca Allen. Ms. Allen has been selected to serve as the health care administrator on the ACMUI. And her paperwork has finally been processed and she is now a full voting member of the ACMUI.

So welcome, Ms. Allen.

Ms. Allen currently serves as the Enterprise Director of Radiology at the University of Cincinnati Health where she is responsible for the primary leadership of all radiology services. She is also the Senior Management Representative of the Radiation Safety Committee at the University of Cincinnati Health. Ms. Allen has clinical service, line oversight experience in diagnostic imaging (audio interference) radiology and cardiology, radiation oncology and perioperative services, pharmacy, respiratory, and laboratory. Ms. Allen is also part

of the board of directors with the Association of Medical Imaging and Management and is responsible for setting curriculum and structure for radiology administration -- administrators nationwide.

All members of the ACMUI are subject to federal ethics laws and regulations and receive annual training on these requirements. If a member believes that he or she may have a conflict of interest as that term is broadly used within 5 CFR Part 26.35 with regard to an agenda item to be addressed by the ACMUI, this members should divulge it to the chair and the DFO as soon as possible before the ACMUI discusses it as an agenda item. ACMUI members must recuse themselves from participating in any agenda item in which they have a conflict of interest unless they receive a waiver or prior authorization from the appropriate NRC official.

Due to the ongoing COVID-19 public health emergency the NRC is continuing to allow flexibility in the telework status. As such we are all working remotely still and each individual calling into this meeting. NRC staff members who are participating on this call are Ms. Theresa Clark, Dr. Celimar Valentin-Rodriguez, Mr. Don Lowman, Mr. Daniel DiMarco, Ms. Kellee Jamerson, and Sarah Lopas.

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

Those of you who did not provide prior notification, please contact Ms. Jamerson at kellee.jamerson@nrc.gov; and that's K-E-L-L-E-E, dot, J-A-M-E-R-S-O-N, at NRC, dot, gov, at the conclusion of this meeting.

Today's meeting is being transcribed by a court reporter. We are utilizing Webex for the audio of today's meeting and to view presentation material in real time. The meeting material and agenda for this meeting can be accessed from the NRC's public meeting schedule.

Dr. Metter, at her discretion, may accept comments or questions from members of the public who are participating with us today. Individuals who would like to ask a question or make a comment regarding a specific topic that ACMUI has discussed should please use the raise hand function in Webex to signal our Webex host Kellee Jamerson that you wish to speak.

If you have called into the Webex using your phone, press *3 to raise your hand and ensure you

have un-muted your phone. When you begin your comment please clearly state your first and last name for the record. Comments and questions are typically addressed by the Committee at the end of a presentation after the Committee has fully discussed the topic. We will announce when we are ready for the public comment portion of the meeting and an NRC staff member will assist in facilitating public comments.

At this time I ask that ACMUI and NRC panelists who are not speaking to please mute your Webex microphones or mute your phones. I would also ask everyone to exercise extreme care to ensure that the background noise is kept at a minimum as any stray background sounds can be very disruptive on a conference call.

I will note two small changes in the agenda for today's meeting: The first is that Ms. Theresa Clark, Deputy Director, Division of Material Safety, Security, State, and Tribal Programs, will provide the opening remarks, and that our afternoon open forum will be at 3:15 p.m. followed by a special presentation from Michael Sheetz at 3:30.

I will now turn the meeting over to Ms. Theresa Clark for some opening remarks.

MS. CLARK: All right. Thanks, Chris,

and good morning, everyone. It's a pleasure to be with you here today.

Again I am Theresa Clark. I'm the Deputy Director of (audio interference) imaging (audio interference) ACMUI support staff (audio interference) in the Division of Material, Safety, Security, State and Tribal Programs at the NRC.

And so first I just want to thank the ACMUI for all of their hard work. We really appreciate getting your expert advice and hearing the roll call (audio interference) that the committee brings to (audio interference) advisory committee. I truly appreciate that and value your contributions particularly as we're tackling new areas in medical uses of radioactive material.

This is the seventh (audio interference) meeting we've held at the ACMUI. I hope that all of you are remaining safe and healthy and I look forward to having future meeting in person (audio interference).

So I'll highlight first a few items that may be of interest to the ACMUI as well as other participants in the meeting. Hopefully folks can hear my audio okay. I'll try to speak up a bit.

So just a few NRC activities that are of

(audio interference). The abnormal occurrence criteria paper. The staff is working on that. ACMUI previously provided input in a May 2021 meeting and that paper is working its way through the staff approval process to get to the Commission (audio interference).

On extravasations, the ACMUI gave its views in the September 2nd meeting of the Committee and we're developing a Commission paper that will recommend the approach to the Commission, and so we're working on that paper right now.

For Regulatory Guide 8.39, which has to do with patient release, we're working on our Phase 2 revision. We've completed the draft and we provided that to the ACMUI Subcommittee for review and comments. And at a public meeting in November we plan to (audio interference) as we discuss that (audio interference) This Phase 2 update updates (audio interference) and methodologies and tables that are about (audio interference) to members of the public (audio interference).

And finally, one of the many emerging medical technologies (audio interference) from that is Alpha DaRT, and in September we provided the Alpha DaRT Subcommittee with draft license and guidance under

10 CFR 35.1000, which is for the Alpha DaRT manual brachytherapy (audio interference). And this draft guidance contains licensing conditions for areas where the regulations don't fully address everything associated with that technology including administration procedures, training and experience, and (audio interference) therapy-related computer systems, labeling, and (audio interference) levels. So the subcommittee has that in their hands interference) right now.

Since the spring 2021 ACMUI meeting, we've had meetings on May 27th and September 2nd, as I mentioned, and those had to deal with the Abnormal Occurrence Subcommittee, which presented a draft of report in May. And in September the Extravasations and Medical Event Reporting Subcommittee also presented a draft report.

And as Chris already alluded to, there have been some changes among the Committee membership, so we definitely welcome Rebecca Allen, who Chris already mentioned. Josh Mailman is our patient's rights advocate. I think he also has a speaking role at tomorrow's Commission meeting, so we appreciate that and look forward to his remarks.

And we also welcome Dr. John Fritz Angle,

who is an interventional radiologist who will be serving as a medical consultant to the ACMUI. And as Chris also mentioned, we're saying goodbye sadly to Mike Sheetz as the radiation safety officer representative. We're pleased that he's going to be able to stay on as a medical consultant, and he'll provide his expertise as needed in a consultant role until that RSO position is filled. And that open period for nominations for the RSO position closes today, October 4th.

So looking forward to today's agenda, it's a full agenda, as I think others have mentioned. We'll hear from Dr. Ennis from the Medical Events Subcommittee about medical events (audio interference). Mr. Green will present his subcommittee's recommendations related to knowledge and specialized practice requirements for eluding radionuclidic generator systems, eluding, measuring, testing, and processing eluate.

Dr. Jadvar will discuss putting in recommendations related to theranostics, specifically practice and policy requirements needed for safe use and handling of emerging radionuclides.

Mr. Hobbs will discuss the work of the American Association of Physicists in and Medicine task

groups on the future of personalized dosimetry.

And finally, Ms. Shober will discuss production methods for emerging therapeutic radiopharmaceuticals and the effects on radiation safety radiation for end users and the challenges of various production methods. (Audio interference) that as we're always looking at emerging technologies for (audio interference).

So thanks for the opportunity to open this meeting. I wish you a productive session today as well as a smooth and interesting Commission meeting tomorrow morning. You'll see me in and out myself. And now I'll turn it over to Daniel DiMarco.

MR. EINBERG: Dr. Metter, if you're speaking, we can't hear you right now.

MS. CLARK: I probably confused her by turning it over to Daniel.

MR. EINBERG: Okay.

CHAIRMAN METTER: Okay. Well, thank you, Mr. Einberg. Can you hear me now?

MR. EINBERG: Yes, we can. Thank you.

CHAIRMAN METTER: Thank you.

Well, good morning and welcome to the 2022 ACMUI fall meeting. And I'd also like to welcome our new hospital administrator for the ACMUI, Rebecca

Allen.

As you can see, today's agenda will be very informative and interesting, so let's proceed on with our old business, which will be presented by Daniel DiMarco with the NRC, who will review the past ACMUI recommendations and provide NRC response.

Mr. DiMarco?

MR. DiMARCO: Good morning, Dr. Metter and the members of the ACMUI.

Kellee, if you could share the old business on the screen? I am not able to share content for this.

Okay. So you can see in front of you the open ACMUI recommendations and action items. The first one is item No. 17 from 2019. This is the endorsement of the Appropriateness of Medical Event Reporting Subcommittee report and the recommendations provided therein. Currently the staff has drafted a best practices document and is in the process of sharing it with the subcommittee. This document will be attached to the annual NMED report and will be posted in the Medical Tool Kit, as well as the NMED website. This is incorrectly labeled as proposed closure. This shall remain open until that guidance document has been posted, and so the target completion date for this action will be spring of 2022.

Going onto item No. 18, this is in reference to the Extravasation Subcommittee report. This, as well as item No. 4 from 2020 -- both of these refer to the Extravasation Subcommittee report as well as the NRC staff evaluation. Both of these the staff has drafted a SECY package that includes a rulemaking plan for Commission consideration. This is currently in concurrence and will go to the Commission in the spring of 2022, and so the target completion date for that is April of 2022. And these both shall remain open until the Commission receives that package.

Going onto item No. 11, this is referring to the Non-Medical Events report with the issue of detection of short-lived isotopes in municipal waste. Currently the NRC staff has presented to the OAS Board and they agree to a survey with the Agreement States. The next steps for this are to draft SEC and survey questions, and the new target date for this is spring of 2022.

If you could scroll down, please? Thank you.

And these are the 2021 open action items. The first item is the scheduled fall meeting for October 4th and 5th. This is the meeting that we're at right now, and so this will be proposed to close.

The second item is the ACMUI Abnormal Occurrence Subcommittee report and the recommendations proposed -- provided therein. These have been voted on in May, and so they -- we propose to close this item.

The ACMUI item No. 3, we formed a new Subcommittee on Radionuclide Generator Knowledge and Practice Requirements. The subcommittee will provide a draft report and any recommendations at this meeting right now, and so we propose to close this action item.

Item No. 4 is another new Subcommittee on Emerging Radiopharmaceutical Therapy Knowledge Requirements and Theranostics. The subcommittee is providing an interim report at this fall meeting and we propose to close this item as well.

And then item No. 5 is the final open action item where the ACMUI formed a new Subcommittee on the Diffusing Alpha-emitter Radiation Therapy, Manual Brachytherapy Source, or Alpha DaRT. This subcommittee is expected to provide a draft report at the spring 2022 ACMUI meeting. The target completion date on this is not correct. It's not spring of 2021; it's spring of 2022. And until that meeting this item will remain open.

And I believe that is all of the old

business.

CHAIRMAN METTER: Thank you, Mr. DiMarco, for your presentation and the update.

Are there any questions from the ACMUI Committee itself on any of these actions?

(No audible response.)

CHAIRMAN METTER: Okay. Hearing none, let's go onto the next item on the agenda.

The next item is Medical Events Subcommittee report presented by Dr. Ronald Ennis, ACMUI radiation oncologist, who will be providing an analysis of the fiscal year 2020 medical events.

Dr. Ennis?

DR. ENNIS: Good morning, everyone, and thank you for the opportunity to present today. This presentation is a presentation of the Standing Committee of Medical Events that presents every one to two years in which we review the medical events of the previous fiscal year in the context of the last several years. For those who have heard these committee reports, some of this will be familiar, but there will be some new wrinkles as always.

Next slide, please? I'd like to thank all of my subcommittee chairmen who all worked on preparing this report: Mr. Green; Dr. Metter; Mr. Ouhib; Dr.

O'Hara; Mr. Sheetz, whose term as you heard just completed; and Dr. Wolkov.

Over summary. First -- next slide, please -- is two overarching themes that we have -- this subcommittee has brought forward over the last couple years still remain worthy of highlight. One is the impression that performance of a timeout and/or use of a checklist immediately prior to administration of byproduct material, as is done commonly now in surgery and other medical settings, could have presented some of the medical events, and this varies a little bit by type of radioactive materials and the setting.

And No. 2, a lack of either recent or frequent performance of a particular administration or potentially inattention during performance also appears to be a contributing factor in a number of cases. This is a nuance, a slight change from prior presentations and we're thankful to some of those new members on the subcommittee for highlighting in discussions that although in the past we, the subcommittee, had thought of lack of recent or frequent performances as the contributing factor the discussions of the subcommittee this year highlighted the fact that some of those events may also actually just be more about inattention as opposed to frequency

of performance.

And it is really impossible from NMED to be sure about any of this, but certainly to be sure about whether one can differentiate between just an issue of lack of frequency or familiarity with the procedures versus inattention. So going forward we will talk about this category with that kind of hybrid designation of either lack of frequent performance and/or inattention.

It's worth noting that NRC has issued an information notice in 2019 in response to the subcommittee's recommendations highlighting the community of users about these issues. To date it would be hard to say whether we've had an impact as the number of events appear stable, but of course that's very hard to know with any certainty.

Next slide, please? An issue that was highlighted last year by the subcommittee was a concern that with increased complexity of unsealed source administrations such as LUTATHERA. They're mainly to more medical events. Happy to report, as you'll see, we haven't seen that yet, but the subcommittee still remains concerned about this issue for the next several years before we can feel reassured that that is not happening.

And finally; and this is a new insight from the committee, or a new recommendation from the subcommittee, we noted, as has been discussed before, that the dominant type of medical events is in the setting of Y90 administration. It should clearly be stated and noted that it is still an extremely rare event within all the cases of Y90 administration. The number of medical events across all modalities is exceptionally low compared to the number of administrations done across the country.

Nevertheless, the Y90 events are the greatest in number, and stubbornly so without a clear trend down or up. But we felt it was our responsibility to highlight this and to suggest creation of a subcommittee that would go into this in more detail and see whether we could come up with some recommendations in collaboration with the community of practitioners and vendors to hopefully come up with some solutions that might help decrease the frequency of medical events. So we think it's also timely that this recommendation be made now in that, as was mentioned earlier, we now have an interventional radiologist -- I forgot the exact terminology of his position, so you'll excuse me, but as part of ACMUI would obviously be a wonderful person to help with this

endeavor.

Next slide? We'll now go through the actual data by each category. And again, for those who have seen these data in previous years, things really are essentially the same, which is certainly maybe not great news, but certainly not bad news either. And a number of events are relatively low in many categories. So for 35.200, unsealed byproduct material for imaging or causation, there are actually no events in 2020. So that's awesome.

Next slide, please? For .300, byproduct material for -- unsealed byproduct material, written directive required, there were only two events, which is a relatively low number even in the context of history, so relatively positive in there as well. And the events really don't stand out warranting further discussion in terms of their details beyond what's already been summarized at the beginning.

For manual brachytherapy, .400, there were six events for the year. And again it's a modest number for this category. Worth noting that the Rule 35 modification that led to a change in the definition of a medical event for low-dose (inaudible) brachytherapy changing it from a dose-based criteria to an activity-based criteria in order to make the true

medical event stand out, but not have medical events reported that were not genuinely thought by the community of (inaudible) medical events has had the impact it was expected in that the number of such events has declined.

A brief note: There was one medical event that might be considered patient intervention, which again was alluded to before, there is some work going on in that space. The exact details elude me at the moment, but it was a patient who had a separate medical condition that intervened, and because of that technically it was a medical event. But again, that's really been discussed at length in that subcommittee's work, so we won't go into that further now.

And again, as you see here, there are some events that -- within this category as well: timeouts, or paying more attention, or getting more experience reviewing procedures before going forward may have had an event. At this category some modest fraction of manual brachytherapy that are felt to be explained by these two categorizations.

Next slide, please? I think this highlights things that I have already discussed. Yes.

So we can just move ahead to the next slide, please? Going onto .600, which is HDR, and the old

gamma knife units. Relatively same number of events as before: 13 this year and 10 last couple of years with similar types of events as a cause. Most of these have to do with HDR delivery and no big trends stand out.

In terms of diseases involved this mirrors HDR's use. The brain is obviously related to the gamma knife units. The rest are HDR treatments, and GYN applications are the dominant use of HDR with probably prostate and breast coming next and then skin and lung, but that varies a lot by practice across the country, so not surprising that GYN would have the lion's share. I think it's probably proportional to the use although we don't actually have data on that to really prove that.

Next slide? So again, some events were thought to be attributed to timeouts. There was a change in the subcommittee this year. I think there's little -- somewhat of a change in attribution and maybe somewhat attributable just to the discussions and the expertise of the people now composing the subcommittee as to before, although it's possible there are some real change as well. I think we'll give that another year to -- and see how that shakes out. That would be my impression.

And one more -- next slide again? Also the issue of infrequent user or inattention in this category. Again a bit of a higher estimation this year from past years, but again possibly just attributable to changes in the subcommittee's makeup. Having been on the committee during these years it's my impression it was more that than actual changes in what's happening in the community, highlighting somewhat the difficulty in making these attributions despite the fact that we do think these are relevant issues.

Now moving on; next slide, please, to 35.1000. You see a few different categories here, so radioactive seed localization. There was only one event.

Next slide? Intravenous cardiac brachytherapy, which does continue, a couple events in the last year, over the last -- in the last couple years, but again not really significantly different.

Next slide? 35.1000 for gamma knife (inaudible) units, just a couple of events in line with other years. No patterns or concerns from the subcommittee in that arena.

Next slide? And that's in Y90, so we look at both TheraSpheres and SIR-Spheres, the two modalities available, two isotopes available, or

companies manufacturing them. And the numbers for both really are stable for years, as you see here, with their spheres; 14 and 15 fifteen events every year. And a decent proportion of them thought to be related to either a time-managed view or an infrequency of use or inattention to detail type of thing, so there may be further work for a subcommittee to ferret this out a little bit more and come up with some recommendations for the community.

Next slide? And for SIR-Spheres, absolute number is a little less. And that seems consistent, too. That would be one interesting thing for the subcommittee to look into to see if there -- these are genuine differences between the two and are TheraSpheres slightly more likely to have events? And if so, why? Or is this just noise and they're all about the same and maybe proportional to market share? I can't say at this point what would be the leading hypothesis, but would be something to look into.

It's possible there are some things that the SIR-Sphere's delivery system does a little better perhaps, but I'm just speculating. And I'm not a practitioner in this area, so I apologize if I'm speaking out of turn. And again there may be an

opportunity for the issues that we've highlighted before to be further highlighted in this domain if we -- if this -- there is agreement to move forward with such a subcommittee.

Next slide? So this has been discussed previously, issues about doing a timeout, confirming everything is correct, making sure all the tubing and everything is proper. Again this would be something the subcommittee could go into more detail about.

And one more slide, I believe, just going into the elements of the timeout. This is something we've already presented before in our reports about the basics of what's being done that should be done in a timeout or checklist format before delivering isotope, as I've said -- as we've said, would diminish or decrease the risk of medical events in several of the categories. We had no changes to this previously shared recommended list.

And with that, I conclude my report and I'll pass it back to Dr. Metter.

(Pause.)

DR. ENNIS: Can't hear you, Darlene.

CHAIRMAN METTER: Okay. Thank you. Thank you, Dr. Ennis, for a very thorough report of the 2020 medical events.

Do I have any questions from the subcommittee members?

(No audible response.)

CHAIRMAN METTER: Any questions from the ACMUI itself?

(No audible response.)

CHAIRMAN METTER: Any questions from the NRC staff?

(No audible response.)

CHAIRMAN METTER: And any questions from the public?

(No audible response.)

MS. LOPAS: So for members of the public, if you have a question, you're going to either -- if you're on your phone, you're going to press *3, or if you open up your participant's panel, which I'm wondering if you all have -- but you're going to have to click on the little raise hand icon. It is very teeny tiny, that raise hand icon. I don't know why Webex makes the raised hand icon so small. It's almost to discourage participation.

But if you can find the little teeny tiny hand icon -- it should be on the right side of your Webex screen. Click on that and that will indicate to Kellee, who's our Webex host, that she's going to

need to un-mute you. So that's how you'll raise your hand and ask questions today. Click on that little hand icon. Or if you're calling in, press *3 on the phone. So we'll give everybody a second to just see if any hands get raised.

Kellee, just interrupt if you see any raised.

(Pause.)

MS. JAMERSON: Sarah, I'm showing no hands.

MS. LOPAS: Okay. Great. Thanks, Kellee.

CHAIRMAN METTER: Thank you, Kellee and Sarah.

Now I'd like to go ahead and see if we can go ahead and approve the subcommittee reports from the ACMUI. Do I have a motion to approve Dr. Ennis' subcommittee report on medical events?

MEMBER WOLKOV: Move approval. It's Harvey Wolkov.

CHAIRMAN METTER: Thank you, Dr. Wolkov.

Do I have a second?

MEMBER MARTIN: Second. Melissa Martin.

CHAIRMAN METTER: Thank you, Melissa.

All in favor?

(Chorus of aye.)

CHAIRMAN METTER: Okay. Any abstentions?

(No audible response.)

CHAIRMAN METTER: Any opposed?

(No audible response.)

CHAIRMAN METTER: Hearing none, thank you, Dr. Ennis. Your subcommittee report is unanimously approved by the ACMUI.

So let's go onto our next item on the agenda.

DR. ENNIS: Darlene?

CHAIRMAN METTER: Yes?

DR. ENNIS: Do we want to discuss -- the committee made a proposal for a subcommittee. When do you want to discuss that?

CHAIRMAN METTER: Yes, I do like to -- I would like to go ahead and -- how would you like to go ahead and propose a subcommittee regarding the -- I believe I thought the subcommittee was going to go ahead and address it itself, or make a subcommittee within the subcommittee?

DR. ENNIS: I guess that's for you -- we could do it either way, I suppose. I'm open to --

CHAIRMAN METTER: Okay.

DR. ENNIS: First I want to know if the ACMUI agrees with the proposal. And then the second question would be should we just do it as part of the subcommittee, or should there be yet a different subcommittee? There certainly would be a need to add the new interventional radiologist to the group, and he is not currently on the subcommittee.

CHAIRMAN METTER: Yes, we are definitely going to have our new interventional radiologist on that subcommittee. We'll go ahead and do this off-line and we can go ahead and discuss it so that everybody's in concurrence.

Any other comments or questions? Would that be acceptable to you, Dr. Ennis?

DR. ENNIS: Sure.

MR. EINBERG: Yes, and this is Chris Einberg. That's acceptable. At the end of the meeting let's just recap that -- what we've decided, to have a subcommittee and what the membership will be so that it goes on the record, and what the charge will be. And we can discuss that at the conclusion of the meeting.

CHAIRMAN METTER: Thank you, Mr. Einberg.

Our next presentation will be by a radiopharmaceutical for the ACMUI, Mr. Richard Green,

who will be speaking on the Radionuclide Generator Knowledge and Practice Requirements Subcommittee report. Mr. Green will discuss the subcommittee recommendations on the knowledge and specialized practice requirements for eluting, measuring and testing, and processing the eluate from radionuclide generator systems.

Mr. Green?

MR. GREEN: Thank you, Dr. Metter.

Next slide, please? I want to acknowledge the subcommittee members: Dr. Vasken Dilsizian, Melissa Martin, Megan Shober, Dr. Harvey Wolkov, and our NRC staff resource Maryann Ayoade.

Next slide, please? We have four charges. We'll go through them briefly. To review and evaluate the knowledge and practice requirements for eluting, measuring, and testing and processing the eluate from radionuclide generator systems based on the evolution of the radionuclide generator distribution, things that have changed.

To evaluate and determine the appropriateness of the requirements and how best to obtain the knowledge, the required knowledge and practice.

Slide? To evaluate whether and how

additional knowledge and practice should be obtained as necessary to supervise the use of any radionuclide generator system and to provide considerations and recommendations to staff.

Next slide, please? A little history to begin with: In 1994 the NRC amended its commercial distribution of radioactive drugs and medical use regulations found in 10 CFR Part 35 and 32 in part to allow properly qualified nuclear pharmacists and authorized users who are physicians with greater discretion in preparing radioactive drugs containing byproduct material for medical use.

Next slide, please? That rule, the preparation/transfer of commercial distribution and use of byproduct material for medical use resulted in the language presently found in 10 CFR 35.290 entitled Training for Imaging and Localization Studies.

Specifically, 10 CFR 35.290(c)(1)(ii)(G) reads as follows: Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs.

Next slide, please? That's the

regulation that was written 27 years ago. How has that changed? Over the last 27 years there has been significant change in the types of radionuclide generators used in clinical nuclear medicine practice, where these generators are housed and used, and the individuals who handle generators.

Next slide, please? Prior to 1972 moly/technetium generators were ubiquitous and were found at every clinical nuclear medicine facility. The first commercialized nuclear radiopharmacy opened in 1972. Today there are approximately 300 commercial nuclear pharmacies in the United States.

Next slide, please? The locations of most moly/tech generators migrated from a hospital nuclear medicine department to a centralized radiopharmacy as nuclear medicine facilities converted to patient-ready unit doses and utilized the services of centralized radiopharmacies for the provision of radiopharmaceuticals -- next slide, please -- to the extent that today approximately 95 percent of all radiopharmaceuticals used in the United States originate from a centralized radiopharmacy.

As a result of this consolidation of activities there are fewer moly/tech generators in use today than were used in the past, the more efficient.

Next slide, please? It is estimated today that the United States utilizes approximately 720 new moly/tech generators weekly with 90 percent of them, around 660 units, delivered to centralized to radiopharmacies for use under the direction of an authorized nuclear pharmacist, and around 10 percent of all generator, 60 units or so, are delivered to hospital facilities for use under the direction of an AU physician or a local authorized nuclear pharmacist.

Next slide, please? Those were moly/tech generators. Specifically the strontium-82/rubidium-82 generators, because of the 75 second half-life of this nuclide used for PET and myocardial infusion imaging

-- all rubidium generators are in the clinical nuclear medicine facility and are used under the direction of an authorized user physician.

Next slide, please? Speaking of germanium-68/gallium-68 generators, it is estimated that currently in the United States 70 percent of germanium/gallium generators are delivered to centralized radiopharmacies for use under the direction of an authorized nuclear pharmacist and 30 percent are delivered to the hospital facilities for use under the direction of an authorized user

physician.

Next slide, please? As we can see, the evolution of where radionuclide generators are located has presented challenges for fellows in training and residency programs. Many residency programs made arrangements with commercial pharmacies for their fellows in training to attend generator training, but due to COVID-19 these radiopharmacies have restricted access to their facilities.

Next slide, please? This increased the knowledge and practice burden that affects fellows in training who are unable to attend commercial radiopharmacies to receive generator training due to COVID-19 closure of those facilities.

Next slide, please? In June of 2020 several professional societies: ASNC, SNMMI, ACR, and ASTRO, united to request that the U.S. NRC consider Title 10 of the Code of Federal Regulations, Training for Imaging and Localization, as a potential area for regulatory relief during the coronavirus disease public health emergency.

Next slide, please? This letter written by this group of organizations states that most of the commercial radiopharmacies that supply portions of this training are closed to visiting trainees because

of the COVID-19 public health emergency and may not reopen for the foreseeable future.

Next slide, please? This letter further states that they believe that this experience requirement can be satisfied virtually via demonstrate educational webinars during the duration of this public health emergency.

Next slide, please? So in the committee we discussed -- we deliberated the intent of the existing rule language including the knowledge elements necessary for AU physicians to possess with regard to generator systems and various methods of acquiring knowledge of these elements.

Next slide, please? The subcommittee recognized the authorized user physicians role as ascribed in 10 CFR 35.27 in supervising nuclear medicine technologists who may be operating generator systems in clinical sites. The subcommittee believes that authorized users, whether or not they personally use radionuclide generator systems, must be familiar with how generators work. They must be familiar with how breakthrough is tested and how reagent kits are used to label radioactive drugs.

Next slide, please? The subcommittee also believes that it is not necessary for authorized

user physicians to have direct hands-on work experience with generators although the subcommittee recognizes that direct work experience is an excellent way to fulfill the training requirements.

Next slide, please? In order to facilitate learning and to provide a training program's flexibility to deliver training the subcommittee discussed the strengths and limitations of in-person, pre-recorded, or live virtual training opportunities.

Next slide, please? The subcommittee believes that training can incorporate any combination of these methods, but the subcommittee believes that it is essential for the training to include an opportunity for physicians to ask questions about the subject material and receive answers in real time.

Next slide, please? In addition it is important for the trainer to be able to assess physician learning as the training is progressing. If pre-recorded material is used to deliver a portion of the training, there should be also -- should also be a live component, whether in person or via virtual meeting technology, where trainees and trainers can directly interact.

Next slide, please? Consistent with existing regulation the subcommittee believes

-- further believes that it is not necessary to mandate training on every radionuclide generator system. Training programs should have the flexibility to modify the training curriculum as the use of generator systems evolves.

Next slide, please? On this slide we have the current rule language found at 10 CFR 35.290. Again, we've quoted (G) before where it's eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing of the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs. The subcommittee proposes this be revised to read participating in educational sessions to gain knowledge and provide supervision of: (1) radionuclide generator systems and their operation; (2) the measurement of radionuclidic impurities and acceptable limits; and (3) the use of reagent kits with radionuclide eluate to prepare radioactive drugs.

This concludes the subcommittee's report. I have two slides worth of acronyms.

Dr. Metter, am I to ask if there are any questions from the ACMUI?

CHAIRMAN METTER: Sure. Thank you, Mr.

Green, for that very excellent report from your subcommittee. Very thorough.

Do I have any questions from the subcommittee itself or the ACMUI?

Yes, Dr. Ennis?

DR. ENNIS: Is this meant to be a recommendation just for public health emergency or for the foreseeable future beyond the public health emergency?

MR. GREEN: The subcommittee's recommendation was to change the regulation. So it is not specific to the present public health emergency or any future public health emergency, but to change the regulations from language that requires physicians' hands-on touching to physicians undergoing training exercises to obtain knowledge to be able to supervise the handling of generator systems.

CHAIRMAN METTER: Thank you.

VICE CHAIR DILSIZIAN: Dr. Dilsizian here. CHAIRMAN METTER: Yes, Dr. Dilsizian? Go ahead.

VICE CHAIR DILSIZIAN: Yes, just to -- again excellent presentation, Mr. Green. And this was a tough topic, and again it came up due to COVID-19 pandemic. But this was an issue, as Mr. Green very

nicely presented, in the evolution of radionuclide generator distribution, the introduction of new generators: rubidium, germanium.

So to Dr. Ennis' answer -- answer to his question, it is -- while it may have started with the pandemic, we -- it gave us an opportunity to review the entire process of other generator distribution, how residents and fellows are being trained, who's being supervised? And given that the majority of the doses are being given as unit doses from a centralized nuclear pharmacy it made sense that -- to have a system that is both -- incorporates both online web-based teaching as well as in-person or a web-based question and answer period as the entire education system is changing as we move forward beyond the COVID pandemic. Thank you very much.

CHAIRMAN METTER: Thank you, Dr. Dilsizian.

Yes, Dr. Ennis?

DR. ENNIS: A separate question, Mr. Green. You kind of explained how the subcommittee felt like interactive type of teaching is necessary, but I don't see in the language, what's proposed, clarity regarding that. Maybe participating is meant to imply that, but I think that could be easily read as just

watching a webinar is participating, too? Comments on that question?

MR. GREEN: We thought we were providing recommendations to NRC staff, and if they want to get explicit and require some live component in the regulations that they write -- I thought we were very clear in our recommendations that to be -- an entirely passive process we thought was undesirable. We strongly recommend an active component of questions and answers, whether it be live or virtual via technology. But we made our recommendations and I think it's up to the staff to take that into the regulatory writing process.

CHAIRMAN METTER: Thank you, Mr. Green.

MEMBER JADVAR: Can I ask a question? This is Dr. Hossein Jadvar.

CHAIRMAN METTER: Yes, Dr. Jadvar.

MEMBER JADVAR: Again wonderful presentation. Thank you.

With regard to this education that you're proposing, I do recall when I was a resident physician this was part of our education. In fact I do remember that I went to a central radiopharmacy and learned most of what you proposed here. So I think it's kind of built into the training of a nuclear medicine physician

at least. I'm not sure about radiology residents.

But what's your proposal with regard to how often this needs to be done? Is this something that needs to be done -- because I believe it is done already as part of being able to sit for the Board of Nuclear Medicine and it's part of the education of all the nuclear medicine physicians. But how often this needs to be done as a refresher? Is that something that you also discussed?

MR. GREEN: The current regulations do not specify any refresher. This is a one-time fellow training prior to receiving your authorized user status. We did not see that changing at all in our proposal.

CHAIRMAN METTER: Thank you, Mr. Green. I do have a question, too. For this training are there going to be any specific credentials for the trainer regarding these sessions that you're talking about?

MR. GREEN: I would refer back to the NRC regulations themselves. I think that training has to be provided by an authorized user physician. Whether that be directly by the physician or under the physician's direction provided by a nuclear medicine technologist I think are acceptable options. Or it

can be provided by an authorized nuclear pharmacist.

CHAIRMAN METTER: Thank you, Mr. Green.

MEMBER OUHIB: This is Zoubir Ouhib. First of all, great presentation, Mr. Green. I have a question on the subcommittee proposed revision. It says participating in educational sessions. My question is that -- is participating good enough or are there some expected performance or whatnot to make sure that the individuals who are participating have actually met certain requirements?

MR. GREEN: We did discuss the need for the trainer to be able to assess the effectiveness of the training. So we would think there would be some type of knowledge assessment, exam, quiz, however you may want to describe it, so that the trainer can be assured that the message was received and the concepts were understood by the trainees.

VICE CHAIR DILSIZIAN: Dr. Dilsizian here. CHAIRMAN METTER: Yes, go ahead, Dr. Dilsizian. Thank you.

VICE CHAIR DILSIZIAN: Thank you very much. Yes, Zoubir, the answer to your question is -- I will speak from the cardiologist's perspective. The cardiology fellows will have the training once during their fellowship period that would involve either a

radiopharmacist or an authorized user with a competent technologist, or they can go to a central nuclear medicine facility.

But at the end of the day; we've all talked about this in several other forums, competency comes from an examination. So once the fellow or resident passes the Certification Board of Nuclear Cardiology, the American Board of Nuclear Medicine, the American College of Radiology, Board of AVR, that is the way you would judge it. And these questions are part, an integral part of the board certification and that's where NRC looks for competency from the organization.

CHAIRMAN METTER: Thank you, Dr. Dilsizian, for that clarification.

Are there any other questions from the ACMUI?

(No audible response.)

CHAIRMAN METTER: Okay. Seeing none, any questions from the NRC staff?

MR. EINBERG: Yes, this is Chris Einberg. So no questions. I just wanted to comment on the process and what we will do with the recommendation.

So the NRC staff will evaluate the subcommittee report and the recommendation to change

the rules. If we decide to move forward, the NRC staff decides to move forward and makes a recommendation to the Commission, then it would go to the rulemaking process. And at that time some of these details as far as what the level of participation would be would be clarified in the rulemaking process. And the public would have the opportunity to comment on that as well.

And I see Dr. Howe has -- would like to add something as well. So with your permission, Dr. Metter, I'll turn over to Dr. Howe.

CHAIRMAN METTER: Yes, thank you.

Dr. Howe, go ahead.

DR. HOWE: Okay. Thank you. I just wanted to point out that some of the statements about our fellows who are already required to do this, and we are required to do this for the boards. If NRC changes its regulations, those requirements will no longer be there and our experience in the past is even though some of the boards require a lot of training and experience before the regulation changes, as soon as the regulation changes it meets the newer lesser requirements.

I'd also like to point out that right now in the new part, in the current revision to Part 35 we did add that the generator training could be provided

either by an authorized user or by an authorized nuclear pharmacist. So that is already in the requirements.

And I think it's important to point out that we've had a number of events with the rubidium/strontium generators in which the authorized users that were responsible for those generators questioned why they (audio interference) generators when there was breakthrough?

And I'm only -- I'm not really focusing on the nuclear cardiologists, but that they are the ones that actually have the generators in their facility, and because of the short half-life they're not able to depend on unit doses coming from the centralized nuclear pharmacists. So that's an especially important generator elution issue that you need -- that needs to be looked at. And I think that's the end of my comments. Thank you.

CHAIRMAN METTER: Thank you, Dr. Howe.

Are there any other comments from the NRC?

(No audible response.)

CHAIRMAN METTER: Okay. I would go ahead then and entertain any comments or questions from the public.

MS. LOPAS: Okay. So for members of the

public, a reminder to use that raise hand icon. So just click on the little hand icon. Or if you have called in using your phone, press *3 on your phone.

We'll give everybody a few seconds to raise their hand and Kellee will be on the lookout to see if we have any members of the public who have raised their hand and need to be un-muted.

(Pause.)

MS. JAMERSON: Sarah, I'm showing no hands.

MS. LOPAS: All right. Thank you, Kellee.

CHAIRMAN METTER: Thank you, Kellee and Sarah, for your assistance on the public comments.

Now I'd like at this time to turn back to the ACMUI and have a proposal -- a motion to approve the subcommittee report.

MEMBER WOLKOV: So moved. Harvey Wolkov.

CHAIRMAN METTER: Thank you, Dr. Wolkov.

Do I have a second for this committee report?

MEMBER JADVAR: Second. Hossein Jadvar.

CHAIRMAN METTER: Thank you, Dr. Jadvar.

All in favor, say aye?

(Chorus of aye.)

CHAIRMAN METTER: Any abstentions or objections?

(No audible response.)

CHAIRMAN METTER: Hearing none, I'd like to conclude that the subcommittee report is unanimously approved by the ACMUI.

So are there any other issues now before we go to the open forum?

(No audible response.)

CHAIRMAN METTER: Okay. So let's go ahead and go to our next item, which is to identify topics of interest for future discussion. Are there any topics for future discussion by the ACMUI and NRC staff? I know we do have that subcommittee that we would like to form, but we'll go ahead and do it at the conclusion of today's meeting.

(No audible response.)

CHAIRMAN METTER: Okay. I do not see any comments. Do you see any comments, Mr. Einberg or Sarah?

MR. EINBERG: I do not.

CHAIRMAN METTER: Okay. So at this point then I believe we're early in our agenda, but we'll take a break for lunch and we'll reconvene at 12:45 because this is a public meeting and other members of

the public may be following our agenda. So with that we'll go ahead and close the morning session. Is that --

MR. EINBERG: Yes, and that's fine. So that's 12:45 Eastern Time for the people who are participating across the country.

CHAIRMAN METTER: Okay. Thank you.

MR. EINBERG: Sure. Thank you, Dr. Metter.

(Whereupon, the above-entitled matter went off the record at 11::08 a.m. to reconvene at 12:45 p.m. this same day.)

CHAIRMAN METTER: Well, good afternoon. I am Darlene Metter, ACMUI Chair and diagnostic radiologist. Welcome back to the 2022 Fall ACMUI Meeting.

Our next presenter will be Dr. Hossein Jadvar, our ACMUI nuclear medicine physician, who will be presenting on emerging radiopharmaceutical therapy knowledge requirements in theranostics, the subcommittee report.

He will discuss the subcommittee recommendations on the knowledge and specialized practice requirements needed for the safe use and handling of emerging radionuclides in theranostics.

Dr. Jadvar.

MEMBER JADVAR: Thank you very much, Dr. Metter.

So, as Dr. Metter mentioned, this subcommittee was formed by her in May 2021. And the subcommittee met four times virtually during July and August of 2021 to form this report and presentation. Can I have the next slide, please?

So this is the agenda. I will introduce the subcommittee members. Then we'll talk about what our charge was for this subcommittee.

I'll give some background on theranostics and some of the current, currently active and also emerging agents in theranostics and some of the challenges that we still face in this arena.

Then we talk about the knowledge requirements that we discussed during our deliberations.

And finally, I'll show you a picture, a sample, or illustration of what a theranostics room setup could be looking like. Can I have the next slide, please?

So this is the membership of the subcommittee, Dr. Vasken Dilsizian, Dr. Ron Ennis, Dr. Mike O'Hara, Mr. Zoubir Ouhib, and Mr. Josh Mailman.

And our NRC staff resource was Ms. Maryann Ayoade.

I want to acknowledge and thank all of them very much for their contributions and participation in the discussion.

I also want to acknowledge Lisa Dimmick, who was very helpful, especially initially with our subcommittee and with me in defining our role and the charge. May I have the next slide, please?

So this is the subcommittee charge, to outline the knowledge and specific or specialized practice or policy requirements needed for the safe use and handling of emerging radiopharmaceuticals in theranostics and also provide considerations and recommendations to the NRC staff. May I have the next slide, please?

So, for background, let's talk about what theranostics is. Theranostics is essentially a systemic integration of diagnostic tools. And this doesn't have to be imaging. But in this case for our purpose, you are focusing on nuclear imaging. But it can be non-imaging tools. It could be other non-nuclear imaging tools.

But again, we are focusing on nuclear imaging and the therapeutic agents. And these therapeutic agents, again for our purpose, we are

focusing on radiopharmaceuticals.

But again, in the general theme of theranostics, it does not have to be radioactive therapies. For example, it could involve nanoparticles or nanomedicine.

In any event, both these diagnostic tools and therapeutic agents are related or targeted to the same biomolecule. And that's how this whole package works. In other words, the idea is to, we see what we treat and we treat what we see. That's the idea behind theranostics.

In a broader definition, instead of having the same biomolecule or target, you can have similar biological parameters. So that's more of a broader definition of theranostics. And I mentioned what I mean by that.

In any event, the whole field of theranostics is very much aligned with current interests and activities in what's called as precision or personalized medicine.

The history of theranostics is credited to Dr. Saul Hertz, who was a thyroidologist at Mass General Hospital in Boston.

When he realized that if he uses radioiodine, he can use radioiodine for treatment of

thyroid diseases based on the basic knowledge that the thyroid gland concentrates iodine.

And in fact, he was attending medical grand rounds at Mass General where the speaker was at the time president of MIT, just across the Charles River. And they were talking about the cyclotron and radioactivity. And Dr. Saul Hertz asked a question regarding whether iodine can be made radioactive with the thinking that that may be, have some medical use.

Although Dr. Hertz did not use imaging and there were other radioactive treatments for cancer or other diseases prior to him, but the fact that he used it in thyroid diseases and the fact that we still use this today is the reason that we credit Dr. Saul Hertz for the initiation of the theranostics field. May I have the next slide, please?

So here is the list of what is currently active within theranostics. As I mentioned, the oldest one is obviously radioiodine both for imaging and for treatment of thyroid diseases. The target here, of course, is sodium iodine symporter.

We also have the indium-111/y90 ibritumomab, which is, with the target of being anti-CD20. This is marketed as ZEVALIN and was approved by the FDA in 2002 for the treatment of

patients with lymphoma.

The next one is a bone scan agent, sodium fluoride for PET scanning or technetium-99m-MDP with planar or a SPECT imaging as the imaging counterpart and the companion being the radium dichloride, radium-223 dichloride for, as alpha therapy as the therapeutic companion.

This is, it falls into the broader type definition for theranostics. The target here is osteoblastic metastases. And we are currently using that for treatment of metastatic cancer disease and prostate cancer.

Also under that broader definition of theranostics, we have the technetium-99m-MAA for mapping the perfusion of lesions within the liver and the Y-90 microspheres with TheraSphere and SIR-Spheres that have been approved for treatment of liver tumors, including metastatic tumors, for example, from colorectal cancer or for hepatocellular carcinoma.

The next one is the I-123 and I-131 MIBG. The I-131 MIBG is marketed as AZEDRA for treatment of pheochromocytoma and paraganglioma. The target, the biological target here is the norepinephrine transporter. This was approved in 2018.

And then we have the gallium-68-DOTATATE,

which is marketed as NETSPOT. And that was approved in 2016 with the target being the somatostatin receptors with, for imaging of neuroendocrine tumors.

Later on copper-64-DOTATATE with a longer half life of 12 hours was approved with the commercial name of Detectnet. That was approved exactly almost one year ago in September 2020. Gallium-68-DOTATOC, which is another similar agent, was approved in 2019.

And finally, the therapeutic counterpart is the lutetium-177-DOTATATE, which is marketed as, with the name of LUTATHERA. And that was approved by the FDA in 2018. May I have the next slide, please?

So what is within the next, near future? This is very, very exciting. And the imaging portion of this theranostic pair has already been approved. The gallium-68 PSMA-11 was approved by the FDA for local use at UCLA and UCSF. That was back in December 1, 2020.

And then very recently, the F18-DCFPyL, which is marketed as PYLARIFY bilantheas, was approved by the FDA on May 27, 2021, relatively recently.

So we have the imaging agents now available. And hopefully that will disseminate in the clinics very fast.

The lutetium-177-PSMA-617 is the therapy

part of this. And there have been a number of clinical trials that have been done with this agent.

The most recent one and the most significant one is the VISION trial. It's a randomized phase III trial that was published in June of 2021 in the New England Journal of Medicine with very positive results.

And so it is anticipated that the lutetium-177-PSMA-617 will also have its FDA approval relatively soon, perhaps by the end of this year or early next year. So we will have a theranostic tool for treatment of a very prevalent disease, and that is metastatic cancer disease and prostate cancer.

What is in the horizon? In the horizon, we have, again, the same target PSMA, but this time with the alpha particles for treatment, the actinium-225 and the thorium-227. There are a number of clinical trials that are going on in this space at this time.

Then also we have the agents both for imaging and treatment targeted, the radionuclide treatment targeting the chemokine receptor 4. These are also very exciting. And the most significant work in this area has been done with multiple myeloma.

The other one is, targeting is

gastrin-releasing peptide receptor, which targets multiple solid tumors, including prostate cancer. And there are a number of clinical trials going on on that.

And finally, another very, very exciting theranostics pair is targeting the fibroblast activation protein, the FAPI. It stands for fibroblast activation protein inhibitor. So it's an inhibitor that targets this protein.

And it has been shown that it can target multiple cancers, especially those that may not be FDG-added sufficiently, such as pancreatic CA.

And, of course, this one provides a completely new way of treating, seeing and treating tumors, tumor lesions, because we are not really looking at the tumor itself, but we are looking at the microenvironment, the stroma microenvironment of the tumor.

So that can also be used not only for better imaging evaluation of patients but also for another avenue for treatment of these cancers. May I have the next slide, please?

There is also more in this space. There's another pair for targeting the carbonic anhydrase with the goal being to have a robust theranostic tool for

key-R cell, renal cell carcinoma.

Integrins have always been of interest. Integrins have a role in cell/cell interaction and cell/matrix interaction, very important for metastatic potentiation and formation.

And so a number of these trials are going on with specific attention to a very difficult cancer to treat, and that is glioblastoma multiforme.

And finally, there are also efforts with the PARP inhibitor, a type of theranostics. These are related to, with the target of looking at the DNA repair enzyme, PARP, PARP1.

It can be used in multiple cancers to basically cause the tumors to have apoptosis and die and do not repair their DNA when they get injured with any type of therapy, including radionuclide therapy. May I have the next slide, please?

So what were the issues with regard to theranostics? There is a very nice paper that I do, in our report in the references with regard to some of the things that still need to be addressed with regard to theranostics.

And some of them are technical. We need standardized and efficient clinical protocols. Some of them have been done. Some of them are in flux right

now. And, of course, as we get new theranostics companions, they need to be formulated.

We will talk about the interdisciplinary teams, because this is something that really requires a team effort for its delivery to the patient.

Also, eventually, these protocols need to be incorporated into the clinical protocols, for example, I mean into the clinical guidelines, for example, the NCCN guidelines, so that it enters into the mainstream treatment cycle of the patients.

And education and training, of course, is very important. And we'll talk about that a little bit later.

There are some economic challenges, including some issues with the need for investment in supporting the supply chain for a steady pipeline of these radioisotopes, especially alpha particles if they become used or if they become available for use in the clinics. And I think they will be.

There needs to be sufficient reimbursement. And, of course, we need to do some cost utility analysis to compare this type of treatment and care in comparison to other available or novel treatments.

And, of course, we always need more R&D

funding to explore more. May I have the next slide?

There are also some biomedical challenges, of course, whenever we need to find out what are the reasonable or plausible biological targets and use those targets to design and conduct pre-clinical animal studies and then first-in-human studies, and finally large prospective clinical studies, either on its own or in comparison to other approved treatments, and to really find out what the added value of theranostics can be in care of patients, for example, with cancer.

And then, of course, when something is approved, there needs to be more trials in the future to see what is the best approach. And this can be a very dynamic picture.

In other words, we can start with a single treatment with a theranostic agent and then reevaluate after a couple of cycles and see if the situation has changed.

If it has changed, do we still need to continue with the single, with the additional cycles of the theranostics, or do we need to adapt ourselves, our treatment to incorporate some other type of treatment into the, as a combination treatment in the middle of the theranostic regimen?

And, you know, so these are very

interesting issues that needs to be addressed in the future.

And, of course, most of these efforts are currently focused on cancer. But cancer, there are also non-oncological diseases that definitely can be some scenarios for theranostics as plausible tools for treatment of those patients. May I have the next slide, please?

So these are some of the things that we discussed. I have organized this in a report, in a more kind of categorized fashion. But here are some of our discussions.

We discussed the healthcare team at the time of the theranostic administration. And we felt that the team administering a dose should consist or may consist of an authorized user, obviously with appropriate training in theranostics, a certified nuclear medicine technologist, a radiation safety officer, typically a registered nurse. This could be a, usually is an oncology nurse to help out with some of the, with preparing the patient with IV administration of various types of needed drugs.

And medical physicists, if available and applicable, especially in, when we start using dosimetry for these patient, that addition could be

very, very helpful, but although the fact is that many clinics and hospitals do not have the luxury of a medical physicist. But it could be very helpful.

The authorized user must be present at the time of the dose administration. Next slide, please.

So the therapy should be done in a dedicated and regulatory-approved room that is appropriate for radioisotope administrations. At the end of my presentation, I'll show you an example of what it may look like that we have here at my place of work at the University of Southern California.

As I mentioned, in this team approach, oncology nurses, for example, can be participating. In fact, they are participating in our case at USC. And in those cases, they may need to wear a radiation badge, which will be determined by the RSO. Next slide, please.

With therapeutics always extravasation is an important issue. Patient release criteria is another important issue, although these two important issues are being addressed by other ACMUI subcommittees.

With regard to the radioactive waste management, this should be referred to the facility established guidelines and regulations.

With regard to possible radiation, radiopharmaceutical therapy induced radiation injuries, the AU we felt should be responsible to address any concerns that the patient has, because the AU is the most knowledgeable regarding possible radiation induced injuries.

And the referring physicians or those who sent their patients to us for treatment with radiopharmaceutical may not have the sufficient knowledge about how to either evaluate or treat those type of possible injuries.

Also, as I mentioned, there are many new theranostics that are in the horizon. And so, as they develop, we have to make sure that these are within, remain within the regulatory guidelines depending upon what they are. Next slide, please.

The AU is, of course, encouraged to avail themselves with all the newest training information by the vendor, by the various societies that offer education and training for these new theranostics.

This is a rapidly developing and moving field. And so, therefore, they need to make sure that they are abreast of all the developments that happen in this very exciting and dynamic area.

Patient dosimetry is another very

important issue. Right now the patient specific dosimetry is not typically performed. And most places do their fixed activity dosing.

However, there needs to be -- this is often an area of very active research and development to find out what can be done to standardize patient dosimetry. And also, and so the standardization is important because you want to keep the same type of protocols across clinics, across medical physicists, or different software so everybody does essentially the same thing.

There are currently still no randomized clinical trials to compare patient specific dosimetry to fixed activity with regard to providing high level evidence to show that actually patient specific dosimetry is associated with substantially or significantly improved patient outcome and least toxicity. But those are types of studies that needs to be performed.

There are, dosimetries can be done by surrogate imaging. But those surrogate imagings have to be developed and validated, of course.

With alpha particles the situation becomes a little more complicated. There needs to be some studies in the micro-scale radiation effects and also

the daughter distributions that can be contributory in, and can be important in accurate patient dosimetry calculations.

And, of course, at the end of all of this, it has to be determined if, again, as I mentioned, the potential patient benefit outweighs the cost and complexity of the logistics that may be involved with patient specific dosimetry.

So this is a very important, active area. And we recommend that the AUs should stay abreast of these developments also.

And finally, outreach is very important, outreach to the authorized users themselves, to the other healthcare providers and support staff, and also to the patients.

And these are typically handled by many organizations such as radiology organizations or nuclear medicine organizations. But it's a very, very important topic. And next slide, please.

So this is an example of a theranostics room setup that we have here at USC. We use this room for LUTATHERA administration. It's a relatively big room. We have only one chair there. But potentially there could be two chairs. There is a bathroom to the left of this picture, which is not shown, and

appropriately prepared for possible radiation leaks or other things.

And so I think as time goes on many hospitals or clinics or medical centers are going to have these type of rooms set up since theranostics is believed to really take off.

I know that at some places, for example, like Stanford, they have a whole corner or one whole part of their nuclear medicine department is dedicated to theranostics. There are multiple rooms. And also we are going to have the same thing at USC.

But this is something that needs to be developed at some other smaller clinic if they don't have it. And I just wanted to show you a sample example of this. Next slide, please.

I think those are my -- the acronyms, okay. So this concludes my presentation. And I, again, want to very much thank all the subcommittee members and the staff support from the NRC. Thank you.

CHAIRMAN METTER: Thank you very much, Dr. Jadvar, for a very comprehensive and exciting report regarding the theranostic future for our patients.

Now, do I have any questions from the subcommittee or ACMUI?

MEMBER SHOBER: This is Megan Shober. I

have a question about the authorized user.

One of your recommendations was that the authorized user must be physically present during administration. That's not currently required per 35.300 administrations.

And I'm just wondering if you could speak to why you felt that extra step is necessary, because that is again asking more than we are requiring currently --

MEMBER JADVAR: Yeah, I think --

MEMBER SHOBER: -- don't agree with it. So I'm just looking for some --

MEMBER JADVAR: Yeah, okay. Thank you.

MEMBER SHOBER: -- extra information.

MEMBER JADVAR: Yeah, I think actually I was the chair of the COVID-19 subcommittee, which was last year. And in that, we mentioned that the AU must be present, but it could be virtual, for example, because of the situation.

And if I recall correctly, in our subcommittee deliberations, we did say this AU should be present, but we didn't say if it's physically. You know, it could be physically. It could be virtually as long as there is a directive and all the required data are reviewed by the AU and the AU observes the

administration.

But if there are anybody in subcommittee who wants to add to this, please go ahead. So I think it's both virtual and, or personal.

(Simultaneous speaking.)

MEMBER JADVAR: Physical, I mean.

MEMBER MARTIN: This is Melissa Martin. I just, I have a question, because I don't see -- I'm looking for input from Megan maybe.

How would this differ from administering iodine-131 on a therapeutic basis, because we do ask the authorized user to be present to deliver the iodine doses?

MEMBER SHOBER: That's not required by the regulations. The only places that require the physical presence of the authorized user are for, or specifically written in the regulations is with the 35.600 and some of the 35.1000 modalities. But that's not in the regulations for 35.300 at all.

MEMBER MARTIN: I would just make, say that that may vary depending on which state you're in, because I think Dr. Jadvar and I are both functioning in California. And we require authorized users to be there.

MEMBER SHOBER: Yeah, that's why I wanted

to point that out. You know, as far as the NRC regulations go, that physical presence of an authorized user is not required at the time of administration.

And maybe somebody from NRC can confirm that for me. But that's been my understanding.

MS. AYOADE: Hi, Megan. This is Maryann Ayoade from the NRC. And, yes, you are correct.

So, for the unsealed type material uses, we don't have the physical presence requirements that we do for the other sealed source type and uses that we have. So 100, 200, and 300 material currently don't require a physical presence for the treatment by the authorized user.

MEMBER JADVAR: Interesting. But I know that --

MEMBER SHOBER: But, Maryann --

MEMBER JADVAR: -- during our deliberations, we did discuss that that would be at least advised.

VICE CHAIR DILSIZIAN: Vasken Dilsizian here. I guess I want to follow up. If the physical presence is not required, the AU has to be in the vicinity, right, in the department, in the division somewhere?

MS. AYOADE: So, yes, the regulations in

35.27 for supervision are still, you know, still hold true where, you know, it's the authorized user or the individual under the supervision of the authorized user that could be performing the treatment.

But we don't, you know, state or we don't specify like we do with the other programs that they need to be there physically.

(Simultaneous speaking.)

VICE CHAIR DILSIZIAN: I'm sorry. Go ahead.

MEMBER OUHIB: Yeah, this is Zoubir. I think I want to echo what Melissa said earlier is that in the state of Florida for our procedures we require the authorized user to be present.

But I really have -- I'm sort of struggling with the language itself of an authorized user itself, you know, so, you know, the AU being, quote, unquote, the user. To me, the way I look at it is the one who will actually be performing the procedure is the user or she is the user or whatever.

So I'm a little bit struggling with the language itself there that -- and I'm surprised to hear that the authorized user might not have to be physically present for the procedure itself, just a thought.

DR. JADVAR: Well, what I can say at least

at our place we have to be present. We are present. The authorized user actually goes into the room, to that room I showed you a picture of, and, you know, looks like all the paperwork for the patient with LUTATHERA, looks at the setup, everything, checks everything out.

And then, you know, the authorized user is the one who actually pushes the button on the pump to deliver the radiopharmaceutical to the patient. It is not done by the registered nurse or by the CNMT or anything else. It's just done by the doctor.

VICE CHAIR DILSIZIAN: Vasken Dilsizian. So, Dr. Jadvar, given that we say presence, which means virtually present or physically present, we've clarified that.

DR. JADVAR: Okay.

VICE CHAIR DILSIZIAN: Clearly virtually present means you can't push the button.

DR. JADVAR: Yeah.

VICE CHAIR DILSIZIAN: So I think we've come to the conclusion that as long as the AU goes through the proper verification of the right person, the right dose, and the indications, all the paperwork is done correctly, and it seems to me that the actual pushing or dosing the medication is less of an AU

requirement, rather than having the AU, make sure that the process and the procedure is going to be done appropriately and he or she is going to be there either virtually or we said physically.

But I guess we are saying physically as long as the person, the AU is in the division or the department somewhere. Is that --

DR. JADVAR: I agree. Do you think we should -- I mean, on our report we can say you must be present and put in parentheses physically or virtually or, you know, or adjacent or reachable --

VICE CHAIR DILSIZIAN: Yeah, within the division or department.

DR. JADVAR: Within division or department, yeah. So we can expand that in the parentheses so it's not, it's a little bit better, more clear.

VICE CHAIR DILSIZIAN: Megan, will that be acceptable to you?

MEMBER SHOBER: The part where I'm just stuck a little bit is that that's a higher benchmark than the regulations currently require. And so I guess I'd just be interested in hearing, you know, what the, what's different about theranostics that would, you know, raise the bar for that presence.

DR. JADVAR: Well, some of the deliveries are more complicated. For example, LUTATHERA is a lot more complicated in delivery of that theranostic than, you know, to make an appeal, of radioiodine. So, and there are things that you need to check with regard to verification, the laboratories.

I mean, those are the things that I think, you know, may require an AU to be somewhat more intimately involved, rather than, you know, something that we have been used to, like just giving a pill to a patient for thyroid cancer.

So I think, as we discussed in our subcommittee and Vasken elaborated just a minute ago, we thought that AU being present or adjacent within the department, virtually, physically, it's something of benefit for these more complicated treatments.

MEMBER SHOBER: Sure. And I agree that that, with that as a good practice. I guess for me I would prefer that it say the AU should be present. You know, when you start to say must, that's where --

DR. JADVAR: I see.

MEMBER SHOBER: -- I have a problem with it.

DR. JADVAR: Okay.

(Simultaneous speaking.)

CHAIRMAN METTER: Go ahead, Zoubir.

MEMBER OUHIB: This is Zoubir. I like Megan's suggestion with a should.

But I think it's an opportunity as these procedures continue to multiply to see whether with medical event the physical presence of the AU would have made a difference or not. And I'm talking about physically present at the time of the procedure. I think that will be an eye-opener.

MEMBER MARTIN: This is Melissa. I want to follow up with Zoubir. I think I'm having the same worry.

If something goes wrong and the AU is not there, then whose responsibility does it fall, or who is the responsible person to basically take care of the misadministration, adverse event, depending on the level of it? I'm looking for who medically would be the responsible person if the AU is not present.

DR. JADVAR: Well, we said the AU is always responsible for, you know, as we said, the radiation injury or whatever happens. But, and so, with that thought, we said that the AU should be present or at least reachable within the division, so maybe next door or next room or in the office.

But this is all after the AU had a chance

to verify everything regarding the suitability of that treatment for that patient and, you know, looking at all the pertinent data.

But that's -- you know, physically present I think maybe -- we never said physically present. We just said must be present. We can change it to should be present and then further elaborate it by virtually or physically or adjacent or something like that, if that makes it a little more palatable.

MEMBER MARTIN: Well, I'm more concerned about these, the requests that are coming from the, they may be authorized users, but they do not want to be on site. They want to send their team out to deliver this, and then they will virtually watch them from many miles away.

DR. JADVAR: Right.

MEMBER MARTIN: And that's what I'm asking. At that point, who is the responsible person if the AU is not there? And that's one of my big questions.

MEMBER SHOBER: So this is Megan. I just want to make sure that we're not kind of being blind to the scope and size here. I mean, like, Dr. Jadvar, the picture you showed from USC, wonderful, great center. That's not going to be the case in your smaller

hospitals.

And so it's already, you know, we are inspecting, like we've been inspecting these Xofigo treatments for a long time. We're seeing LUTATHERA start to, you know, go down to smaller level hospitals. And, you know, it's not uncommon at all, especially with the Xofigo treatments, to not have an authorized user there.

And so that's just, you know, from a practical standpoint, that cat's out of the bag already. And so I fully understand what you're saying about the responsibility and all that.

And I just -- if that's something that the subcommittee wants to advocate for, like you mentioned, just if you can give more reasoning or rationale for why that's a good place to land, that would be great.

So thank you very much for entertaining that question. And it's been a good discussion.

DR. JADVAR: Thank you.

CHAIRMAN METTER: Let me just -- this is Darlene Metter. I would like to just summarize. Megan, would this be, if Dr. Jadvar, instead of must just replaced with shall --

MEMBER SHOBER: Should.

CHAIRMAN METTER: Or should.

DR. JADVAR: Should, yeah.

CHAIRMAN METTER: Okay. Should, would that be adequate, because then --

MEMBER SHOBER: Yeah.

CHAIRMAN METTER: Okay. Is that acceptable, Dr. Jadvar?

DR. JADVAR: Acceptable to me. I want to ask my, you know, the rest of the subcommittee also to make sure that they're okay with it. It's fine with me.

MEMBER OUHIB: This is Zoubir. I'm fine with that. I think that's a great suggestion.

DR. JADVAR: Okay.

MEMBER ENNIS: This is Ron. So I would just say, say should be physically or virtually present would be good. That would be acceptable.

I'd be a little less excited about watering it down further and just saying should be somewhere in the facility. I think our group felt like actually really being present was better.

And though Megan's points are valid about the current state of affairs, that we don't want to completely disrupt what care that currently goes on there, I think the should allows us to finesse that while still stating a preference for what we think is

maybe a goal that we can work towards over decades.

DR. JADVAR: Okay.

VICE CHAIR DILSIZIAN: This is Vasken Dilsizian. I agree with the should as well.

CHAIRMAN METTER: Thanks. So can we just -- Kellee, can you go to that, the proposal on the slide so we can see what it reads?

MEMBER MAILMAN: So, and this is Josh. I don't mean to be contrarian here. But what does should actually mean? It's a preference but not a requirement. So does it hold anything other than just a suggestion?

And I guess I'm a little concerned of, you know, should just doesn't seem to hold any weight. Either it's something we think should happen, something that should happen or something that doesn't matter whether it happens. So I'm a little unclear on the usage of the word should.

MEMBER ENNIS: So I would say it's trying to finesse the reality versus the ideal. And it doesn't carry any actual weight. It gives wiggle room.

But it does express a preference that people who aspire to do higher quality might look at that and say, well, we're should kind of people and, therefore, we're going to start to do that. And

if -- so I think that that's where it's coming from. And I think that's what we're trying to say.

MEMBER MAILMAN: I guess as a patient how do I know if I'm going to a place that's a should kind of place or not a should kind of place?

CHAIRMAN METTER: Well, Josh, this is Darlene Metter. The AU is still responsible for the administration. So, you know, I think that's the main thing on this is that the AU is still responsible, and they should be present at the time of dose administration.

MS. AYOADE: Dr. Metter, this is Maryann Ayoade from NRC. Again, I just wanted to clarify that ultimately the authorized user, you know, is always going to be responsible for the procedure whether or not they're present in the room.

CHAIRMAN METTER: Correct. Thank you. Yes, that's better clarifying. Thank you, Maryann.

PARTICIPANT: Yeah, that's right.

DR. JADVAR: So it looks like the consensus is to just change the word must in that second bullet to should. And we can also, as Ron suggested, say should be physically or virtually present, if you want to add those couple of words also in there just to be a little more clear.

MEMBER MARTIN: Dr. Jadvar, would you also be willing to add -- I think it needs to be emphasized that it might read the AU should be present at the time of dose administration, either physically or virtually, and is responsible for the administration, for the dose administration under all circumstances or something like that just to emphasize that they are the ones responsible.

DR. JADVAR: Yeah, actually, yeah, I kind of like that. It brings up the -- I mean, we know that already, but it just kind of reemphasizes it.

CHAIRMAN METTER: Well, this is Darlene. Maybe instead of adding that, just say the responsible AU must be present, should be present at the time of dose administration either physically or virtually. And you put that up front.

DR. JADVAR: Well, I think what Melissa said is a little different. I mean, when you say the responsible AU, it seems like there is an irresponsible AU, too.

So what I think Melissa was mentioning -- we can put it as a separate bullet so it's not a very long sentence. But I think, although as Maryann just mentioned, it is already known. It is already ingrained. But we can just put it up there

just to make sure it's reiterated in a sense with this field of theranostics.

MEMBER OUHIB: This is Zoubir. I believe that statement is already in there somewhere else, isn't it?

DR. JADVAR: Oh, it's regarding to radiation injury, yes.

MEMBER OUHIB: Right. So the, is responsible. I think --

DR. JADVAR: Yeah, the AU is responsible for patient concerns related to RPT. Oh, yeah, we kind of mention that the AU is responsible for patient concerns related to RPT, including, so anything related to RPT.

MEMBER OUHIB: Right.

DR. JADVAR: But we kind of added on for more explanation including radiation induced injuries.

MEMBER OUHIB: Right.

CHAIRMAN METTER: Okay. So, to clarify, then, we would just amend the "AU must" to "AU should"?

MEMBER JADVAR: Yes.

CHAIRMAN METTER: Any other discussion?

MEMBER JADVAR: Do you want to add, at the end of that, do you want to add "either physically or virtually"?

CHAIRMAN METTER: That's fine with me. We'll have to vote on it.

Is there any other comments from the Subcommittee or the ACMUI regarding that?

(No response.)

And if not, we'll go ahead and make that addendum to "physically or virtually present".

Okay. So, the amended will be "The AU should be present, either virtually or in person, at the time of dose administration."?

MEMBER JADVAR: Right.

CHAIRMAN METTER: Any other discussion or comments or suggestions?

(No response.)

Hearing none, are there any comments or suggestions from the NRC staff?

MR. EINBERG: Yes. Excellent discussion here.

Yes, Chris Einberg.

I wanted to point out, also, that, as it's been discussed here that the Authorized User is ultimately responsible, there is another section of the regulation that kind of lends a little bit more credence to this. And basically, the 35.41 procedures for administration requiring a written directive

states, "For any administration requiring a written directive, the licensee shall develop, implement, and maintain written procedures to provide high confidence that each administration is in accordance with a written directive."

So, that actually puts it back onto the licensee and to the Authorized User that the administrations have to be done in accordance with the written directive.

CHAIRMAN METTER: Thank you, Mr. Einberg.

Any other comments or questions?

MS. HOWE: Dr. Metter, I have two comments.

One is there was earlier discussion on the value of a medical physicist. And so, my question to the Subcommittee and to the ACMUI is, currently, we only have one medical physicist, and that's the Authorized Medical Physicist, which is 35.600, HGR units, Gamma Knife Perfexion.

Is the Subcommittee thinking about maybe having a different medical physicist that might assist the Authorized User for the theranostics? So, it's a point for thought.

My second comment is that maybe it would be, as Mr. Einberg suggested, it may be better to

suggest that the licensee develop procedures under 35.41 to ensure that all of the setup is correct. And we have had medical events where, especially with LUTATHERA, where they haven't started the amino acid drip before they did the LUTATHERA. And so, they ended up with a medical event and more dose to the kidney. So, those things might be covered in the licensee's procedures to ensure the administration is in accordance with what is in the written directive.

Those are just two thoughts that the Committee ought to maybe think about.

VICE CHAIR DILSIZIAN: Yes, Vasken Dilsizian.

I remember this discussion quite vividly. And the conclusion was, that you can see in parenthesis, "(if available and applicable)". And the reason we did that is because the AU, as you can imagine, can be a nuclear medicine physician, a radio diagnostic radiologist, or a radiation oncologist. And the practice of the team in each of those divisions are different. Radiation oncologists are very much dependent on their medical physicists. When it comes to nuclear medicine, for example, we hardly use medical physicist in anything that we do.

And so, we're being respectful of the

different aspects of AUs coming in from different backgrounds and different setups. And that's why we included the medical physicist with a parenthesis "(if available and applicable)," which in our mind was going to be predominantly in the radiation oncology arena. I think that's my recollection.

MEMBER MARTIN: This is Melissa.

MEMBER JADVAR: That's exactly right, yes.

MEMBER MARTIN: I just have a question. Many RSOs are either therapy physicists or radiologists. How much do you expect them to know about doing LUTATHERA administrations? I'm just not sure how useful they're going to be.

MEMBER OUHIB: This is Zoubir, if I may.

I think Melissa raised a good point there. And I really think that, first of all, the process and the participation of the medical physicist cannot be avoided. With dosimetry coming up very soon, it will be required, in my opinion. I think the medical physicist has to be qualified in performing dosimetry for RPT, basically. So, I'm not sure how we can label that, but I think that's going to be automatic and a no-brainer.

MEMBER JADVAR: I agree. I think that,

if and when the dosimetry becomes routine in clinic, medical physicists will be definitely needed.

VICE CHAIR DILSIZIAN: Vasken Dilsizian.

Melissa, I think the question that you bring up, the RSO, you know, we are guilty, I would say, of thinking therapies in general in what we do. And as you know, with the I-131 therapy, particularly in-patient high dose, you always have the RSO there. I think that we just put the therapy team together with the background of I-130. I agree with you, for example, when we give radium-223, we don't have an RSO. And then, it should be depending on what therapy we give.

Hossein, maybe you can expand on that.

MEMBER JADVAR: Yes. That's true. We also don't have -- but, remember, that the sentences may consist of. So, you're right, it's also the --

MEMBER MARTIN: Okay. It doesn't say, "must consist of".

MEMBER JADVAR: It's not "must," yes, exactly. It's "may consist," yes.

MEMBER MARTIN: Okay.

MEMBER JADVAR: And we discussed that, I think, in our discussions. I remember that.

CHAIRMAN METTER: Thank you, Dr. Jadvar.

MEMBER JADVAR: Sure.

CHAIRMAN METTER: Good point.

Does that answer your question?

You're muted.

MS. HOWE: I think it did. I was also kind of putting out there that maybe the ACMUI in the future, as theranostics becomes more important, with some of these that have to have personal dosimetry, might want to think in terms of a medical physicist with more experience (audio interference) source area with more dosimetry information on pharmaceuticals.

MR. EINBERG: Correct. Yes.

CHAIRMAN METTER: Thank you. That's a very good insight.

Any other comments on the Subcommittee report?

(No response.)

Okay. Thank you.

Can I open it up to the public, if there are any public comments to be made?

MS. LOPAS: Yes, Dr. Metter, we do have one comment, and we'll get started with him in just a minute.

But just a reminder to everybody to just use your "Raise Hand" icon to raise your hand, and that

will let Kellee know that she needs to unmute you. You may also press *3 on your phone, if you have called in.

So, Kellee, if we could start with the first person in line.

And just start. When you begin your comment, please speak clearly. Please begin by introducing yourself.

I think that was Calvin potentially.

DR. HAN: Good afternoon. Yes. Good afternoon. My name is Calvin Han. I'm a radiation oncologist with FDA in the Division of Imaging and Radiation Medicine.

And I would like to thank Dr. Jadvar for an excellent summary of the theranostics. As you all know, theranostics is a hot area of research and there's a lot of commercial interest in these isotopes.

And the reason that I was listening in is, having been a radiation oncologist in the military and, also, in academia and private practice, I think it's very important that the NRC clearly defines the definition of Authorized User and where the Authorized User has to be at the time of administration. Because having just joined FDA a little over a year ago, having been in private practice, I see how Xofigo is given,

and I've given many Xofigos. And you can have an issue with the injection. It's not always that everything goes smoothly. Sometimes the catheter kinks, and then, you can't push the isotope solution. And also, there's always a risk of extravasation.

So, I think the Authorized User has to be at least close by where the drug is being administered because many times in private practice physicians are running around from building to building, and even hospital to hospital, and what they want to do is they want to just give the responsibility to the nurse after the physician sees the patient and have them do the injection.

So, I think it's important that the NRC clearly defines where an Authorized User needs to be for these theranostics because the doses are getting higher. And if you develop extravasation or if you have issues, then I think the Authorized User needs to know how to take care of it.

So, that's my comment.

MS. LOPAS: Thank you very much.

Okay. So, if anybody else has a comment, please raise your hand.

Okay. I see, I think, Mike Sheetz.

So, press the Hand icon if you need to make

a comment.

Mike, it looks like you're unmuted. So, just introduce yourself.

MR. SHEETZ: This is Mike Sheetz.

An excellent presentation, Dr. Jadvar. Very comprehensive, well presented.

I have a question on your opinion on what you think the role is, if any, for a medical oncologist on the theranostics team, since they will be initially responsible for the referral and potentially responsible for patient follow-up.

Thank you.

MEMBER JADVAR: Yes. Well, I mean, as you mentioned, they are the individuals who see the patient initially. And according to their clinical guidelines -- and typically, they follow the NCCN guidelines -- see if a patient is appropriate for a particular type of theranostic, which at this time is relatively limited to LUTATHERA and, then, Xofigo, and Azedra, and the ones that I mentioned.

So, typically, they don't directly participate with this type of treatment. They just refer the patient to us. They order the type of treatment, and that's when we basically take it over in nuclear medicine, or whoever is, whatever medical

center, however they set up to handle the referral.

And then, there are certain laboratories or things that needs to be done for preparation, and all that, at least, again, I can always give you the example that we have in here. We have worked very closely with our medical oncologists. If they feel that a patient is appropriate for a particular treatment, they already know what type of labs need to be ordered. They already do that. They make an order; they put it in the system. We see the order, and a nuclear medicine physician will look at the order. Sometimes they call back the oncologist, if they have any questions with regard to the referral, and making sure that all the laboratories, or whatever, the data that is needed in preparation, is done properly and correctly.

And then, they it from there. We order the dose. We administer the dose. We take care of any possible radiation injuries or extravasations, if it happens -- it hasn't happened, thankfully -- but if it happens.

And then, the patient just comes back for the next cycle, and we report. We make a report, of course in our system that this was done; the patient tolerated it well. This was the dose that was given.

This is the cycle number, what of what, you know. So, basically, it's a report that goes back to the referring physician.

So, I'm not sure if I answered your question, but, definitely, they are on the team in a sense that they are the first people who see the patient. They take care of the patient in general terms, and they are the ones that, typically, determine if a patient is appropriate for a certain type of therapy.

Of course, participation in tumor boards by the nuclear medicine physician is very important, so that you always teach -- you always share your knowledge in theranostics with them, so that they are always on top of what's going on in the field. We give them grand rounds. We give them papers, things of that sort. So, again, it's all teamwork in that sense for the benefit of the patient.

CHAIRMAN METTER: Thank you, Dr. Jadvar.

I think we'll take one more question. Dr. Ennis, I see you have a question.

MEMBER ENNIS: Just some additional comments. I think that there's nothing intrinsic about theranostics that involves any other specialist per se. The referral aspects of medical care are just

part of regular medical care that goes on with all kinds of things. And depending on the kind of disease that we're talking about, the medical oncologist may or may not be involved.

One could envision a future not too far down the road where theranostics are very early in a prostate cancer treatment course, and a medical oncologist may not yet be involved at all. It may be something that the urologist and radiation oncologist who have done the primary care remain engaged, and just engage with nuclear medicine directly.

That's not the practice, currently, for radium-223, because that's only indicated in hormone refractory disease. And generally, those patients are going to have to be seeing a medical oncologist, although it should be said that there are some radiation medicine physicians who stay very engaged and actually take proactive management of even people on hormone therapy.

So, it's not a given necessarily that these patients will be seeing medical oncologists, although, currently, for sure, that is typical, but, again, not intrinsic to this therapy and how it should be done to be done safely.

MEMBER JADVAR: Yes, absolutely. Thank

you, Ron.

CHAIRMAN METTER: Thank you, Dr. Ennis.

And I do see, Mr. Mailman, you have a comment or a question?

MEMBER MAILMAN: No, I just wanted to -- Ron said that perfectly. Yes, I think it's the referring physician who may not always be the oncologist. So, we just need to be clear on that.

MEMBER JADVAR: Yes.

CHAIRMAN METTER: Okay. Any other comments or questions from the ACMUI or the public?

MS. LOPAS: I don't see any other hands raised from the public, Dr. Metter.

CHAIRMAN METTER: Okay. Thank you.

So, do I have a motion to approve the Subcommittee report with the addendum of the "AU should be present in person or virtually at the time of dose administration."? With that amendment, do I have a motion to --

MEMBER WOLKOV: So moved. This is Harvey Wolkov.

CHAIRMAN METTER: Thank you, Dr. Wolkov.

Do I have a second?

MEMBER O'HARA: Second. Michael O'Hara.

CHAIRMAN METTER: Thank you, Dr. O'Hara.

Any other comments?

All in favor, please say aye.

All opposed or abstain?

Hearing none, the Subcommittee addended report is unanimously approved.

Thank you very much, Dr. Jadvar, for an excellent presentation --

MEMBER JADVAR: Thank you. Thank you.

CHAIRMAN METTER: -- and for everybody for an excellent discussion.

So, the next item on the agenda is being presented by Mr. Hobbs from the AAPM. He'll be talking about the future of personalized dosimetry and discuss the new work at the AAPM on personalized dosimetry.

Mr. Hobbs?

MR. HOBBS: Yes. Thank you very much. Thank you for inviting me to give this talk. It's really nice to hear all this great discussion that's going on.

I, first, have to specify our Radiopharmaceutical Therapy Subcommittee is relatively new, such that we really don't have very many official positions, and if there are a few, then they are outdated. I'm going to be presenting a lot of my own perspective, a lot of things that we are

working on that, hopefully, will get official AAPM endorsement at some point in terms of what the AAPM stands for. So, take some of this AAPM perspective with a grain of salt because it's still in development.

Next page, please.

So, I'm going to first talk about what we mean when we talk about prospective personalized treatment planning, some basic concepts that are probably pretty familiar to you. Then I'll talk about examples, roadblocks, the importance of biotech modeling, combination therapies, and finally, alpha-particle therapy, if we have time, although I see that we're running pretty late. So, we may have to keep it short.

Next, please.

So, currently, there really is no personalization. You know, standard FDA-approved treatments are all fixed activity, (audio interference) and mass based measurements, with the exception of some amount of dosimetry for yttrium-90 microspheres, although, currently, most of that dosimetry is really an activity measurement in disguise.

So, how do we get there? So, that's basically treating radioactive or radiopharmaceutical

therapy like radioactive chemotherapy. And that's a standard right now. When we introduce the drug with phase 1/phase 2 escalation trials where the only escalation variable is the administered activity, and then, the patient (audio interference) the maximum toxicity set, the administered activity.

But this radiation, and we know that we what delivers damage. We know that it's absorbed dose, and we know that, since it's radioactive, we can actually measure this. If we give a tracer amount, a pre-therapeutic amount of the same drug or a surrogate, we can image the patient and we can see where the drug is going and quantify it. And we understand that the absorbed dose to the different organs at risk is really a product not only of the administered activity, but also the retention in different organs.

So, we can, in theory, personalize the amount of activity to give to every patient. So, is this really an important thing?

Next slide, please.

And the example I'm going to show to you dates back almost 20 years now. And so, there was mention about Zevalin, but there was also another I-131 anti-CD20, or another anti-CD20. This was labeled I-131, called Bexxar.

Can you keep going? I think there are some more things on this slide.

And this was personalized dosimetry done back in around the year 2000.

And can you keep moving forward? I think there are some pieces missing there.

And what is very simple personalized dosimetry, where there is just planar imaging and there was a whole-body surrogate of dose that was used for bone marrow toxicity that they previously established; 75 centigrade to the whole body would increase RM toxicity.

And here, you can see the activity as a function of the different patients required to get that 75 centigrade. And you can see the huge variability that exists. It's not just minor variations. It's very large. And this has been borne out. Even though prospective dosimetry isn't really being used, there's a lot of retrospective dosimetry that's going on. And we see this in modality after modality, organ after organ. The range of activity and the range of doses for fixed activity is just huge, often up to an order of magnitude.

Next, please.

So, the reality is that we are massively

underdosing most patients. This next example is actually the first example that I'm aware of of actually fully 3 (audio interference). So, what we would really like to be able to do -- this is an example of an I-131 treatment of metastatic differentiated papillary thyroid cancer. There was heavy lung involvement and there was a lot of concern about giving just a fixed activity or an ad hoc method. So, we injected the patient with I-124 and took PET/CT measurements over five different days.

Next.

And here, you can see the uptake in the lungs.

Next.

And this is the implementation of this personalized dosimetry method. You convert the activity that's measured from I-124 to I-131 modularly because of the different half-lifes, and then, you run Monte Carlo for each different time point. You register the images. You draw your contours on the organs at risk. In this case, it was the lungs. You correct the energy. You divide by the math, and then, you have a dose rate as a function of time with a functional fit. The area under the curve is the dose to the lungs. So, you have a dose-per-unit activity

or a dose coefficient for the lungs, you can, then, scale how much activity you should be able to give to the patient in order to not exceed lung, the maximum dose, which in this case we took to be 27 Gy.

Next slide.

Now this is very anecdotal, obviously, but it with this very, very moving anecdotal case where the patient recovered completely; everything disappeared, including the brain lesions. Her globulin dropped and she's moved on. This was 12 years ago, and now she's become a nurse. Just quite remarkable.

So, there are a couple of lessons to be learned here. First of all, there's a lot you may hear -- there are two different methods to doing dosimetry. One is based on activity and is called the MIRD method, or the absorbed fraction, and the second is, as it was just shown, using Monte Carlo, each different time point, called voxelized.

And there's a lot of talk about the fact that (audio interference) is so much better than the MIRD method, but the reality is, the important thing here is that we (audio interference) both methods and found very similar values. And this is something that we're trying to push, is that you need to have, just

like you use (audio interference) or some other software to check your external beam therapy, you need both to really converge in order to validate that you're doing the right thing.

Next.

And, of course, the third example, the final example, which is a really big one that came out last December, is microspheres. This is a report of a clinical trial, a randomized clinical trial, by Garan (phonetic), et al, where they would use the pre-therapeutic technetium-99-MAA with SPECT/CT to predict normal organ versus the tumor uptake and dosimetry, and then, apply that, and using a combination of normal organ toxicity threshold with dosimetry, they showed that using that personalized dosimetry, there was an overall survival benefit of (audio interference). It went from 10.7 months median to 26.6. So, this is a very promising. And obviously, technetium-99 microspheres are not exactly the same thing as radiopharmaceutical therapy, but they share a lot of the same characteristics, the dosimetry is similar, and the principles of personalized dosimetry are the same.

Where we would like to go, obviously, is placed like LUTATHERA, which is ripe for that kind of

a clinical trial. However, currently, the amounts are unavailable beyond 200 millicuries.

Next.

So, there is a huge interest, obviously, by the companies, the drug companies, developing radiopharmaceuticals. This is the new renaissance of radiopharmaceutical therapy. Nuclear medicine physicians are onboard.

But both are still somewhat reluctant to use or trust dosimetry for personalized treatment planning. The mantra has long been, as we've heard, that the onus is on dosimetry. Dosimetry has to prove that it is going to be beneficial for each and every modality, in spite of the fact there's a lot of circumstantial evidence which, although it's true, would kind of incline people to want to actually test this out in clinical trials. But it has been very difficult to try to get clinical trials funded by, or even allowed by, the (audio interference).

Standardization, as we've heard, is very, very important. This was a key point that was brought up by Dr. Jadvar. We need to make sure -- and this is one of the critiques that the drug companies have which is absolutely valid -- that, currently, a lot of people are doing dosimetry, but we really don't know

that everybody is getting the same result. If you give the same people or different people the same set of data, are you going to get, within reasonable approximation, the same quantitative results? And so, that is something that is being worked on hard by SNMMI, AAPM, and ASTRO.

Let's go to the next slide.

The lack of qualified physicians and physicists. Actually, we'll come back to that.

Radiation oncology has become very interested in this, which I think is a really good thing. I think that radiation oncology and nuclear medicine have very complementary expertise when it comes to radiopharmaceutical therapy. I think that radiopharmaceutical therapy, even though it's considered therapeutic nuclear medicine, has a lot of things that could benefit from the expertise that radiation oncologists have QA, the dosimetry, just understanding therapy under certainty analysis and error reduction. This is something that the radiation oncology and the physicists have worked on radiation therapy (audio interference).

Now SNMMI has a number of really good groups that have developed recently. They've taken the people that have had longstanding expertise in

therapy, and they have been working on a number of projects to really expand and bring all of their expertise to the rest of their Society as well.

They've had a challenge, a dosimetry challenge. Again, this goes to standardization, understanding, sending out -- they have done this exactly. They've sent out a dataset to people and said, "Tell us what your dosimetric results are," so that they can take a look and understand where the differences are coming from and how to learn from that. They have a registry.

They're looking at education, just as AAPM and ASTRO are, in terms of not only retrospectively training physicists and physicians to understand dosimetry and how it works in personalized treatment planning, but also to prospectively put it into their curriculum.

The NCI is very gung-ho. All of these societies -- the ICRU, IAEA, ASTRO, MIRD -- all are advocating very strongly for dosimetry-based treatment planning. So, there are a lot of good reasons to think that this will come at some point.

And, of course, there are other companies that are also very interested in this. And we talked about drug companies, but there are also software

companies now that are providing commercially available software that will make dosimetry more accessible and more standardizable. So, now longer do we have to depend on in-house software that is different from place to place.

Next.

And so, this is the nice graph that I got from John Sunderland at the University of Iowa. If you keep going, there are a few more pieces to it. Where the expertise traditionally lies. These are nuclear medicine and he came up with this.

So, traditionally, there's nuclear medicine physicists, which is in small ellipse; many more Certified Radiation Therapy Physicists. And the true expertise in radiopharmaceutical therapy doesn't really lie at a cross section between the two or within nuclear medicine, but somewhere a little bit to the outside -- as I said, complementary expertise that really we're hoping for a lot of collaboration between the different Societies.

And our belief is that nuclear medicine physicists can become radiopharmaceutical therapy physicists, but radiation therapy physicists can also become it. Both have some amounts of expertise, and both require additional training to be competent.

Next.

So, originally, I was hoping there was going to be more collaboration at the physician level. This hasn't panned out as much as we would hope. As I said, we're really hoping we do oversee, in theory, medical physicists, both nuclear medicine and radiation oncology, although SNMMI also has the ABNM certification. And we believer neither are ideal, but both can be trained, as long as further education, either retrospective or introducing more RPT-specific into the curricula will help both of these subgroups become competent physicists.

Now, going to the point that was brought up and the discussion about whether physicists are needed, certainly at this point, for the fixed administration, there is no need, we believe, for physicists to become involved, although we think it might be preferable. And also, nuclear medicine doesn't really have the numbers needed. So, technologists can certainly cover most of those.

But we do stand -- and I think this was alluded to, if not mentioned explicitly -- we do believe that medical physicists will be necessary once dosimetry and personalized treatment planning (audio interference).

Next.

So, what have we been doing? So, unfortunately, AAPM moves kind of slowly. We've had a Nuclear Medicine Subcommittee for a while under Imaging Physics, but this Radiopharmaceutical Therapy Subcommittee is brand-new only since March, although it had an ancestor, an ad hoc committee whose main goal was to determine where in the AAPM tree it would fit.

What we've decided on is kind of a grid strategy to providing guidelines. We are looking at guidance needed for the different FDA-approved RPTs -- so, yttrium-90 microspheres, lutetium. We've decided that lutetium, PSMA, and DOTATATE from a physics standpoint are close enough that we can satisfy both with a single TG. I-131, so the radium is going to fall under an Alpha-Particle Radiopharmaceutical Therapy Working Group. So, that's the kind of column approach.

And then, the grid strategy, meaning the layered approach, will restart at the bottom and say, what is needed across the board? First of all, activity quantification, dose calibraters, standardization, traceability of standards or collaborating with the EPC and NIST to come up with a task group for that. On top of that, we have another

proposal already, which is how to upgrade the QA for your SPECT/CT in order to bring it up to the standards that are needed for therapy, rather than just diagnostic. And we will move up in that role.

Education, as I mentioned, is primordial. We're proposing a summer school in 2023. There is a track, so a full-day track at the Annual Meeting being organized for next year, and then, we have ongoing collaborations with SNMMI and ASTRO at their annual meetings to try to provide as much education as we can and advice for the longer education, such as curricula, as we can.

Next.

This may be the slide that is of most interest to this Committee. This is the only one that we've had time to really put a decent amount of work in. And we have some of those "should/must" statements that, obviously, have not been confirmed yet, since nothing has been published. But, then, we are trying to work on more of the details.

The bottom line on yttrium-90 microspheres is for a long time it evolved in kind of a vacuum or separately from the rest of it. And it has a lot of its own nomenclature and formalism which don't make a lot of sense in the context of RPT. And so, one of

the things we're trying to do is to standardize and bring the formalisms and the nomenclature back to a common RPT board.

We had an issue with the activity specification. We're not really happy that manufacturers are okay and only committed to providing activity within 10 percent. We're pushing hard on them to go to 5 percent. Again, as you know, total activity difference is 20 percent for a misadministration. So, if you're already starting with something 10 percent off, that's not giving you a lot of wiggle room and it's not very good for a precise dosimetry-based treatment plan.

The lung shunt fraction, we're trying to be a little bit more -- put some more ding in there that will, hopefully, encourage people to be more precise in their lung shunts. So, that's the amount, when you do your technetium-99m study, it's how much of the product is leaked from -- so, it's injected into the hepatic artery. It goes and it embolizes into the liver, but, then, some of it may leak and go into the main bloodstream, which ends up back into the lungs.

And very often, only a single study will be done, even though two lobes may be treated. And there are different ways to get around that. Sometimes

the technetium-99 will be administered to the entire liver and say, well, that's kind of averaging things out. Or it may take one lobe, based on the tumor burden and say, well, that's the worst-case scenario.

But we're trying to recommend to have a corresponding lung shunt fraction, lung shunt study with SPECT/CT for each administration. Thresholds for toxicity are really not well-known; the segmentectomy prescriptions are kind of a workaround where they use lobar dosimetry, and then, just put all the activity in the segment instead of the lobe.

This is one of the big ones. Relative dosimetry is generally used, not absolute, meaning that the dependence is that all the activity is going to the lungs or the liver. But, if you make that assumption and never check it, then there's always the potential that you are missing activity that is going elsewhere. And so, we are really pushing hard for post-therapy imaging for QA checks, just like is done in brachytherapy for post-treatment dosimetry.

Next.

All right. One of the other standardizations that we work on is the radiobiological or the bio-effect modeling standard. And radiobiology is a huge subject, and I'm not even sure why I put up

this slide to just kind of introduce it, because I don't have the knowledge or the time to talk about all of this.

The one recognized biotech model that works well for external beam and for radiopharmaceutical therapy is how the dose rate affects the biological (audio interference), right?

So, next slide.

This is based on the linear quadratic model, and it's basically calculating a standardized biological dose, either the BED or the QD2

Can I get the next slide, please?

So, if you're looking at surviving fractioning, cells or any other biological end point, if you have a single bolus of either external beam or radiopharmaceutical therapy, you get a response that is quadratic at the blue line on the log when you're (audio interference). The red line is for the high LET alphas. We'll talk about that.

And then, if you want to standardize that, then you have several methods. The most popular one reaffirms (audio interference) therapies. The BED, what would that does be if it were given at infinitely small fractions, basically? So, a tangent to the blue line. And the BED formula here is similar to what you

would see in external beam, with the addition of a G factor, which is a repair between potentially first and second hits on the double-strand break. We know that, radiobiologically, it's not clear that that's what's really going on, or if it is, it's in very, very gross simplification. But the model seems to work, and that's with that G factor.

Next.

And how it actually is relative to actual clinical outcome was first proven back in a landmark case by Barone, et al, at the Universite Catholique de Louvain in Belgium, where they were looking at toxicity in kidneys, as measured by creatinine clearance loss per year versus observed dose. And it didn't really look like much.

And then, they realized they needed to do better; they needed to put in personalized kidney volumes. Still didn't get anywhere. And then, the middle slide is when they said we need to take into account the dose rate. The dose rate is the middle slide versus that creatinine clearance loss per year. And now, you can see that, all of a sudden, you're getting a real correlation.

Then, the MIRD took that a step further, in the right panel. And they said, if the BED is really

the BED, and all radiation is, at least from a low LET standpoint, is equivalent, then we should be able to compare this to the results of external beam. And that's what they did. And this is why this is important, because we show that this biotech modeling is reasonably good and consistent, period.

Next.

And so, it's important to take that bio-effect standard. The tricky thing with radiopharmaceutical therapy is it's not the fraction, it's not the physician that decides what is the dose rate; it's the individual patient's pharmacokinetics. The same absorbed dose with the same modality may give you different biological dose.

And where this is going -- and this is being tried and experimented with everywhere; it's something that we did about 10 years -- is, then, you can combine, since you have the doses, the values, that are the same, that you can combine external beam and radiopharmaceutical therapies. So, it's like I said a while ago in the case of pediatric metastatic osteosarcoma, where RPT was Sm-EDTMP.

Next.

And so, how do you do that? Again, this is exactly what we talked about. The BED is the BED

in both. They are equal to each other, even though the formulas are slightly different. So, if you set them equal to each other, then you can take an absorbed dose, biological dose map from one and translate it to the other.

Next.

So, what did we do? So, CTsim was used. And the nice thing about this is that, if you use the CTsim from external beam, then you get a much better registration from time point to time point to nuclear medicine. Nuclear medicine imaging tends to be they're comfortable, right? They're (audio interference.) And so, the patient can be a very different position. Whereas, if you use the fixation devices from external beam, you get something that's much more consistent.

And you have your pre-therapeutic, what we call the low dose of samarium. You image at three different time points. You do exactly the same thing that we showed before with the thyroid, image reconstruction; calculate the dose coefficients, and then, you can actually export this plan, so this dose map, into the external beam planning system and use it as a beam, so that you can prospectively plan combinations that include not only how much beam you're

giving, but also how much dose you're giving for your pharmaceutical therapy.

Next.

So, this is an example. We treated a lesion here. And the reason we did was because external beam was limited by the port, of course.

Next.

So, this was a scientific success. It wasn't a very good clinical success. The patients were too far gone. This is not so important. The importance is underscoring how and why the standardized biological dose is going to be important going forward, because this is something that people are fiddling with, doing, even publishing on, combining rationally -- rationally -- prospectively external beam and radiopharmaceutical therapies.

And now, what quite often happens is there is a lot of poorly understood effects. Often, you will see people taking maximum tolerated doses for organs from external beam experience, and then, wondering why they could go higher, because, of course, those values are in EQD2.

Even within, for example, LUTATHERA, what people are looking at often is accumulated absorbed dose. Whereas, even though the shape of the kinetics

may be the same, oftentimes, you know, uptake decreases as a function of fractions in the tumors. And if you're adding absorbed dose from different dose rate effects, you're not adding apples and apples anymore.

Anyway, next.

So, it's important to standardize not only how you get your dosimetry, but to standardize to a biologically standard dose.

This next example, again, is not so much to show what we do, but, again, more about lessons learned. We did a combination of Bexxar and Zevalin, based on orthogonal toxicity.

Next.

So, why would this be important in myeloablative regimens? Because bone marrow is dose-limiting. And Oliver Sarphor (phonetic) did a fair amount of -- I can't remember if it was Zevalin or Bexxar; I think it was Bexxar -- myeloablative regimens at the University of Washington. But, once you go beyond the bone marrow, then the lungs -- sorry -- the dose on the organs are different from one to the other. Bexxar tended to be limited by lung; Zevalin tended to be limited by liver.

And so, if you set up your NTDs as constraints, multiplying the amount of activities

you're giving the Zevalin and the Bexxar by the dose coefficients that you're getting from your patient's kinetics, you can get a plot where you see that the amount of activity of Bexxar on the X-axis and Zevalin on the Y-axis can be anywhere that's constrained by those two axes and the solid lines. Now this formulaism was developed for I-131 MIBG a while ago by Matson (phonetic).

Next slide.

But we are going to do this with biology. So, we did the same thing, except for the BED. Now, instead of straight lines, it's just curves. And then, you can throw in tumor dosimetry, where, instead of saying, okay, you're showing what the limits are, but would the intersection point really be the best point, if what you're trying to treat are tumors? So, then, you say, well, let's take a look at what the tumor dose would be, BED would be, as a function of the maximum amount of activities we could give, as a function on the bottom here. It's (audio interference).

And we had done this. We wrote this up. The company was going to give us the activity. It was going into the grant. And then, they understood that we were going to be doing personalized dosimetry, and then, they (audio interference).

Next.

And the lesson here is that there really is a strong resistance by the drug companies to any type of dosimetry. And it's like, where are these drugs now, Bexxar and Zevalin? We saw that Zevalin is still around. Bexxar I don't think exists anymore.

Often, the fact that they didn't succeed is blamed on dosimetry, but only Bexxar had the basic dosimetry; Zevalin did not. (Audio interference) really went as far as they did. You know, there was a New York Times article that questioned: "We have something now for (audio interference). Why is this not being used as much as should be?" And being an European and somewhat of a socialist, my initial thought was that it was because the physicians were being greedy and they wanted to keep the money for themselves. But, it turns out, in Europe, the problem was pretty much the same.

And really came down to a lot of territorialism. And this goes to one of the observations that was brought up before. It is that, ideally, what we want is we want a huge collaboration. Just like we have multidisciplinary clinics for disease sites, we want oncologists and nuclear medicine and radiation oncologists to come together and bring

their expertise and work as best that they can.

So, we are still looking at -- actually, go back; sorry -- actually, we are still looking at fixed activity, fractionated regimens, based on classes of patients. And obviously, experts and physicians understand so much better than physicists could ever what potential problems can arise; what the best class-based therapies can be. But, oftentimes, there is still a lot of reticence to quantifying what could be going on.

And when dosimetry is being used, it's generally being forced to adapt to the chemotherapy paradigm rather than trying to change the paradigm itself. What is being looked at a lot right now is trying to reduce the number of time points to do some basic dosimetry, rather than trying to reduce the number of fractions for it.

Next.

And one of the historical examples of what happens when we use imprecise and poorly standardized dosimetry was back in the 2000s, again, when a number of people tried to do some dosimetry for thyroid, and a lot of it was with planar imaging. And obviously, we've come a long way since then, and our SPECT and PET CTs are so much more quantitative than planar, but

it was often done with a minimal number of time points and not very well. And eventually, the American Thyroid Association just said, no, we cannot recommend in good conscience to do dosimetry. It just becomes, you know, it hasn't proven anything.

So, the single time point. Yes, we want to reduce costs and patient inconvenience, but the reality is that this is measured against often a nuclear medicine diagnostic paradigm. So, obviously, there is more cost, more patient inconvenience if they have to come in three or four times in a single week to get SPECT or PET images than just getting a diagnostic procedure.

But, if we compare it to other therapies, like, for example, in external beam, I mean, yes, we are moving to more and more hypofractionations, but for a long time that norm was five to eight weeks of daily therapy. That should be the basis for cost and inconvenience rather than the diagnostic procedure.

And again, the studies have been for single time point dosimetry. And I have to say, when I look at them, I really like the mat. I mean, there's some really remarkable papers out there from a theoretical standpoint, but from a clinical, I'm just not sure that it's good. Most of them are for a single organ, because

they can only be optimized for a single organ. Most assume monoexponential fits. Technically, uncertainty is given as 10 percent, but that's only to the mean; whereas, we're looking at personalization of the individual, and certainly, it can be that much higher. And the compromise is that you don't have any information on the kinetics. And so, then, all of a sudden, you have even less certainty, greater uncertainty of what the biological effect of this is. So, ideally, if we could use this highly precise multi-time point dosimetry, we could be reducing the number of fractions rather than reducing the number of imagings per fractions.

Next.

All right. So, I'm kind of running out of time, although I know it started late. So, I'm just going to go quickly through here and try to skip through.

Alpha-particle therapy is really coming in a very big way. Alpha-particles are much more massive than the electrons that we typically use in radiopharmaceutical therapy. They're about 8,000 times heavier. As such, they tend to plow through tissue and create much more damage per unit dose than the electrons. Thus, the so-called Relative

Biological Effect, the RBE.

First, you could say, well, they're so much better; we should be using them more. But, of course, if they can do more damage to tumors, they could also do more damage to normal tissue. They have a very short range, though, 50 to 100 microns. Typically, have energy of 5 to 10 MeVs.

And what this lower graph shows you is, ideally, in theory, they are better suited for micrometastases, right? If you see this is the percentage of energy absorbed -- so the absorbed fraction -- as a function of tumor diameter. And you can see the longer range of the isotope like yttrium-90, the bigger the tumor has to be before you can get some noticeable amount of energy that's deposited. Yttrium-90 you really only want to use on tumors that are 1 centimeter or larger. With lutetium and samarium, it can be down to a millimeter, and you know, the alpha-particles, much lower still.

Next.

So, currently, only radium-223 is FDA-approved, but there have been a lot of preclinical studies going on and a number of clinical trials with lead-212, astatine-211. As was mentioned, actinium-225 is undergoing trials and has been used

in Europe already with peptides and PSMA. Thorium-227, Bayer has a whole platform of all kinds of different ligands that they have.

Next.

So, there are clinical examples of actinium-225 peptides, some of them after unsuccessful lutetium. So, here you see this one was, the top one was in Germany. Patient was cleaned up. The bottom one was in India. This is an example of a patient who was previously treated with lutetium, and then, treated with actinium-225 in here. So, anecdotally, remarkable.

Two things could be percolating in your mind. Why isn't this being used everywhere now? Secondly, why is this working at all? Didn't I just say that, dosimetrically, it should only really be working with micrometastases? And yet, clearly, we're looking at images that have more than just micrometastases. So, we'll come back to that.

Let me just address the first question. Mostly, it has to do with dosimetry. Next. We really don't understand -- well, we do understand; we're just not good enough at quantifying the dosimetry yet.

Could I get the next slide, please? And actually, let's just skip this slide. Let's try to

move fast. Next slide, please.

Basically, there are a number of different challenges. One, as we mentioned, the RBE. So, what is the biological effect per unit dose? And it can and should vary from tissue type to tissue type. It could vary from alpha-particle to alpha-particle.

One of the things that it's also lacking is standardization. There is no -- well, we'll get to that. But there are problems in terms of standardizing the value, and we really don't -- we just have very little information in terms of the parameterization of the alpha-particles.

The other thing is, the second one is sub-organ localization of activity. Because this has such a short range, and radiopharmaceutical uptake is driven by physiology, not by mean geometry, as an external beam. And so, if there are different cell types, it (audio interference) the uptake for different functional subunits of an organ. That's where most of the dose is going to go. If you have a longer-range isotope, there's going to be a smearing effect that will generally compensate for that. And if you use normal organ or entire whole organ dosimetry, you can generally get a good idea of what's going on.

But that isn't necessarily the case with

the alphas. So, the fear is localization in cell types with functional subunits. You need to have a dosimetry that accounts for that.

The third one is the relocalization of daughters. So, not only are there a lot of daughters, which you say, well, that's great if the primary goes to the tumor, and then, the other daughters don't leave. Then, that's just more dose to the tumor. But, within the normal organs, those daughters, after radiolysis of the first decay, will be able to relocalize, and they often do. So, you need to take that into account.

And finally, it's a technical issue. There's a low (audio interference) count. And it's not intrinsic to alpha-particles per se, because most alpha-particles in their decay chain that we use clinically have protons. The problem is that we are giving such low quantities -- 4 is a magnitude less than your diagnostic, typically -- that it's really hard to quantify.

So, all four of those are being worked on. And I'm not going to take the time to go into the details, but we're just going to skip through some of these slides.

Next.

I just want to say that the RBE is now

being -- a new standard for RBE is being adopted by the ICRU consistent with their standardization of a reference dose for EQD2, and it will be called the RBE2. And the big advantage to it is it eliminates dose-dependency. If you take a look at the top, you see that there's your low LET, which is quadratic in the middle part of that. And the high LET is linear. And the RBE is defined for a given biological end point as the ratio --so across this dotted line -- between the blue intersection and the red intersection. But, then, of course, you can see that, if you vary what the biological outcome is, you will have a different value. And so, by standardizing it to the EQD2, which is linear, you will get a single (audio interference).

And this is just an example of this.

Right, but the important thing is that, of course, this is not going to solve everything. But what it does is it eliminates the artificial variability, because it's not that we don't expect now that there are going to be variations in the Relative Biological Effect, but they, hopefully, now will be due only to actual real biology, instead of artificial reference stresses.

Next.

And so, one of the ways to deal with the

localization is to look at what's called small-scale modeling. So, going back to the MIRD methodology, which classically uses metamorphic phantom and has organs for their S values, this is the same approach, except we're using -- and there are a number of different ones. For salivary glands there's protestie (phonetic); there's for kidneys; there's for the bone marrow, where you're looking at a smaller scale and you're establishing S values, so that once you can apportion activity to the different subcompartments, then you have an activity to dose conversion.

Next.

And, of course, the tricky part, then, is you have to say, well, how do I know which compartment is the activity going to?

Next.

And that is done by doing ex vivo studies where you compare dosimetries from whole organs side by side in parallel with imaging at the subscale. So, this is the whole organ component of it. And the interesting thing here is that you can now -- these curves are taken, for example, in the kidney where you're measuring as a function of time the counts after they've been removed from a sacrificed mouse.

And it changes like this because you are

seeing the contribution of two different isotopes. You are seeing the contribution of the bismuth that is there, the free bismuth that's there, as well as the contribution from the labeled actinium-225. So, when you look at these as a function of time, you can see how the free daughters are moving in and out. So, you're not just getting the quantification of the parent; you're getting the quantification of the daughters as well.

Next.

And then, you compare this to what the localization of activity is by drawing the different compartments on these phytostat slices, histology-stained. So, this one is activity as measured in an Alpha-Camera, and then, you register them to consecutive slices that have some kind of histological stain, and then, you can assign what kind of activity. And the end result is that you can know, when you see in an organ, the future for that specific radiopharmaceutical. When you measure activity in an organ, you can associate where the activity really is placed in the different subcompartments, and then, you can use your geometrical modeling in a Monte Carlo MIRD system in order to convert the dose.

Next.

For the tumors, there are other problems. So, that was small-scale dosimetry. It should not be confused with microdosimetry, which is how you're going to start thinking about quantifying your tumor fits. Because the paradigm of thinking that this radiopharmaceutical is giving kind of a uniform dose to everything just really doesn't hold true anymore. They are giving you a very small number of alpha-particles. They are giving large amounts of energy in single shots. And so, really, you're looking at a Poisson distribution, a statistical distribution of numbers of hits that each cell is going to get.

And you really should be looking even lower than that. And if you think, okay, really, the dose now has to go into a nucleus, and what is the chance, what is the probability -- how many hits is a single nucleus going to get from a decaying particle? And so, you're going to run Monte Carlo and take a look at your probability distribution.

So, then, you can take a step further and say, well, it's not just whether I'm getting hits or not; it's how much of the trajectory and the decay is going to be traversing the nucleus, and do I need to convolve this? Because if it's going through the end part, then I'm going to be at Bragg peak. Whereas,

if it's going to the beginning part, it's going to be much less. And so, that's where the (audio interference) dosimetry is going. And this is called the microdosimetry.

Next. Keep going until we get to the next. Okay. Right.

And so, the end result of this, going back to why is this working at all, even though it's likely that normal organ dosimetry is going to be important, especially small scale, it's not clear that true dosimetry is going to correlate very well to effect. And we know that two really strong effects are happening.

One is the bystander effect, and this has been documented very well, where if you irradiate your cells with alpha-particles, and you take out the cells from the media that they were in and put fresh cells in there, those fresh cells are going to die because the chemicals -- I think cytokine is released by irradiated cells -- are just going to kill the new cells. So, there is the neighboring bystander effect.

And then, there's also the immune response. And this is coming to all radiation therapy, and in even external beam, there's this theory that it should be considered a systemic treatment because

the radiation to the tumor interacts with the immune system, and the immune system reacts at the systemic level.

But there's strong evidence to suggest that, for alpha-particles, this works much more effectively than other kinds of radiation. And there are several potential hypotheses.

One is that cells are dying a much more dramatic death because the high LET that is pounding through these cells, such as that they are more than represented in the immune system to generate the reaction.

But the other one is that we saw that there's a much shorter range. And so, there's a high level of conformality. So, there is much, much less damage to the tumor microenvironment. And so, it's very possible that this tumor microenvironment, which is undoubtedly strongly linked to the immune system, is much less affected by the radiation from alpha-particle therapy than it is from anything else.

Next.

So, in conclusion, even though some personalized dosimetry has been done with yttrium-90 microspheres, even though we are probably ready to move more and test it out more on things like LUTATHERA or

lutetium PSMA, when it comes to alpha-particle therapies, we're still a little ways away. It's much more complex, but a lot of work is being done. Hopefully, in the next few years there will be a tool, but it's not there yet.

Next.

So, as I said, dosimetry-based treatment planning is catching on. For now, the chemo paradigm still dominates. There is a lot of hope, but there's also a lot of roadblocks, too, as well.

Standardization, as has been mentioned; education, and guidelines.

At the end, not overemphasize this, but the Bio-Effect modeling standardization is also just as important as the methodology.

Thank you.

CHAIRMAN METTER: Well, thank you, Mr. Hobbs, for a very insightful presentation on the varying issues and concerns in personalized dosimetry.

And I appreciate your patience on the timeframe here. So, we will move on to the next presentation.

This will be done by Ms. Megan Shober. She's an Agreement State member on the ACMUI, and she will present on Production Challenges for Therapeutic

Radiopharmaceuticals. She'll be discussing production methods of emerging therapeutic radiopharmaceuticals and effects on radiation safety for end-users, and the challenges of various production methods.

Ms. Shober?

MEMBER SHOBER: Thank you.

Over the past decade, there's been an explosion of research into novel radiotherapeutics with both alpha-emitting and beta-emitting materials advancing through clinical trials. But before you can administer a radiopharmaceutical to a patient, there's three basic steps that need to happen. First, you have to make the isotope. Second, you have to chemically separate that isotope from either the target or the parent material. And third, you have to attach the isotope to a pharmaceutical that will deliver the radiation to the intended treatment site.

And while there's palpable excitement on the clinical side for these new treatments, there has been to date less information available on the production methods for these isotopes and on the methods for processing the radiochemicals that are ultimately used to produce the radiopharmaceutical. Clearly, there is a strong demand for these therapy

radionuclides, but they do have significant supply challenges. The shortages have prompted investment into alternative production methods, and some of those I will highlight today.

I also want to emphasize that the radiation safety issues facing radioisotope producers can be very different from the radiation safety issues that face the clinical users.

So, today, we will examine four nuclides for emerging radiotherapies. We're going to look at copper-67, lutetium-177, actinium-225, and thorium-227.

The goal of radiopharmaceutical production is to provide a high purity product at a high specific activity. To that end, we will review some of the methods of production and discuss some of the challenges associated with their production. As a caveat, I'll say upfront that I don't know very much about the economics, either the cost of production or the cost to get a drug to market. I'm a regulator, and the issues that you see on the screen are the areas that I'm concerned about.

I do also want to point out that sometimes the choices that are made by the radioactive producers have radiation safety consequences for the end-users,

particularly regarding product impurities. So, I will highlight a couple of examples of how this plays out in radio-choice space.

Next slide.

So, to get started, take a quick look here at copper-67. It's a beta-emitter, has a two-and-a-half day half-life and it decays to stable zinc-67.

All right. Next.

Copper-67 is accelerator-produced. It's produced from a stable target using stable zinc-68. Basically, if you knock a proton out of that, it becomes copper-67. It has a known target separation chemistry. Humans have been separating copper and zinc for many, many, many years, and there's lots of YouTube videos out there on how to do this at home, if you want. So, you know, sometimes the chemistry is complicated, and I don't mean to say that it's really simple, but this is a very known target separation chemistry.

Next.

And the other attractive thing about copper-67 is that you can pair it with a copper-64 diagnostic agent. The copper-64 does have a 12-hour half-life and allows you to give both the diagnostic

and therapeutic portions with the same (audio interference).

Okay. So, why isn't this drug or this isotope more common?

Next, please.

So, historically, copper pharmaceuticals have been difficult to develop due to the tendency of copper ions to break and reform chemical bonds. So, this means it's been very hard to keep the copper connected to the pharmaceutical compound. Once copper becomes free in the body, it's taken up by the liver, and these drugs have led to increased liver doses as compared to I-131-labeled products.

However, a new chelator has been developed which seems to be able to hold the copper ions in place, and early stage clinical trials are currently underway in the United States with this new product.

Next.

At present, research-grade copper-67 is commercially available in military quantities. And because production of copper-67 does not depend on nuclear reactors, it will be much easier to scale production as demand increases.

Next.

All right. We'll move on here to a few

words about lutetium-177. As we all know, lutetium-177 is FDA approved as LUTATHERA, and numerous other lutetium-based pharmaceuticals are in various stages of development in clinical trials.

So, lutetium-177 has a six-and-a-half-day half-life and it beta decays to stable hafnium-177. Lutetium-177. Lutetium-177 is produced in a nuclear reactor, and there are two primary production methods.

Next.

So, the first method of production is called direct production. It begins with a lutetium-176 target. Lutetium-176 has a high thermal neutron cross-section and is able to absorb those neutrons to become lutetium-177. The target processing is relatively simple, and processing generates relatively smaller amounts of radioactive waste.

One big disadvantage is that you have to enrich the lutetium-176. It has a low natural abundance of 2.59 percent. And then, during this irradiation, it also creates lutetium-177 metastable which has 160-day half-life. Metastable lutetium-177 contributes a fraction of a percent to a patient dose, but can become a waste disposal issue.

Next slide.

Indirect production uses a ytterbium-176 target, and it yields a high radionuclidic purity. There's fewer waste disposal issues for the end-user because the indirect production of lutetium-177 does not result in the coproduction of the metastable lutetium-177m. So, specific activity is independent of the neutron flux, and the disadvantages are a poor thermal neutron cross-section for the ytterbium-176.

Can you go ahead to the next one, Kellee?

There's a very complicated, challenging lanthanide chemical separation to be able to separate the ytterbium-177 from the lutetium-177. This process involves generation of relatively more radioactive waste. It's more expensive, and companies must recover and recycle the ytterbium targets.

The indirect production method is referred to as it can be carrier-free, no carrier added. And recently, there's been an observable market shift to the non-carrier-added lutetium-177, meaning its production via the ytterbium-176 targets, which both eliminates the concern about the lutetium-177 metastable and allows for the production of higher specific activity product.

All right. Next slide.

So, the biggest challenge for the

lutetium-177m -- or I'm sorry -- lutetium-177 produced by the direct method from lutetium-176 is the coproduction of the lutetium-177 metastable, which is not eligible for decaying storage disposal due to its 160-day half-life. This is a concern for both the producers and the end-users.

The biggest challenge for lutetium-177 produced via the indirect method from the ytterbium-176 is the challenging chemical separation. In addition, the difficulty of acquiring ytterbium incentivizes recycling of the ytterbium-176 targets, and questions remain about how many times a given target can be recycled.

Next slide.

All right. The two final isotopes that we will look at today are alpha-emitters. I'm going to start with actinium-225. Right now, that's the poster child for the targeted alpha therapeutics. Actinium-225 has a 10-day half-life, has a decay chain that involves four alphas and two betas and, eventually, ends with bismuth-209. Of course, the biggest challenge with actinium-226 is its extremely limited supply.

Next slide.

So, right now, all or virtually all of the

actinium-225 that's in the United States is produced by the Department of Energy through its Tri-Lab Project, which is a partnership between Brookhaven National Lab, Los Alamos National Lab, and Oak Ridge National Lab. Oak Ridge can supply a few dozen millicuries of actinium-225 every six weeks from legacy thorium-229 stock. To supplement this, Brookhaven and Los Alamos National Labs also produce actinium-225 via proton bombardment of a thorium target in an accelerator, which is then chemically processed at Oak Ridge. The National Isotope Development Center is providing somewhere around 100 millicuries every other month, and they are working to increase both the batch size and the batch frequency.

Next slide.

By now, most of you are aware that the thorium target irradiation produces actinium-227 as a trace contaminant. This actinium-227 has essentially no impact on the dose to the patient, but it can be an enormous problem for licensees, both producers and end-users.

So, much actinium-27 is there? Tallies I've seen are around 0.2 percent at the end of irradiation. And, of course, the percentage increases -- can you go ahead to the next, Kellee? -- it increases

as the actinium-225 decays due to the actinium-227 long half-life. So, .02 percent is 2 parts in 1,000. So, remember that. I'll come back to that in a minute.

Actinium-227 is most easily detected by its daughter products, but once the actinium has been chemically separated, it takes time for those daughter products to in-grow again.

Next slide.

So, I want to take a closer look at three radiation safety parameters for actinium-225 and actinium-227. Ultimately, all of our regulatory infrastructure is set up to limit the potential for radiation doses to individuals or releases to the environment. So, okay, how do we do that?

One way relative risk of radioisotopes is captured in regulatory space is by the term "annual limit on end state". So, this is an amount of radioactive material which, if taken into the body, leads to certain dose thresholds. These values are listed in 10 CFR 20, Appendix B, and as presented here, represent the amount of actinium which, if inhaled, would cause (audio interference) surface.

The annual amount on intake is also used in other ways; for example, to determine reporting thresholds for spills. So, as you'll notice, the

annual limit on intake for actinium-225 is very low, 0.3 microcuries, and the limit for actinium-227 is three orders of magnitude less than that. Three orders of magnitude is a factor of a thousand. And wait, where did we just hear that? From a dose-risk perspective, the risk that's posed by the trace actinium-227 contaminant is actually on even par with the risk from the much larger amount of actinium-225. So, this leads to some interesting radiation safety features.

For isotopes with a half-life of more than 24 hours, a spill is reportable to regulatory authorities if the spilled quantity exceeds five times the annual amount on intake. The reportable spill threshold for actinium-227 is 2 nanocuries. So, we very quickly run into practical limitations. How is a radiation worker going to estimate a spilled activity of 2 nanocuries? And I also want to point out that the reportable spill threshold for actinium-227 is less than the threshold for reporting a leaking sealed source, and that level is 0.005 microcuries.

So, why does this matter? A couple of years ago in Wisconsin, we had a licensee who spilled radium-223 dichloride during injection. The licensee appropriately identified the spill and attempted to clean the area. Cleaning efforts could not reduce the

contamination to background levels.

Like most nuclear medicine departments, this licensed site primarily handles technetium-99m. When they had the radium contamination event, they treated it like any other spill. They covered the area with shielding to allow for decay and put up a sign that said, "Do not mop." And they believed that their actions were adequate.

So, when we inspected the site, we discovered that neither the radiation workers nor the radiation safety officer were aware that there are reportable spill thresholds, because they are accustomed to working with short-lived isotopes. Although they had estimated the amount of material involved, they did not compare the spilled amount to the reporting threshold. It turned out to be below threshold, and the licensee did not appreciate the increased hazards associated with alpha-emitting material. And for comparison, the reportable spill threshold for radium-223 is 3.5 microcuries. So, actinium-225 is a little less than half of that.

The final radiation safety area that I want to mention is financial assurance for recommissioning. So, licensees are required to post financial assurance when they possess radioactive material with a half-life

over 120 days in unsealed form in quantities exceeding the levels in 10 CFR 30.35. Financial assurance is not required for actinium-225 due to its half-life, but financial assurance is required for actinium-227 in quantities exceeding 10 microcuries. Licensees will have to know how much actinium-227 they possess and closely track inventory to make sure they are in compliance with financial assurance requirements. This all sounds complicated. But is there a way to make more actinium-225 without also making actinium-227?

Next slide.

Okay. So, I actually started laughing when I typed this slide because it runs contrary to everything that we've learned as health physicists.

Radium used in the early 20th century has left quite a legacy, and my office still routinely gets calls from scrap yards or movers of the public when items containing radium turn up. What is there to like about radium-226? Well, it doesn't produce actinium-227. And as we've seen with lutetium-177, the market pushes for carrier-free and no-carrier-added methods of production. I expect this to happen with actinium-225 after the supply can meet the demand. So, as this technology is developed, we

are facing many, many radiation safety questions.

Next slide.

These are just a few of the issues that we are facing trying to regulate potential interest in radium-226 targets to produce actinium-225. There's issues with the highly radioactive target. Targets must be built and rebuilt inside (audio interference). Radium-226, of course, decays into radon gas, which also leads to significant concerns about maintenance of (audio interference) systems. And then, sites also must limit the accelerator beam strength to reduce the production of impurities.

So, the National Labs have begun researching production of actinium-225 from radium-226 targets. And over the next 10 years, I expect actinium-225 production to also be supplemented by private sector efforts using a couple of different technologies and production methods.

Next slide.

To close things out today, we'll take a look here at thorium-227, which has a longer half-life than the other isotopes we've examined. There are several clinical trials in process thoriated compounds. Thorium itself, thorium-227, has an 18-day half-life and a long decay chain with five alphas and

two betas that leads to stable lead-207.

Thorium-227 is the daughter product of our friend actinium-227. So, all the actinium-227 radiation safety issues that we discussed previously would also be challenges for thorium-227 production, although the actinium-227 for this is contained within a generator, and maintenance activities would also carry high radiation safety risk.

And I do want to point out, too, that there is already an (audio interference) supply of thorium-227 because it is the parent material for radium-223.

Next.

So, aside from the actinium-227 issues that we've already discussed, there are a couple other challenges with using thorium-227.

First, thorium-227's primary daughter product is radium-223, which has a decently long half-life of 11 days. This means that, as the thorium-227 decays, the radium-223 will in-grow, leading to a longer decay-in-storage period than would normally be anticipated. This is easy to overcome, but licensees need to be prepared for that and perform surveys accordingly.

Additionally -- and I want to apologize,

this didn't make it on a slide -- licensees who produce alpha-emitting isotopes also need to be aware of possession limits that would require consideration of an emergency plan for responding to a release. This is per 30.72 Schedule C. And for most alpha-emitting isotopes, including actinium and thorium, licensees must consider an emergency plan when there are possession limits with a unity calculation that exceeds 2 curies. So, preparing and evaluating an emergency plan is very complex and resource-intensive.

On the clinical side, a major concern with thorium therapy is with the potential migration of daughter products in the body. When the thorium-227 decays, the energy breaks the bond between the isotope and targeting compound, and the resulting radium will be free to move. So, this characteristic will present challenges for dosimetry and may also cause undesirable bone doses.

Next slide.

So, just to sum up, there's rising interest in producing these novel radiotherapies via accelerators and generators, and we expect to see an increasing number of isotope producers over the next several years. To that end, reducing impurities is paramount. Radiation safety concerns about these

impurities are significant, and some of them may not have easy answers as far as how to handle and work with those materials. But, regardless, the radiation safety concerns are driving decisionmaking for both the isotope producers and for the end-users.

So, hopefully, this has been a little bit more information for you all about what happens before you get to the clinical piece of it, and some of those concerns definitely feed into how we regulate these materials.

So, thank you for your time today.

CHAIRMAN METTER: Thank you, Megan. That was really an excellent report and a lot to think about for the future.

Do I have any questions from the ACMUI for Ms. Shober?

(No response.)

Okay, I don't see any. Do I have any questions from the NRC staff?

(No response.)

I don't see any there, either. And go ahead and open it up to the public. So, we can do that and see if they have any questions.

MS. LOPAS: Sure. So, please just hit the (audio interference), that you need to be unmuted or

press *3 on your phone, if you've called in using your phone.

And at the moment, we don't have any hands raised, but we'll give it just a couple more seconds.

This is for members of the public to raise their hands and to be unmuted to ask a question.

(Pause.)

Okay, Dr. Metter, we're not seeing any raised hands.

CHAIRMAN METTER: Okay. Thank you, Sarah.

MS. LOPAS: Oops, I see one. One just popped up.

Go ahead.

MR. ELDEN: Okay. Thank you.

MS. LOPAS: Yes, you're unmuted.

MR. ELDEN: Thank you. My name is Thomas Elden.

Is there a way in which we can determine like how those limits, say impurities or the limits on the -- I think you said it was Part 20, Appendix B -- how those were derived in terms of like their bases?

MEMBER SHOBER: Yes, that's a really great question. And I don't know if anyone with the NRC has a ready answer for that.

The annual limits on intake were derived to be the level at which you would reach either a 5-rem whole body dose or a 50-rem organ dose to the most vulnerable organ. I am not sure for the emergency plan table how those values were originally determined.

MR. ELDEN: Okay. Thank you.

MS. LOPAS: Okay, Dr. Metter, I don't see any other hands raised.

CHAIRMAN METTER: Okay. Thank you very much.

Thank you, Megan, for a really excellent presentation and a lot of insight for the future here.

So, the next item on our agenda is the open forum, where we'll discuss medical topics of interest. Does anybody have any topics that they would like to bring up for the future?

(No response.)

Okay. I do have an item. On Dr. Ron Ennis' Medical Subcommittee reporting, he did suggest that the ACMUI form a subcommittee. And so, the following will be the subcommittee and this will be the charge: "To evaluate the issue of Y90 medical events in more depth and, in consultation with the vendors, propose methods to decrease the number of Y90-related medical events."

The Subcommittee will be chaired by Dr. Michael O'Hara. Subcommittee members will be our Dr. John Angle, Ms. Megan Shober, Mr. Josh Mailman, Dr. Vasken Dilsizian, and Ms. Melissa Martin.

Now do I have NRC staff for that, Mr. Einberg?

MR. EINBERG: So, I would say let me get back to you on that point.

CHAIRMAN METTER: Okay. Thank you.

So, the timeline of this Subcommittee will be that we would like a report for the spring 2022 meeting.

Are there any other items or questions?

MEMBER GREEN: Dr. Metter, this is Richard Green.

CHAIRMAN METTER: Yes, Mr. Green?

MEMBER GREEN: Do we want to be specific and say this is Y90 Microspheres? By the broad definition of Y90, you're including Zevalin.

CHAIRMAN METTER: You're exactly right, Mr. Green. Thank you for the clarification. So, evaluate the issue of Y90 microspheres medical events in more depth. Thank you very much.

Any other topics that would like to be brought up for the future?

(No response.)

Okay. Seeing none, I'd like to turn the --

MS. AYOADE: Dr. Metter?

CHAIRMAN METTER: Yes?

MS. AYOADE: This is Maryann Ayoade from NRC.

CHAIRMAN METTER: Yes.

MS. AYOADE: I wanted to bring up a new medical technology that's currently under evaluation of where it should be regulated in Part 35.

CHAIRMAN METTER: Yes.

MS. AYOADE: Okay. It is the Liberty Vision yttrium-90 source. It's a new medical eye applicator brachytherapy source that has been cleared by the FDA for episcleral brachytherapy of ocular-related tumors and benign growths. It is a temporary implant source that's intended for use within a manual brachytherapy system, and the source falls outside of the regulatory requirements that had been afforded to ophthalmology in Part 35 because it's a yttrium-90 source and not a strontium-90 source.

So, specifically, the regulatory requirements in 10 CFR 35.491, which allows for other physicians that do not meet the regulations in 490 to be able to use strontium-90 sources for ophthalmic

treatments. And so, these types of physicians are generally ophthalmologists. And so, we also have subsequent regulations that are related to ophthalmic use of strontium-90 that are important as well, but, again, this eye applicator source is a yttrium-90 source. And so, that is currently under evaluation to see where it should be regulated.

If we do move forward with the source, with regulating under 10 CFR 35.1000 via guidance, then we would be sending it to the ACMUI for review and recommendation.

CHAIRMAN METTER: Okay. Thanks, Maryann.

I would like to think about the members of the Subcommittee, and then, can I get back to the NRC on that?

MS. AYOADE: Yes, that should be fine.

CHAIRMAN METTER: Thank you. Thank you very much for bringing that up.

Any other items?

MR. EINBERG: Yes, Dr. Metter, Chris Einberg again here.

Regarding the Y90 Subcommittee, the NRC staff resource will be Dr. Katie Tapp.

CHAIRMAN METTER: Thank you very much.

Okay. Well, let's move on to the next item, which is a Special Presentation by the NRC to Mr. Michael Sheetz, who's been a very valuable member as a Radiation Safety Officer to the ACMUI. And it is with great sadness that I say that we will be missing you because we will, but I do appreciate all the effort and dedication you've given to our Committee.

So, I believe it's going to be R. Lewis from the NRC.

MS. VALENTIN-RODRIGUEZ: Dr. Metter, this is Celimar from the NRC.

We should probably just take a break. Mr. Rob Lewis will be here on 3:30.

CHAIRMAN METTER: Okay. Thank you.

So, we'll reconvene at 3:30.

MS. VALENTIN-RODRIGUEZ: Thank you, Dr. Metter.

CHAIRMAN METTER: Thank you.

(Whereupon, at 3:10 p.m., the foregoing matter went off the record and went back on the record at 3:30 p.m.)

CHAIRMAN METTER: Welcome back to the 2021 fall ACMUI meeting.

And we have a Special Presentation to Mr. Michael Sheetz by Mr. Robert Lewis from the NRC.

MR. LEWIS: All right. Thank you, Dr. Metter.

Can everyone hear me?

CHAIRMAN METTER: Yes.

MR. LEWIS: Thank you.

My name is Rob Lewis. I am the Deputy Director of the Office of Nuclear Material Safety and Safeguards.

And I have not had the opportunity to address the Committee in this position. I did used to work a lot with the ACMUI. I had Kevin Williams' job for four years about 10 years ago. So, it's good to see the Committee again.

And I just want to say, before I get into the business I'm here for, we really, John Lubinski and I really thank the Committee members and the ACMUI for all their work and time and expertise that they provide to NRC. We truly believe you guys help us make good decisions with respect to our regulatory activities for medical uses of isotopes, both therapeutic and diagnostic, and in a way that doesn't unnecessarily interfere with the practice of medicine.

As you know, application of radioactive materials and radiation doses to people is the only area NRC regulates where we intentionally give a high

dose of radiation to people. So, clearly, it's a huge contribution that the Committee makes towards radiation safety and NRC's mission. So, I'll just thank you very much.

And I just wanted to mention, in just the past year, we've had several great accomplishments, and the Committee helped us with those: streamlining training and experience guidance, emerging technologies guidance; working closely with Agreement States through all the COVID issues and with licensees on relief requests that are needed; learning lessons from COVID that we're now going to apply to our licensing and oversight programs in the future, and work on extravasations as well. So, great progress over the last year on all of those topics, immense amount of progress. So, thank you.

But, today, I'm here to recognize the particular contributions of Mr. Michael Sheets, who's our Radiation Safety Officer member of the ACMUI. And he has been that since September 2017 and his term expired last week on September 28th, which he's retiring from the Committee, but, also, as I understand, retiring more generally. So, we congratulate him.

And during his time on the ACMUI, he's

contributed to several high priority activities and initiatives and has given us great leadership from the RSO perspective -- those including chairing several initiatives on the AO criteria and Patient Intervention Subcommittee, and his active participation in multiple subcommittees on the training experience, as already mentioned; Xcision GammaPod Licensing Guidance; Medical Events; Infiltrations and Medical Event Reporting; Germanium-68/Gallium-68 Pharmacy Grade Generator Licensing Guidance, and Regulatory Guide 8.39, "Release of Patients Administered Radioactive Materials."

So, all of those were key activities for NRC, and we are going to miss him on the Committee, but we're grateful for his contributions and happy for his retirement.

Just like when I used to have Kevin's job, the RSO does present annually the non-medical events and medical use facilities presentation to the Committee. It keeps our pulse on the operating experience, not just hospital settings, but radiopharmaceutical events as well. So, we really do appreciate that work as well.

And I did want to mention as well, you know, he came to us with great prestige and accolades

throughout his career. So, I did want to recognize his leadership as well, not only at NRC and the ACMUI, but over his career at the Health Physics Society, the AAPM, the American Academy of Health Physics, American Board of Medical Physics, and Society of Nuclear Medicine and Molecular Imaging.

So, thank you, Mr. Sheetz, for that work.

And we do have -- and I guess virtually; I wish I was there in person -- but we have some things to show our appreciation and gratitude for his service to the NRC, and three things, in particular.

First, a flag that was flown over the U.S. Capitol and a certificate to go with it from Chris Van Hollen, his Senator for Maryland. I think you're from Pittsburgh, but Senator Van Hollen is clearly the Senator for NRC Headquarters. So, that's the connection there.

And a Certificate of Appreciation as well from Chairman Hanson, and a label pin from the NRC.

So, again, thank you for your service, and I just wanted to say, on behalf of all the NRC management and staff, it's through the work of you and others like you that we provide our service to the American people and provide for public health and safety and protection of the environment in the medical uses of materials.

So, we don't take that lightly, and we know it was a huge investment of your time. And we are very grateful for you.

So, with that, I'd like to turn the meeting back over to Dr. Metter for the Open Forum participation -- I'm sorry -- the Open Forum portion of the meeting.

Dr. Metter?

And I'll stick around with everyone for a half hour here. And I'm free if you have any questions for me, Chris, if you're permitting, but, certainly, interested to hear your Open Forum. Thanks.

CHAIRMAN METTER: Thanks, Mr. Lewis.

And thank you, Mr. Sheetz, for your expertise and dedication to the work of the ACMUI. I wish you all the best.

Before we start our Open Forum, any other comments from the ACMUI members for Mr. Sheetz?

MEMBER JADVAR: This is Hossein Jadvar.

I just want to say happy retirement, Mike, and although our overlap serving the ACMUI was relatively brief for me, but I enjoyed my time with you very much. I learned much from you. And again, happy retirement. Thank you for everything.

CHAIRMAN METTER: Thank you, Dr. Jadvar.

MEMBER MARTIN: Yes, this is Melissa Martin.

Oh, go ahead.

VICE CHAIR DILSIZIAN: It's all right, Melissa.

MEMBER MARTIN: I was just going to say we will certainly miss Michael's expertise on here. It's been a pleasure to work with Michael on several committees, and both at AAPM and this Committee. But I hope he enjoys retirement.

VICE CHAIR DILSIZIAN: Hi, Michael. Vasken. I just want to echo everybody's best wishes. I'm not sure the word "retirement" is proper. I really wish that you could have served four more years. This is going to be my eighth year with the ACMUI. I've worked with a number of members. I have to say that your attention to detail, your leadership on the subcommittees, is just fantastic. And I think that ACMUI could have benefitted from four more years of your time, but we respect your decision and wish you the best.

MEMBER O'HARA: Mike, this is Mike O'Hara.

And I want to echo all of the things that everybody has said. I will certainly miss you on the

ACMUI, and I'm very happy for you going into retirement. Enjoy your retirement and take care.

MEMBER ENNIS: This is Ron.

I just want to also echo the sentiments. I have learned a lot from you, Mike, and found you to be always very insightful, straightforward, thoughtful, balanced, and honest, and tried to emulate some of those characteristics in learning how you operate. And it's been a really pleasure to know you. I also wish you were sticking around, but totally get it. And enjoy the log cabin.

MEMBER OUHIB: Hi. This is Ouhib.

Michael, I'll tell you one thing; I think what has been said is 100 percent, or 110 percent, accurate here. We will miss you; no doubt about it. And you have made a great contribution to the ACMUI, and your presence will definitely be (audio interference). I wish you all the best retirement and enjoy your (audio interference).

MEMBER GREEN: This is Richard Green.

I just wanted to say, Michael, I thought you had impossible shoes to fill when you came in after Sue Langhorst, but I think your foot is even bigger than hers.

(Laughter.)

I appreciate what you've done and the expertise. And I'm very envious of sunsets and perhaps some fishing. Good luck to you.

MEMBER WOLKOV: Michael, this is Harvey Wolkov.

I just wanted to let you know it's been such a pleasure to work with you. I've appreciated your expertise, your input in all the committees that I've served with you. And as pointed out by others, I think your shoes are going to be very difficult to fill.

MEMBER MAILMAN: Michael, this is Josh Mailman.

I only got the opportunity to work with you on one committee for I think one month, but I must say that it was a pleasure working with you. I wish I had a longer opportunity to work with you as well. But congratulations on your retirement and I hope our paths cross at some point.

MR. EINBERG: So, this is Chris Einberg.

And once again, on behalf of the NRC staff and the medical team, Michael, you've provided such excellent leadership, such a work ethic. You've been so active on the Committee and provided sound advice to the NRC staff. We've valued everything you've told

us. You'll be missed.

Right now, just for the people of the Committee, so that they know, Michael will be kept on as a medical consultant for us. So, he can still serve and provide us with some advice until we backfill for his position. So, we look forward to your continued support in that area, but we do wish you all the best in your retirement.

MR. SHEETZ: Thank you, everyone, and thank you, Mr. Lewis, for those very kind words and acknowledgment of my service to the ACMUI.

I am truly honored to have served on the ACMUI with the best leaders and look on it as my most rewarding professional accomplishment. It was a very difficult decision, but since I have retired, I did not think it was appropriate to serve a second term. The RSO representative should be actively working in the field of radiation protection and current in the latest medical technologies and practices, and ideally, with hands-on experience.

I appreciate the opportunity to have collaborated with and worked with all the ACMUI members and the NRC medical staff team. Everyone is so supportive and dedicated to the work of setting the proper policy and level of regulation for the medical

use of radioactive material. And as Mr. Lewis stated, it's very challenging because it's the only area where individuals are intentionally exposed to ionizing radiation.

I am again honored that the NRC has invited me to stay on for a while as a medical consultant, and I look forward to working with the NRC medical staff team and the ACMUI.

Thank you.

CHAIRMAN METTER: Thank you, Mr. Sheetz. And really, all the best, and we still look forward to seeing you and your expertise and your input. Thank you very much.

So, let's go back to the Open Forum, and I believe we have a few other topics that need to be addressed.

I think, Chris, are you muted?

MR. EINBERG: Oh, yes, I am. Yes, thank you for that, Dr. Metter.

I'm not sure that there's, actually, anything else for the Open Forum from the NRC staff perspective. If there's anything else from the ACMUI perspective that they'd like to discuss -- you know, we don't have anything. And if not, we can move to the Administrative Closing and the Action Items.

CHAIRMAN METTER: Okay. Thank you, Mr. Einberg.

So, we'll go to the Administrative Closing with Mr. DiMarco of the NRC.

MR. DiMARCO: Hello, Dr. Metter and Members of the ACMUI.

First of all, Kellee, if you could bring up the calendar and the handout, we'll talk about scheduling the spring meeting, the spring 2022 meeting. I sent out a form to the members of the ACMUI to get some responses for what dates would be good for that spring meeting. The two dates that were most requested were April 4th and 5th and March 21st and 22nd.

So, you can see up here we have the calendar with some of the major meetings that are also going on around that time. I believe this is the March calendar.

So, is there any discussion about those two dates, April 4th and 5th and March 21st and 22nd?

MEMBER JADVAR: Either one is fine with me. March 21st is the Persian New Year, by the way.

CHAIRMAN METTER: This is Darlene Metter. Both dates are fine with me.

MEMBER GREEN: Daniel, this is Richard. Did you rank those, with the April dates taking first

and the March dates taking second place in your polling?

MR. DiMARCO: That's correct. The April dates had one vote ahead of the March dates.

MEMBER GREEN: The April dates, it appears to be, are completely free of professional society conflicts.

MR. DiMARCO: Correct.

MEMBER O'HARA: Both dates are fine with me.

MEMBER WOLKOV: Both dates are fine with me. I'm just curious, though, if any of the physicists would be affected by the AAPM meeting.

MEMBER MARTIN: The AAPM meeting is actually March 26th through the 29th.

MEMBER WOLKOV: Thank you.

MEMBER MARTIN: Yes, some of us will definitely be affected by that. But the two proposed dates would work around that meeting.

MEMBER GREEN: And at this point, we are not certain whether this is an in-person meeting or virtual meeting? There would also be flying time, if we were in person.

MR. DiMARCO: So, for these meetings, the NRC will be back in the office in person by November. So, I believe these meetings will be assumed, will

be in person. Chris, correct me if I'm wrong on that.

MR. EINBERG: Yes, that's the working assumption right now, that these meetings will be in person, since we will be going back to the office in November. We're going back to the office on November the 7th.

CHAIRMAN METTER: And this is Darlene. Can I ask, will these times be the same with the Commission? We're not meeting with the Commission, then, right? No. So, it shouldn't really matter, I guess.

MR. EINBERG: That's correct, in the spring you will not be meeting with the Commission. That's usually for the fall meeting.

CHAIRMAN METTER: So, we're going to be switching all our Commission meetings to the fall then?

MR. EINBERG: Well, that's a good question. We can take it up with the agenda planning, but since we're already moved to the fall, I'm not sure if having another Commission meeting six months from now is necessary, unless something comes up.

MEMBER MARTIN: So, choose one. It sounds like you've got an open slate.

MR. EINBERG: Daniel, I would suggest that we can go with the October (sic) 4th and 5th as your

first.

MR. DiMARCO: Yes.

MR. EINBERG: And then, the other one, the second date is your backup.

MR. DiMARCO: Yes, that's seems to be the consensus, for the 4th and 5th as the primary and the 22nd, I believe, yes, the 21st and the 22nd as the backup, Dr. Metter.

CHAIRMAN METTER: Okay, that would be fine. It's the 4th and 5th as the first choice and March 21 and 22nd as the second choice. Do I need to vote on that?

MR. EINBERG: Was it March 21st and 22nd --

CHAIRMAN METTER: Yes, yes.

MR. EINBERG: -- or April?

CHAIRMAN METTER: No.

MR. EINBERG: Okay.

CHAIRMAN METTER: No, March.

May I just make a comment, though. When Daniel first mentioned this, he said that there was one less vote for April. Would that make a difference for that individual?

MR. DiMARCO: There was actually one more vote for April.

CHAIRMAN METTER: Oh, I'm sorry, I

misheard you.

MR. DiMARCO: Yes.

CHAIRMAN METTER: So, we'll do April as the first choice and March as the second choice.

MR. DiMARCO: Okay.

MEMBER OUHIB: This is Zoubir. Not that there's a difference, but there will be a weather difference doing it in early April versus March. For the locals, you probably know that better.

CHAIRMAN METTER: I'm sorry, Zoubir, can you repeat? You kind of broke up.

MEMBER OUHIB: Oh, I'm sorry. I was just asking, you know, April 4th and 5th sounds better as far as the weather is concerned probably.

MR. EINBERG: Yes, it's very rare that we would have snow or anything in late March.

MEMBER OUHIB: Okay.

MR. EINBERG: So, I don't think that's really a factor.

MEMBER OUHIB: Okay.

CHAIRMAN METTER: Okay. So, do I have a motion to make the spring meeting? The first choice is April 4th and 5th, and the second choice is March 21st and 22nd.

MEMBER WOLKOV: So moved.

CHAIRMAN METTER: Do I have a second?

MEMBER MARTIN: Second.

CHAIRMAN METTER: Who's the one who so moved? Thank you, Mr. Wolkov. And then, Melissa was second. Thank you.

All in favor?

All opposed or abstain?

Okay. So, the dates are set for the spring meeting, unanimously approved by the ACMUI.

MR. DiMARCO: Okay. Thank you, Dr. Metter.

I will now get into the summary of the meeting.

First of all, we heard the Medical Events presentation that was unanimously approved by the ACMUI. Then, we heard the Generator Subcommittee, which was also unanimously approved, and the Theranostics Subcommittee presentation that was also unanimously approved.

There were two subcommittees that were formed, one on the Y90 Microsphere Events, to explore those in more depth, as well as a Subcommittee on the Liberty Vision Y90 Source.

And that is the summary for this meeting.

CHAIRMAN METTER: Thank you, Mr. DiMarco.

Now I turn the meeting back over to Mr. Einberg for the official closing.

MR. EINBERG: Okay. Very good. Thank you, Dr. Metter.

Before I close the meeting, I just wanted to let the ACMUI know or ask them to check their emails regarding an announcement regarding tomorrow's Commission meeting, regarding a briefing in preparation for that for the members that are going to be briefing. So, if you could check your emails regarding that?

And as far as closing the meeting, I would like to thank all of the ACMUI members and the NRC staff for their preparation and participation in this meeting, as well as members of the public who have provided comments.

Like Mr. Lewis had indicated, your advice is very important to the NRC staff. And new members on the Committee, please feel free to reach out to the NRC staff if you have any questions about your roles or the regulations. We are here to assist and provide support.

Each of the subcommittees have NRC staff members assigned to the subcommittees, and they're there to help you understand the NRC regulations and

to guide you through the NRC regulations and through the NRC processes, whether it be rulemaking or guidance development.

But, with that, we had very great discussion on multiple topics. And so, once again, I thank everyone for all their support, and we look forward to tomorrow's Commission meeting. And so, that should be interesting as well.

And so, with that, I adjourn the meeting. Thank you.

(Whereupon, at 3:55 p.m., the meeting was adjourned.)