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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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SPRING 2019 MEETING

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WEDNESDAY,

APRIL 3, 2019

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The meeting was convened in Room 1-C03/1-C05, Three White Flint North, 11601 Landsdown Street, Rockville, Maryland, at 8:30 a.m., Christopher J. Palestro, ACMUI Chairman, presiding.

MEMBERS PRESENT:

CHRISTOPHER J. PALESTRO, M.D., Chairman

DARLENE F. METTER, M.D., Vice Chairman

VASKEN DILSIZIAN, M.D., Member

RONALD D. ENNIS, M.D., Member

RICHARD L. GREEN, Member

MELISSA MARTIN, Member

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

ZOUBIR OUHIB, Member

ARTHUR SCHLEIPMAN, Ph.D., Member

MICHAEL SHEETZ, Member

MEGAN L. SHOBER, Member

LAURA M. WEIL, Member

NON-VOTING MEMBER PRESENT:

HARVEY B. WOLKOV, M.D.

NRC STAFF PRESENT:

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

MARYANN AYOADE, NMSS/MSST/MSEB/MRST

JENNIFER DALZELL, R-III/DNMS/MCIB

SAID DIABES-FIGUEROA, NMSS/MSST/MSEB/MRST

LISA DIMMICK, NMSS/MSST/MSEB/MRST, Team Leader

SARA FORSTER, R-III/DNMS/MLB

CASSANDRA FRAZIER, R-III/DNMS/MLB

ROBERT GALLAGHAR, R-I/DNMS/MLAB

VINCE HOLAHAN, NMSS/MSST

SOPHIE HOLIDAY, NMSS/MSST/MSEB

ESTHER HOUSEMAN, OGC/GCRPS/RMR

DONNA-BETH HOWE, Ph.D., NMSS/MSST/MSEB/MRST

KELLEE JAMERSON, NMSS/MSST/MSEB/MRST, ACMUI Coordinator

DONNA JANDA, R-I/DNMS/MLAB

JANELLE JESSIE, COMM/OCMJB

ERIN KENNEDY, R-III/DNMS/MLB

PENNY LANZISERA, R-I/DNMS/MLAB

SARAH LOPAS, NMSS/MSST/MSEB/MRST

HENRY LYNN, OCHCO/ADHRTD/STTSB

ROBERT MACDOUGALL, NMSS/DRM/MRPB

JANICE NGUYEN, R-I/DNMS/MLAB

DENNIS O'DOWD, R-III/DNMS/MIB

PATTY PELKE, R-III/DNMS/MLB

DAVID PELTON, R-III/DNMS

SHAWN SEELEY, R-I/DNMS/MLAB

VERED SHAFFER, RES/DSA/RPB

KATIE TAPP, Ph.D., NMSS/MSST/MSEB/MRST

KEVIN WILLIAMS, NMSS/MSST, Deputy Division Director

IRENE WU, NMSS/MSST/MSEB/MRST

MEMBERS OF THE PUBLIC PRESENT:

JENNA ABBOTT, Illinois Emergency Management Agency (IEMA)

DANNY ALLEN, NuTech, Inc.

ERIC ANDERSEN, Dana-Farber Cancer Institute

MICHAEL BAXTER, American Pharmacists Association

BETTE BLANKENSHIP, American Association of Physicists in Medicine (AAPM)

KENDALL BERRY, Fox Chase Cancer Center

JEFF BRUNETTE, Mayo Clinic

JANET BUKOVCAN, British Technology Group (BTG)

MARY BURKHART, IEMA

STEVEN CHILINSKI, Radiopharmacy

ASHLEY COCKERHAM, SirTex Medical

WHITNEY COX, IEMA

WILLIE (JACK) CRAWFORD, Virginia Office of Radiological Health

CORY DAIGNAULT, Virginia Office of Radiological Health

NICK DORRELL, University of Virginia

ARIEL DOUCET, Virtua Health

MARK DRISCOLL, University of Michigan

BRIAN ERASMUS, BTG

LYNNE A. FAIROBENT, *Unaffiliated*

SHERRIE FLAHERTY, Minnesota Radioactive Materials Unit

MARK FLICKINGER, Virginia Office of Radiological Health

MICHAEL FULLER, Virginia Office of Radiological Health

SANDY GABRIEL, *Unaffiliated*

REID GADZIALA, PharmaLogic

WENDY GALBRAITH, University of Oklahoma Health Sciences Center

NOELLE GEIER, Froedtert & the Medical College of

Wisconsin

VINSON GIBB, IEMA

REBECCA GRABARKEWITZ, Virginia Office of Radiological Health

MATTHEW HADDEN, Virginia Office of Radiological Health

GARY HALL, Virginia Office of Radiological Health

MATTHEW HALL, North Shore University Health System

STANLEY HAMPTON, Eli Lilly

CURTIS HICKS, Brigham and Women's Hospital, Harvard Medical School

WILLIAM HINCHCLIFFE, Yale New Haven Hospital

WILLIAM HOUSE, Virginia Office of Radiological Health

SARAH HUGHES, University of Louisville

PAUL KANABROCKI, Virginia Office of Radiological Health

HEATHER KARMANSKY, SirTex Medical

CAITLIN KUBLER, Society of Nuclear Medicine and Molecular Imaging (SNMMI)

RALPH LIETO, St. Joseph Mercy Health System

WILLIAM LORENZEN, Boston Children's Hospital, Harvard Medical School

RICHARD MARTIN, AAPM

JEFF MASON, Virginia Office of Radiological Health

STEVE MATTMULLER, Kettering Health

ANDY McKINLEY, American Society of Nuclear Cardiology (ASNC)

ANDREW McKUSICK, *Unknown*

ASHLEY MISHOE, University of California, San Francisco

CHRISTOPHER MITCHELL, Kettering Health

JOSHUA MYERS, Pennsylvania Department of Environmental Protection

CHRISTOPHER NATION, Virginia Office of Radiological Health

SCOTT NEMMERS, U.S. Air Force

JOSEPH OBERENDER, Virginia Office of Radiological Health

BRAD PRICE, GE Healthcare

PRYIA RAYADURGAM, Cleveland Clinic

JOE RUBIN, United Pharmacy Partners, Inc. (UPPI)

MANAR SAKALLA, Georgetown University

EUGENIO SILVESTRINI, Northwell Health

ED SIMS, Cleveland Clinic

ANDRES SINISTERRA, UConn Health

LAKSHMI SIVASUBRAMANIAN, University of

Massachusetts Medical School

DIANA THOMPSON, University of Illinois at Chicago

CINDY TOMLINSON, American Society of Radiation Oncology (ASTRO)

DAVID TOWNSEND, *Unaffiliated*

MICHAEL UJHELYI, BTG

MATTHEW WHITE, SSM Health

WILLIAM WHITE, Rush University Medical Center

NEIL WHITESIDE, Yale New Haven Hospital

MATTHEW WILLIAMS, Georgetown University

MATTHEW WILLIAMSON, Memorial Sloan Kettering Cancer Center

ROBERT WILSON, University of Tennessee Health Science Center

MELONIE WISSING, Virginia Office of Radiological Health

MIYUKI YOSHIDA-HAY, Northwell Health

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

P R O C E E D I N G S

8:36 a.m.

CHAIRMAN PALESTRO: Good morning, and welcome to the spring meeting -- spring 2019 meeting of the ACMUI. And at this point, I will turn the meeting over to Mr. Einberg for opening remarks.

MR. EINBERG: Okay. Thank you, Dr. Palestro. As the designated federal officer for this meeting, I'm 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 Branch 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. Present today as the designated federal officer is Sophie Holiday. Also as a designated officer and ACMUI coordinator is Kellee Jamerson.

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 then may also be transcribed or recorded by others. The

meeting was announced in the February 19th, 2019 edition of the Federal Register, Volume 84, Page 4858.

The function of the committee is to advise the staff on issues and questions that arise on the medical use of byproduct material. The committee provides counsel to 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 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. Christopher Palestro, Chairman, Nuclear Medicine Physician?

CHAIRMAN PALESTRO: Present

MR. EINBERG: Dr. Darlene Metter, Vice Chairman, Diagnostic Radiologist?

VICE CHAIRMAN METTER: Present.

MR. EINBERG: Dr. Vasken Dilsizian, Nuclear Cardiologist?

MEMBER DILSIZIAN: Present.

MR. EINBERG: Dr. Ronald Ennis, Radiation Oncologist?

MEMBER ENNIS: Here.

MR. EINBERG: Mr. Richard Green, Nuclear Pharmacist?

MEMBER GREEN: Present.

MR. EINBERG: Ms. Melissa Martin, Nuclear Medicine Physicist?

MEMBER MARTIN: Present.

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

MEMBER O'HARA: Present.

MR. EINBERG: Mr. Zoubir Ouhib, Radiation Therapy Physicist?

MEMBER OUHIB: Present.

MR. EINBERG: Dr. A. Robert Schleipman, Healthcare Administrator?

MEMBER SCHLEIPMAN: Present.

MR. EINBERG: Mr. Michael Sheetz, Radiation Safety Officer?

MEMBER SHEETZ: Present.

MR. EINBERG: Ms. Megan Shober, State Government Representative?

MEMBER SHOBER: Present.

MR. EINBERG: Ms. Laura Weil, Patients' Rights Advocate?

MEMBER WEIL: Present.

MR. EINBERG: At the table today, we also have Dr. Harvey Wolkov. Dr. Wolkov has been selected as the ACMUI Radiation Oncologist. He is pending a security clearance but may participate in the meeting. However, he does not have voting rights at this time.

I would also like to add that this meeting is being held via GoToWebinar so other individuals may be listening through webinar. The webinar ID number is 144-519-715. You must register for the webinar in order to obtain the bridge line and unique pin assigned per individual.

Individuals who would like to ask questions or make comments regarding a specific issue the committee has discussed should request permission to be recognized by the ACMUI chairperson, Dr. Christopher Palestro. Dr. Palestro, at his option, may entertain comments or questions from members of the public who are participating with us today.

Comments and questions are usually addressed by the committee near the end of the presentation after the committee has fully discussed the topic. We ask that one person speak at a time as

this meeting is also closed captioned. I would also like to add that the handouts and agenda for this meeting are available at the NRC's public website.

At this point, I'd like to turn the meeting over to Kevin Williams who's the Deputy Director of the Division of Materials Safety, Security, State, and Tribal Programs for some opening remarks.

MR. WILLIAMS: Thank you, Chris. Good morning and welcome today to the spring 2019 meeting. As Chris stated, my name is Kevin Williams. I am the Deputy Director in the Division of Materials Safety, Security, State, and Tribal Programs in the Office of Nuclear -- sorry about that -- Materials Safety and Safeguards, or as we commonly call it, NMSS. I started this position in May of 2017.

I want to first begin by thanking ACMUI for all of your hard work and support to the NRC. We greatly appreciate that. We truly value your contributions, your knowledge, and your experience. I would like to highlight a few areas that may be of interest to ACMUI and the meeting attendees.

The final rule of 10 CFR Part 35, the Medical Use of Byproduct Material-Medical Event Definitions, Training and Experience, and Clarifying

Amendments, was published on July 16th of 2018 and became effective January 14th, 2019. I, again, would like to thank the ACMUI on your work with the staff on this major initiative.

In October of 2018, the staff published a Federal Register notice requesting specific feedback on our training and experience requirements, including whether requirements should be tailored, and if so, how. The comment period ended on January 29th of 2019. The staff is considering the comments received as part of its evaluation and plans to provide for the Commission's consideration a notation vote paper by the fall of 2019.

On May 14th, 2019, the NRC staff plans to hold a public meeting to inform stakeholders of the staff's proposed options for a limited scope AU pathway. Once the date has been confirmed, a meeting notice will be published in the Federal Register, announced on the medical list server, and directly communicated with ACMUI.

Shortly after the May 2019 public meeting, the NRC staff will draft its Commission paper. The paper will be provided to the ACMUI for its review. We anticipate receiving the ACMUI's comments on the staff's draft Commission paper during a public

teleconference meeting in the summer of 2019.

On March 27th, 2019, the ACMUI Regulatory Guide 8.39 subcommittee was provided with NRC's staff's draft revision to Regulatory Guide 8.39. We look forward to receiving the subcommittee's comments and recommendations as part of a separate teleconference meeting this summer.

We recognize that the ACMUI had a public teleconference on February 26, 2019 to discuss the T&E for all modalities subcommittee draft report for T&E requirements for 35.300 uses. As stated in the report, the subcommittee recommends maintaining the current board certification pathway and the 700-hour T&E alternative pathway under 10 CFR 30.390 which is consistent with the full committee's position in 2016. Thank you to the subcommittee for its efforts.

Now to talk about some NRC organizational changes. The Office of Nuclear Material Safety and Safeguards, or NMSS, Marc Dapas retired. He was the Office Director. He retired in January of 2019. John Lubinski is now going to be the NMSS Office Director, and he began Monday, April 1st of 2019. John will be stopping by to speak with us during the luncheon.

Andrea Kock was selected as the Division Director of Material Safety, State, and Tribal

Programs in November of 2018. Dan Collins previously held that position, and he has taken a position at Region I. Andrea is on travel today. Otherwise, she would be the one speaking with you. But she really wanted me to let you know that she appreciates ACMUI's efforts and all that you do to help the NRC think outside of the box and the things that you provide the staff.

We recently just underwent a reorganization. Specifically, we consolidated from a five branch model to a four branch model. This resulted in an additional staff member being added to the medical group.

Additionally, NMSS is planning an office-wide reorganization in which two divisions will merge, our fuel cycle division and the division of spent fuel. The Division of Rulemaking will expand to include two new centers of expertise, one for environmental review and one for financial assurance. This reorganization is not expected to occur until fiscal year 2020 and will have no impact on our division, MSST.

ACMUI membership changes. This is Ms. Laura Weil's last in-person meeting as her second term with ACMUI ends in August. Many thanks to you for

your contributions over the past eight years. We found those to be very valuable. Tomorrow morning, our Deputy Office Director, Scott Moore, will be here to present you with a special presentation thanking you for your service.

Dr. Chris Palestro's second term will end in September. The NRC posted a solicitation for both the Patients' Rights Advocate and the Nuclear Medicine Physician representative positions in the Federal Register as a call for nominations on February 20th, 2019. The nomination period closes April 22nd, 2019. So that does leave us an opportunity to celebrate your contributions, Dr. Palestro, at a later time.

The ACMUI subcommittees have been working hard, and there are a number of subcommittee reports that will be discussed and brought before the ACMUI today.

Dr. O'Hara will discuss the subcommittee's recommendations on NRC's draft revision 10 to the Yttrium-90 Microsphere Brachytherapy Licensing Guidance.

Ms. Shober will discuss the subcommittee's recommendations on the NRC's draft revision to the Germanium Gallium Pharmacy Grade Generator Licensing Guidance.

Dr. Ennis will discuss the subcommittee's interim report on the appropriateness of the required elements of medical event reporting.

This morning, Lucerno Dynamics will provide a presentation on their LARA Infiltration Detection device which assists with detecting nuclear medicine injection infiltrations.

The Commission meeting with the ACMUI will be held tomorrow at 10:00 a.m. at the Commissioner's hearing room.

I will now turn the meeting back over to Dr. Palestro.

CHAIRMAN PALESTRO: Thank you, Mr. Williams. Next item on the agenda is old business. Ms. Holiday will review the past ACMUI recommendations and provide NRC responses. Ms. Holiday?

MS. HOLIDAY: Give me just one minute as I pull up the PDF, and excuse my hoarse voice.

(Pause.)

MS. HOLIDAY: Okay. Good morning. So like I always like to say, this is your most favorite presentation that you will hear at every single meeting, and this is referred to as old business. This is the part of the meeting where we review all of the open or pending or open delayed recommendations or

actions that have come forth from the committee. Luckily at the last fall ACMUI meeting, a lot of the recommendations were closed. So my voice is very grateful for that.

On the screen, you see the 2007 chart. As we always say, Items 33 and 34 are related to 35.491. These are listed as open and delayed, and that means that the NRC staff accepted these recommendations. However, they were not included in the Part 35 rulemaking that we just completed and issued last year. So that means it will be considered in the next round of rulemaking.

Okay. Now what you see on the chart is 2008. Again, the same things for Items 19, 26, and 27. These all say open delayed because they were not included in the current or the most recently issued Part 35 rule. They will be considered in the next round of rulemaking. So we leave those on the charts.

Okay. Item 6 in 2011 is the lone item for the chart, and this is where the ACMUI created an item to review its reporting structure on an annual basis. It is open indefinitely as this is an item that the committee has recommended that we discuss every single year. You will hear that presentation from Ms. Kellee Jamerson later on tomorrow -- or tomorrow morning,

sorry.

So this brings us to the 2016 chart. The first item is the formation of the training and experience requirements for all modalities in 10 CFR Part 35 subcommittee. This item is open indefinitely. The idea is that this group of individuals or this subcommittee body will review the training and experience requirements for all authorized users under Part 35 on a continual basis.

While it does not mean that it's evaluated every year, it means that this subcommittee will review these requirements on a frequent basis to determine if those requirements need to change. As you're aware, we had a teleconference just two months ago where that subcommittee provided a report.

The second item, Item 24, is that the ACMUI, as part of its efforts to partner with NRC to do a better medical community outreach, the members on the committee agreed to contact and interact with their respective professional organizations to encourage those interactions. So we've benefitted quite greatly. We've had interactions and presentations at SNMMI, AAPM, ACR. Later on this summer, we will have one at HPS. So thank you for those efforts.

Item 39 is related to where the committee requested that the NRC staff issue a generic communication and information notice regarding tubing issues during the administration of Yttrium-90 microspheres brachytherapy. That item is still pending. We have not issued a generic communication. So that's still on this chart.

Item 42 and 43 are related to recommendations from the same Yttrium-90 microspheres subcommittee for modifications to the Yttrium-90 microspheres licensing guidance. You will hear from that subcommittee later on today as well.

Items 44 through 53 are related to the NorthStar licensing guidance. While this licensing guidance was issued a couple of years ago, we've left these items on the chart until, as the ACMUI requested, the NRC staff issue its memorandum to the committee to inform you of how we dispositioned your recommendations.

We had anticipated that this memorandum would come this week. But since it has not, we will leave these items on the chart until it does come forth. So I suspect that we will request that there be a motion at the fall meeting to close these items. But until then, they will remain on these charts.

Okay. So that brings me to the 2017 recommendations and actions chart. The first item is that the committee requested the changes to the Part 35 rulemaking be reviewed and discussed at the ACMUI meeting. At the time that the recommendation was made, the rule had not been published yet. However, it has been published and it went into effect in January of this year for NRC licensees. So you will hear a presentation from Ms. Lisa Dimmick today at 10:45 a.m. regarding the Part 35 rule.

Items 13 through 20 are related to the medical event reporting and impact on medical licensee patient safety culture subcommittee's report. Excuse me. I have left these items as open on the chart because, again, a memorandum has not come forth to the committee to inform you of how NRC has dispositioned your recommendations. My understanding is that I think Mr. Doug Bollock perhaps gave a presentation a year ago. But again, no formal recommendation, so these items will stay on the chart.

Okay. This brings us to 2018. Item 1 and Item 2 are related to the nursing mothers' guidelines subcommittee report. These two items are also tied to a couple of other items later on the chart. But the subcommittee finalized that report. The ACMUI

endorsed the report with a modification for some language regarding FDA approved radiopharmaceuticals. That was passed at the September meeting.

However, we have left these open because my understanding is that, one, a memorandum has not been issued to the ACMUI, and two, the intent is that the NRC staff consider this as part of its changes to Regulatory Guide 8.39. So until such time, this item will also stay open on the chart.

Items 3, 4, and 5 are related to the physical presence requirements subcommittee report. They were also superseded by the subcommittee's report that was presented at the fall 2018 meeting related to the Leksell Gamma Knife Perfexion and Leksell Gamma Knife Icon licensing guidance.

So for Items 3 through 5, and I'll have to follow up with the other item that corresponds to this, I have marked these as closed. And this is my asking the committee if there is a motion to close Items 3 through 5 because the NRC staff issued the licensing guidance on January 29th of this year. And the subcommittee report that came forth from the committee stated that the committee endorsed the NRC agreement state working group's draft guidance.

So at this time, is there a motion?

MEMBER ENNIS: So moved.

MS. HOLIDAY: Dr. Ennis. Is there a second?

MEMBER DILSIZIAN: Second.

MS. HOLIDAY: And do we have a vote to close these items?

CHAIRMAN PALESTRO: All in favor?

MS. HOLIDAY: It's unanimous. Thank you. Okay. Thank you.

Item 6 and Item 7 are both open indefinitely. Items -- this is where NRC staff took an action to create a recommendations web page. Again, this is so that the ACMUI and future members and members of the public are able to see historical information as it relates to the recommendations and actions that have come forth from this committee. So last year, that website went live and we anticipate updating it at least on an annual basis.

Item 7 is where we, NRC staff, agree to send out a medical list server announcement to inform the ACMUI -- to inform members of the public who are subscribed to the list server every time that the medical event slides are posted onto the medical tool kit. These slides are for the PowerPoint presentations that both the ACMUI gives and that the

NRC staff gives.

As are you aware, in the springtime, the NRC staff provides that presentation. And in the fall time, the ACMUI subcommittee provides that presentation. And all of the presentations have been loaded, including the subcommittee's slides from the most recent fall 2018 meeting.

Okay. Item number 9 is the other item that was related to the physical presence requirements for the Leksell Gamma Knife Icon subcommittee. So similar to Items 3 through 5, I am asking if there is a motion to close Item number 9. Dr. Ennis. Is there a second?

VICE CHAIRMAN METTER: Second.

MS. HOLIDAY: Dr. Metter.

CHAIRMAN PALESTRO: All in favor?

MEMBER SCHLEIPMAN: I just had a quick question.

MS. HOLIDAY: Yes.

MEMBER SCHLEIPMAN: I realize after I voted. I think my security clearance is still --

MS. HOLIDAY: No, you have a full security clearance, Dr. Schleipman.

MEMBER SCHLEIPMAN: Okay, thank you. They were just in my office.

(Simultaneous speaking.)

MS. HOLIDAY: No, you are perfect. Thank you.

MEMBER SCHLEIPMAN: Thank you.

MS. HOLIDAY: Okay. Item 11 is, again, tied to the nursing mother guidelines subcommittee report. As I stated not too long ago, this item will be left open until the NRC staff dispositions it and considers it as part of the revision to Regulatory Guide 8.39.

Oh, Item 12 is also related to the Leksell Gamma Knife Perfexion Icon. Is there a motion to close Item 12? Dr. Ennis and Dr. Metter. Is there a vote? It is unanimous.

Okay. Item 13 is where NRC staff committed to providing the ACMUI with a copy of the briefing on the Agency Action Review Meeting, also known as the AARM, specifically, the presentation slides related to the Yttrium-90 microspheres. And I believe Ms. Kellee Jamerson provided that to the ACMUI last week.

So at this time, I'd like to ask if there is a motion to close Item 13. Dr. Metter. Do we have a second? Dr. O'Hara. And is there a vote? It is unanimous. Thank you.

Item 14, Dr. Palestro amended the membership of the training and experience for all modalities subcommittee. I've left this item on here because, for obvious reasons, this subcommittee is still active.

Okay. Item 15, Dr. Palestro formed a subcommittee to review the germanium/gallium-68 pharmacy grade generator licensing guidance. We will hear from that subcommittee later on today with their subcommittee report.

Item 16, Dr. Palestro formed a subcommittee to review the revisions to Regulatory Guide 8.39, release of patients administered radioactive material. Excuse me. The draft Regulatory Guide 8.39 -- no, sir. Thank you. Pardon the interruption. The draft Regulatory Guide 8.39 was provided to the respective subcommittee members last week. And we anticipate that there will be a teleconference this summer to receive the subcommittee's recommendations and to have a discussion with the committee.

Item 17, Dr. Palestro formed a subcommittee to review Yttrium-90 microspheres brachytherapy sources and devices, TheraSphere and SIR-Spheres licensing guidance. We will hear from

that subcommittee later on today.

Item 18, Dr. Palestro formed a subcommittee to review and update the ACMUI bylaws as needed, including a review of the role of the ACMUI chair in his or her participation on subcommittees. We will hear from that subcommittee tomorrow.

Item 19, Dr. Palestro formed a subcommittee to review the appropriateness of the required elements of medical event reporting, the adherence to these requirements, and recommend actions to improve reporting. We will hear from that subcommittee later on today. The subcommittee's report for this particular topic is an interim report.

Item 20, the committee recommended that the NRC draft an information notice on the best practices that could help prevent medical events. The NRC staff accepted this recommendation and will draft such a generic communication pending resource availability.

Item 21, the committee requested a list of all of the current ACMUI members, their contact information, information regarding each member's term, and the subcommittees they serve on. The committee also requested that the NRC staff create a web page that lists the active subcommittees and subcommittees

that have been sunset, their members, the term expiration, NRC staff resource, and the specific charge of the subcommittee.

I perhaps have jumped the gun putting closed on this. However, the latter part of the action, we did create ACMUI subcommittee's web page, and that went live yesterday. And this information was shared with the committee last night. And I do have a contact sheet which will be circulated. So perhaps we will review closing this item during the administrative closing part tomorrow.

Item 22, the committee tentatively scheduled the spring 2019 meeting for April 15th and 16th. And alternate meetings date are April 3rd and 4th subject to Commission availability. We're here today. It's April 3rd. Is there a motion to close this item? I saw Dr. Ennis and Dr. Metter. Is there a vote to close this item? It is unanimous.

Okay. We're on our last chart. So as I stated earlier, we had a teleconference meeting in February, specifically February 26th, to receive the subcommittee's report as it related to the training and experience requirements for authorized users under 35.390.

Item 1, the committee recommended adding

language into the report regarding the committee's desire to work with the NRC staff to develop a curriculum for limited scope authorized user pathway. So that language was added into the final report. And Item 2 is that the committee endorsed the training and experience requirements for all modalities subcommittee report and the recommendations included therein.

So I guess my question to the committee is, is there a motion to close either items? My recommendation would be that the committee close Item 1 because that's an administrative item just to add the language into the report. However, the committee may consider leaving Item 2 open as the NRC staff has not done anything in terms of issuing any revisions or putting out an official statement on whether or not there will be changes to 35.390

VICE CHAIRMAN METTER: I move that we close Item 1.

MS. HOLIDAY: Did you hear that, court reporter? Okay. So for the record, Dr. Metter made the motion. Dr. Schleipman seconded. Is there a vote? It is unanimous.

Okay. That concludes old business. Yes ma'am?

MEMBER WEIL: I had a question for you. If you can just go back to 2016, Item 39. This relates to the generic communication about tubing issues.

MS. HOLIDAY: Yes.

MEMBER WEIL: So that's a 2016, and it's 2019. And it's still open. Can you explain that?

MS. HOLIDAY: Dr. Katie Tapp will come to the microphone to address your question.

DR. TAPP: This is Dr. Tapp. That generic communication was in regard to the Yttrium-90 microsphere brachytherapy and specifically it was in regard to kinking, connection, hub, et cetera. When the staff began evaluation of that, we realized that the kinking and connection was related to the catheter and the selection of the catheter. And we were really delving into that and determined that was very much practice of medicine. And we were concerned if we issued guidance, we would be providing something that would be interfering with the practice of medicine.

What the staff is considering now is issuing a generic communication in a careful manner that just alerts licensees that these are happening and that they have to be diligent in their selection with other medical events related to Y-90 and ways to

prevent them. So we are working on that one now to close it. But in 2016, we evaluated it and just didn't release it at that time.

MEMBER WEIL: So when do you expect this communication to be available? I mean, it's been three years. Patients are endangered. And I'm not sure I agree with you that it's a practice in medicine issue but defer to NRC policy on that. It just seems to me that this is not a complicated thing and that I think the medical community would appreciate the notification.

DR. TAPP: We do expect that to be out this year.

CHAIRMAN PALESTRO: Any other comments or questions from the committee?

MEMBER OUHIB: I'm just curious. If there is such what I consider as a defect perhaps, should that fall under the FDA?

MEMBER O'HARA: If it is a product defect, it does fall under the FDA. It would be our jurisdiction to look at it.

MEMBER OUHIB: Right. So would you consider this as a defect, the kinking? If a catheter is kinking which should not be?

MEMBER O'HARA: I can't talk about FDA's -

- what we're currently doing. But we are looking at that.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions? Mr. Sheetz?

MEMBER SHEETZ: The NRC may want to consider including this recommendation on appropriate catheter use for Y-90 microspheres and including it in the guidance document that was requested from the subcommittee on best practices to avoid a medical event. Because that was one of the issues that was brought up with respect to the Y-90 microspheres. So you may be able to accomplish both items with one guidance document.

CHAIRMAN PALESTRO: Any other comments, questions? Right. Move on to the next item on the agenda which is the open forum. Are there any topics, medical topics of interest that anyone wishes to bring up for discussion? Dr. Ennis?

MEMBER ENNIS: Actually, this really is just kind of a continuation of the prior conversation. I was going to ask the same thing as Ms. Weil, and there's some things from 2017 that also are still open. I'm wondering whether this committee needs to look at timeliness of the responsiveness and perhaps make some recommendations about improving that.

CHAIRMAN PALESTRO: Actually, you raise an interesting point, Dr. Ennis. One of the questions that I have is some of these items are open because the memorandum from staff has not been issued yet. And I believe, and there were a lot of items, that some of them go back perhaps two years; is that correct? So is there a requirement or a definition of timeliness for such a memorandum?

MS. HOLIDAY: NRC staff doesn't have a defined date for when it should issue. We do try our best to be timely in our responses to both ACMUI and members of the public. However, as you guys are aware, the medical team has suffered great resource constraints. I, myself, was gone for roughly nine months, and there have been some rotations and other shifts on the team as well.

So we've had to prioritize our work based on the direction that we received both from the Commission and from our senior management. However, the -- for example, the NorthStar guidance memorandum, the staff member that was responsible for that has been directed to other projects as well. And understanding that, just like the ACMUI members here, everybody is a subject matter expert for their respective field. And so the individuals that are

responsible for some of these items, they are one of the few that can also respond to them.

However, we have tried our best to try to go back and go through the charts and resolve any open items to the best of our ability. The NorthStar guidance memorandum should be coming out ideally by the end of this week or next week. So for things like that with the memorandums, some of it may be oversight. Some of it may just be resource constraints.

But ideally, we do our best to -- and this is a Sophie fictitious time line. We try to issue a memorandum reasonably within 60 days. But sometimes that can't happen because of other higher priority work issues.

MR. EINBERG: Dr. Palestro?

CHAIRMAN PALESTRO: Yes, Mr. Einberg?

MR. EINBERG: Yeah, Chris Einberg here. Yeah, thank you, Sophie, for that explanation. We'll take a look at the list and go through there and see if we can prioritize these and make sure that they get closed in a timely fashion.

CHAIRMAN PALESTRO: Thank you. Other comments? Dr. Dilsizian?

MEMBER DILSIZIAN: Thank you, Dr.

Palestro. Recently, we received an important drug safety information from the FDA. It's relating to CardioGen Rubidium-82 generator which is used quite commonly for myocardial perfusion imaging. And the subject matter is that there's been a recent shortage in normal saline. And you need the normal saline to do the generator.

And the pharmacies have been sending instead of normal saline Lactated Ringer's solution. The problem with the Lactated Ringer's solution is that it has calcium in it and that's not good because calcium exchanged with strontium results in strontium-82 and strontium-85 with half-lives of 30 days or a month, 25 days or two months. And that goes to bone marrow and results in excess radiation exposure to patients.

The memo says patients were exposed to such high levels of radiation. I guess that's how they found out about it. And the question is, is this simply a medical event or should the NRC be addressing this?

CHAIRMAN PALESTRO: Comments, responses to Dr. Dilsizian?

MEMBER GREEN: This is Mr. Green. Not having read the directions for use for the CardioGen

or the Ruby-Fill, I'm fairly certain that the license commitments when a licensee obtains one or permission to have one, they commit to following the manufacturer's directions for use. And apparently, if they're substituting other solutions for elution purposes, they're not following directions for use.

DR. HOWE: This is Dr. Howe. The events have been happening in the state of Colorado which is an agreement state. And we have been in contact with Colorado, and there were medical events associated with it.

My understanding is that a patient that had a strontium rubidium procedure was at the hospital for a different reason. And a survey was done, and they were determined to be radioactive when they weren't expected to be. And that's how the events were identified, then they went back and saw that they had about eight medical events -- six to eight with a strontium breakthrough. It was too high. So we do have medical events. Okay?

But we don't have all the information yet. Colorado is still collecting information. And we're anticipating putting out maybe a generic communication to remind people about the issues associated not only with this series of medical events which was a Lugol's

solution with the calcium. But also the previous one from Nevada and Florida where individuals were not eluding the generators correctly or were overusing the generators.

There was also an issue here with the licensee not understanding that the generators had breakthrough even though they were performing a breakthrough measurement. So there are many issues here.

CHAIRMAN PALESTRO: I think the question is -- or certainly one question that arises is, can the NRC do anything proactively to reduce the likelihood of some of these events occurring?

DR. HOWE: We already have guidance and requirements for licensees to perform the breakthrough test. We have new requirements that went into effect in January for licensees to report breakthrough when they discover it to the NRC and to the distributor within seven days. So we have regulatory elements that would help discover these. But when you've got individuals that are doing breakthrough and they don't understand the results that they're getting and they don't identify that they have breakthrough in a timely matter. It is an issue.

So that is our biggest problem right now

is people don't appreciate that they have breakthrough and don't take quick action on it. It's set up so that they -- if they recognize breakthrough, they should not be using the material on patients. But because they're not recognizing, patients are getting overexposed.

CHAIRMAN PALESTRO: Thank you.

MS. KUBLER: Hi, good morning. Caitlin Kubler with the Society of Nuclear Medicine. We were also alerted to this and we have had a couple different conference calls. And we are working with ASNC. We are actually scheduled to send out a release to our members to remind them that this is standard of practice.

We did some informal surveying amongst our members, and the feedback that we got was positive, that most of our members are aware that this is standard of practice. The Lactated Ringers are not supposed to be used. The feedback that we did get where those situations occurred were incorrect or it was an accident, the person that grabbed the accidental Lactated Ringer and then did not notice that they had done so.

So we are sending that alert out with ASNC today just to remind our members that this is standard

of practice and to be aware. And if there is a situation that they have noticed a Lactated Ringer has been attached, to immediately stop the infusion. And of course, we work with Bracco to make sure that the language that we are sending out is accurate and what is required.

Thank you.

CHAIRMAN PALESTRO: Mr. Ouhib?

MEMBER OUHIB: Yeah. I guess my feeling is listening to this, should the manufacturer send out a notice that all users should respond to with some sort of a form that they will have to sign and confirm that they fully understand the process? This is something that probably needs to be done in my opinion.

CHAIRMAN PALESTRO: I'm not sure that that's the responsibility of the NRC to send out that sort of form. Mr. Einberg?

MR. EINBERG: I'm not sure. I was going to ask if Dr. O'Hara wanted to comment and see if that's an FDA responsibility.

MEMBER O'HARA: The FDA is looking -- has been looking into this issue. The FDA sent out the dear -- I call a dear doctor letter to inform people of the issue. And they are working with the sponsor

on various corrective actions.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions from the committee? Attendees in the room? Bridge line? Dr. Dilsizian, does that answer your question?

MEMBER DILSIZIAN: Yes. It seems to me that FDA is addressing this issue and that the medical events will be reported, the medical events. So that's, I guess, all that NRC can do at this point. Thank you.

CHAIRMAN PALESTRO: Dr. O'Hara?

MEMBER O'HARA: Also the medical events end up in the medical event database. It's at FDA too.

CHAIRMAN PALESTRO: Thank you. The next item on the agenda is the Yttrium-90 microspheres brachytherapy licensing guidance subcommittee report. It'll be presented by Dr. O'Hara.

MEMBER O'HARA: Next slide, please. I'd like to thank the subcommittee members, Dr. Dilsizian, Ms. Martin, Dr. Metter, Dr. Ouhib, and Dr. Schleipman for their efforts on this. And I would also like to thank Katie Tapp for being the expert. It occurred during a time when FDA was partially shut down, and I was not officially allowed to work on any of this. So

I do appreciate everybody's efforts.

For background, this is a manual intra-arterial brachytherapy implant with unique properties for primary and secondary hepatic malignancies. It's regulated under 10 CFR 35.1000 and titled, other medical uses of byproduct materials or radiation from byproduct materials. Next slide, please.

The licensing guidance was published in 2002 and revised in 2004, '07, '08, '11, and '16. October '16, the ACMUI provided comments on the initial draft revision 10 of the licensing guidance. Specific topics that were addressed included consideration of the elimination of Pathway 2, a manufacturer of the authorized user training, update of waste and disposal section and review Y-90 radiation safety issues in autopsy and cremation. Next slide, please.

November 2017, the NRC published a draft on revision 10 of the licensing guidance in the Federal Register for public comment. The comment period ended in January 2018. In July of 2018, the final Part 35 rule, Medical Use of Byproduct Material-Medical Events, Definitions, Training, Experience, and Clarifying Amendments, was issued. The rule went into effect January 14th, 2019 for NRC licensees. Oh,

sorry. I was waiting for you to change it.

The NRC agreement state working group updated the draft revision to licensing guidance to include the criteria for training and experience and medical events reporting, inventory requirement specifications, and waste disposal issues and align the guidance with Part 35 rule. After addressing public comments, the 2016 ACMUI comments, and the rule changes, the working group provided the subcommittee with revised draft guidance for its review and comment.

Our charge for this subcommittee was to review the staff's draft revision 10 of the Yttrium-90 microspheres brachytherapy source and devices, TheraSpheres and SIR-Spheres licensing guidance and to provide any comments or recommendations for change or acceptance of the guidance.

The subcommittee believes that this is a well-written and well-documented licensing guidance document. The subcommittee endorsed the draft revision 10 of the licensing guidance subject to the following changes.

We believe that the manufacturer's representative for training should be documented. We also feel that three hands-on cases for each type of

microsphere delivery device should be kept. The Y-90 spheres are slightly different, being glass or polymeric, and the delivery systems of the two devices are slightly different. We also feel the RSO familiarity would require all device uses at the facilities. So the RSO should be familiar with both manufacturers' devices.

Evaluation of a possible medical event for unexpected dose or activity to an organ or tissue other than the treatment site that is caused by catheter placement should be looked at as a medical event. Next slide, please.

Delineating the site to be treated more specifically is another recommendation, i.e., left hepatic lobe or right hepatic lobe. Adding activity, date of administration and route of administration should also be looked at. We question whether the term, intervention, should be defined in the licensing guidance document. And last, the explicit labeling should include patient's name, dose, date, and treatment site, if feasible. Next slide.

That's it. I'd like to make one point to our earlier discussion. The FDA is also under -- I was going to use the word, difficulty. But it's not a difficulty. The FDA does not -- we don't regulate the

practice of medicine. So if an interventionalist, at his or her own insistence, changes the catheter, we usually don't have much to say about that. And I just wanted to make that clear.

CHAIRMAN PALESTRO: Comments or question from the committee? Excuse me, from the subcommittee first. Comments or questions from the committee?

Dr. O'Hara, I have two questions regarding the slides, specific comments on the licensing guidance. Your first bullet says, defining the manufacturer's representative. I'm not sure I understood that. Does that mean stating the individual's name, or does it mean listing the qualifications of the individual or both?

MEMBER O'HARA: Listing the qualifications of the individual.

CHAIRMAN PALESTRO: Okay. And then my second question on that same slide, further down, it says, RSO familiarity required with all devices used at the facility. Is there a more precise or a more structured term other than familiarity? Because that could be taken in a lot of different ways.

MEMBER O'HARA: What I meant was that the RSO should be experienced with both delivery devices and on both manufacturers' devices.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions from the committee? From attendees in the room? Dr. Tapp?

DR. TAPP: Dr. O'Hara, I just had a quick clarification. On this slide and the comment -- the next slide, the delineation of the site to be treated more specifically. You said, for example, left hepatic lobe, right hepatic lobe. Are those just examples for the staff to consider, or are those the recommendation of the --

MEMBER O'HARA: Examples to consider.

DR. TAPP: Thank you.

CHAIRMAN PALESTRO: Any other comments or questions from attendees here in the room? From the bridge line?

MS. HOLIDAY: I'm not showing any.

CHAIRMAN PALESTRO: Ms. Holiday, at this point, do we move to -- all right.

MS. HOLIDAY: Yes. Is there a motion to approve the report and the recommendations as stated? Sure. Dr. Dilsizian has a question.

MEMBER DILSIZIAN: I guess bullet number three, how does the staff handle that? When we say, question whether the term, intervention, should be defined or not, how do we address that?

MS. HOLIDAY: Dr. Tapp, I think that question was directed for you.

DR. TAPP: Sure. I think in the written report, it was clear that it was a recommendation if the staff believed patient intervention was defined and to provide more definition into the guidance to make it clearer to the user. So the working group can add the patient intervention and clearer for the user to see.

CHAIRMAN PALESTRO: Dr. Metter?

VICE CHAIRMAN METTER: I have a question regarding the last bullet point there about the explicit labeling to include the patient name. Is that part of what we need to do, or is that -- can you just explain that whole bullet point there?

MEMBER O'HARA: There was discussion amongst the subcommittee that if it was feasible, all of that information should be provided from the person doing the intervention. I forgot the exact phraseology. But it wasn't clear that all of that information could be found in a small label. That's what I meant by feasible.

VICE CHAIRMAN METTER: Oh, the label?

MEMBER O'HARA: Yeah.

VICE CHAIRMAN METTER: You mean the

labeling of the dose?

MEMBER O'HARA: Yes.

VICE CHAIRMAN METTER: I understand. Thank you.

CHAIRMAN PALESTRO: Mr. Ouhib?

MEMBER OUHIB: Yes. This is actually just a clarification because there was a medical event where there were two different doses. And by accident, the wrong dose was actually administered to the wrong patient. And therefore, the vial should be explicitly labeled so that way people will not make those sorts of mistakes.

CHAIRMAN PALESTRO: Dr. Schleipman?

MEMBER SCHLEIPMAN: If I could just add, the current sentence prior to that recommendation read, label syringes and syringe radiation shields for the radioactive drug. And we felt perhaps that wasn't sufficient enough to promote patient safety as in that event. Added that, where feasible, it should also be identification of the patient receiving that dose.

CHAIRMAN PALESTRO: Thank you. Yes?

MS. FAIROBENT: Lynne Fairobent, member of the public. Dr. O'Hara, if we could go back and just revisit the bullet on the RSO familiarity again because I got more confused listening to your

clarification.

I'm not sure in all cases that the RSO would have experience with the devices. They would have familiarity with the rad protection and rad safety aspects of the devices. But I'm not sure what type of experience you are referring to with it because the RSO would not be the one that would be involved in the use, only simply in the rad safety and the rad protection of it.

MEMBER O'HARA: I think that is what the subcommittee members wanted was familiarity with both types of devices.

MS. FAIROBENT: Thank you.

CHAIRMAN PALESTRO: Mr. Green?

MEMBER GREEN: To follow up on the -- on Dr. Schleipman' s comment. It's line 16 where they say the patient label syringes and radiation syringe release and labels with the radioactive drug.

I just want to point out that neither of these SIRTS products are drugs. Their license is medical devices. And that term should be device type but not drug.

MEMBER O'HARA: Yes. That's correct.

CHAIRMAN PALESTRO: Thank you. Mr. Ouhib?

MEMBER OUHIB: Yeah. Just to comment on

the RSO. I think it's not necessarily using it per se. Because there are other people involved in that.

But the event -- in the event that there is a malfunction or something that went wrong, the RSO should understand the device itself. And be able to sort of evaluate and make some recommendation or intervene or what not.

CHAIRMAN PALESTRO: Thank you. Mr. Sheetz, not to put you -- I was just going to ask you if you would comment because you're the RSO representative here.

MEMBER SHEETZ: Thank you. I think it's very important for the RSO to understand the delivery apparatus. Understand all the plumbing, the connections, the limitations, catalysts that are appropriate for use with that device and so forth.

While they are not typically involved in the administration process, it's very important for them to understand that device. And all the aspects of it and how it works.

So, I support the Subcommittee's position on that.

CHAIRMAN PALESTRO: Thank you.

MS. COCKERHAM: This is Ashley Cockerham with Sirtex Medical. To add onto what Mr. Sheetz just

said.

The -- for Sirtex, they would provide manufacturer training specific to the RSO. And provide certification and documentation of that training specific to that device.

And they are very different devices with different training. And it would be completely different on the nuke med side and the administration as a whole.

So, I would think for each device is very specific. The training is different for both of them. And that the manufacturers are able to support that at least from the Sirtex side I can attest to that.

On the labeling, I wanted to make one quick comment on the syringe shields. And so I guess this would only apply on the SIR-Sphere side because there's an actual dose draw.

I think the way that the guidance is currently written, it's actually impractical to label. You would be covering what you're trying to see through the syringe shield. And that's not something that would actually go to the patient anyway.

So, to back up a step, a shipping vial would come in with SIR-Spheres in it. And they would remove using the syringe and syringe shield, a portion

of that specific to the patient.

And then they would inject that into another vial. All of those are clear. And you need to be able to see between one and three milliliters.

So these are small amounts. You need good visual on this. And if you're putting labels over all of that, it's not going into the patient room anyway.

You're drawing it up in the hot lab. Using it there. And then you inject it into another vial that's going to go actually into the patient room.

That vial you also need to be able to see. The physician is looking at it. And watching the meniscus. So, if you're putting labels, or putting things over this, that's going to be a significant problem just to be able to see what the admin -- what you're doing with the administration.

So, the shipping vial that comes in complies with the labeling. And I think the intent. But everything after that, I think we're kind of going into a space where maybe more discussion could be had around that labeling.

CHAIRMAN PALESTRO: Thank you. Mr. Ouhib?

MEMBER OUHIB: I guess my question is for the -- how would you avoid using the wrong dose for

the wrong patient?

If you have two cases that are sent back to back. And you have two doses sitting there, how would you -- what would the manufacturer recommend?

MS. COCKERHAM: I don't have a quick answer for you. I was going to say, I feel like there -- we need more discussion on it.

Because you've got a clear acrylic, you know, you've got 360 view on it. And you've got to be able to see it.

I don't know where you realistically put a label. Because you're watching the spheres as you're administering.

That visual feedback is -- is critically important. On the cart?

MEMBER OUHIB: I fully understand that. But I think whatever we introduce, we have to make sure that it does not introduce additional errors per se.

CHAIRMAN PALESTRO: Dr. Schleipman?

MEMBER SCHLEIPMAN: I would just agree that you do need to have that visual observation. But, there are transports --

MS. HOLIDAY: Dr. Schleipman, can you make sure your microphone is on?

MEMBER SCHLEIPMAN: I'm pushing the -- oh, there we go.

MS. HOLIDAY: Thank you.

MEMBER SCHLEIPMAN: Oh, totally agree that you need that visual monitoring. But, if we could make a -- perhaps make this less specific to vial.

But, at least that there is some patient identification with the transports shield or what have you.

MEMBER OUHIB: Perhaps further discussion is needed.

MS. HOLIDAY: Mr. Ouhib, for everyone's awareness, I do have someone on the webinar who is responding to this comment. His name is Matthew Williams.

And his response is that, they label the top of the vial shield. Thank you.

MS. COCKERHAM: Okay. You could do that with a sharpie on top.

CHAIRMAN PALESTRO: Okay. Any other? Dr. Ennis?

MEMBER ENNIS: I would imagine if we or NRC made a requirement, that the company would be imaginative and come up with another design for the device that would allow the important visualization.

But also, for reporting patient name and other things for safety purposes.

MS. COCKERHAM: That's a big ask to redesign it and get an FDA approved new device.

CHAIRMAN PALESTRO: Mr. Sheetz?

MEMBER SHEETZ: It's not clear to me if the Subcommittee endorses retaining the alternate pathway with the vendor training for the AUs. While they're implying the three cases should be retained, I'm not sure if there's -- I don't see a specific statement to that.

And if you could comment?

CHAIRMAN PALESTRO: Dr. O'Hara?

MEMBER O'HARA: I think, and I don't want to speak for the Subcommittee here, but I think we are.

CHAIRMAN PALESTRO: Comments from the Subcommittee? Mr. Sheetz?

MEMBER SHEETZ: I would like to make the recommendation that does the draft guidance imply or suggest removing the alternate pathway for vendor training of AUs. And so I would recommend that that AU pathway, alternate pathway remain.

And make this a very important pathway for the authorized users. I think they do a very thorough

job of training its equivalent or superior to being supervised by another authorized user.

So, I strongly endorse retention of the alternate pathway for Y-90 microsphere authorized users.

CHAIRMAN PALESTRO: Yes. Ms. Shober?

MEMBER SHOBER: Just a clarification on that, on Mr. Sheetz' comment. With the alternate pathway in number two that we're talking about, the previous versions of the guidance had allowed a physician to be named on a license before receiving the three cases.

And at this point, could those -- do the cases from the manufacturer need to happen -- does the authorized user need to get named on the license before those three cases happen?

Or are there sufficient preceptors around to -- we could allow that second pathway through the manufacturer. But, they would have to get those cases before being named on the license.

Is that -- so, it's a question about timing. It's very difficult from the regulator side to put someone on a license when they're not fully qualified, and then track whether or not someone is allowed to preceptor another position.

And so I guess my comment on that is that if we're talking about the second pathway, can that be structured so that manufacturers' training happens before the physician is named on the license? If the licensee chooses to use the manufacturer as the preceptoring cases.

CHAIRMAN PALESTRO: Dr. Tapp?

DR. TAPP: The draft guidance did not remove the manufacturers -- the pathway right now of the working group. It just added a little bit more requirements to that.

But they could still, the current draft is still allowing the license to occur. And then the three cases to happen.

They just had to be -- the three patient cases would have to be supervised by a physician. That was still in the draft.

CHAIRMAN PALESTRO: Any other comments? Questions?

MS. COCKERHAM: This is Ashley Cockerham again with Sirtex. I get to answer your question. Unequivocally yes.

They need the ability to be able to -- their AUs are not going to voluntarily on their own dime, visit other people's sites to train other

physicians. That's just not the reality of how it's going to happen.

And it's not imbedded in every fellowship program where every IR coming out is going to have the hands-on cases, especially with both products. Because their fellowship could be one product or the other.

And so your pool is going to be significantly limited of your fellows coming out with specific hands-on training.

So, really the only way to open a new site now where you're in the community hospitals and where you're out further, not in the major academic centers, that pathway has to exist. And the manufacturers support that by providing someone to supervise.

CHAIRMAN PALESTRO: Ms. Shober?

MEMBER SHOBER: Yes. I mean, that's what we expect from every other radiopharmaceutical therapy. So I'm not sure why the microsphere is a special case.

MS. COCKERHAM: I guess the difference is, if you're doing iodine, and I'm not a physician. I don't know if there are any physicians that could attest to the fellowship if you're coming through doing iodine therapy or another therapy.

But that's built into every fellowship. It's standardized across the programs. How would that look for Y-90 if you could explain how that was different?

I understand it's different.

CHAIRMAN PALESTRO: Dr. Metter?

VICE CHAIRMAN METTER: Well thyroid for thyroid therapy, which is originally 392 and 394, these are imbedded within the training experience for the radiologists and nuclear radiologists in nuclear medicine, the radiation oncologists.

So it's embedded within their training at the time of graduation. And so they have completed the required therapies before graduations.

And then they apply to be on licenses where they are -- they proceed to their practice.

So, I think Megan's question is, when are they put on the license? Is that it?

MEMBER SHOBER: Yes. And I -- I mean, we see this all the time with some of these other drugs that are parenteral administrations.

So the same situation where you have radiologists that want to do this at a community hospital, but we require those physicians to have the three cases somewhere. And then get on the license.

So, I just don't see this as a different situation.

MS. COCKERHAM: So, I guess the getting it somewhere is the issue from the physician perspective. You can't go to someone else's hospital.

You can't treat someone else's patient. You can't practice medicine in a hospital where you're not credentialed and where -- or in a state where you aren't authorized to practice medicine.

And so you have to treat your patient at your hospital with your radioactive materials license. And if you can't get the material on your license to get the experience, you're stuck in a situation of you can't go elsewhere and get it, and it can't be brought to you.

And so this was the whole between 2007, '08, '09, and then 2011, the major revision happened for -- to basically bridge that gap. To not have a regulatory barrier.

CHAIRMAN PALESTRO: Mr. Sheetz?

MEMBER SHEETZ: Yes. Maybe I was not clear previously. But that's the point I was trying to make. For a new device, you're at a brand-new facility, no one is an authorized user approved.

The only practical pathway is for the

vendor to come in and train that authorized user or that physician to become an authorized user. They actually do need to be named on the license so that they can perform the procedure prior to being supervised of doing their actual first live patient case.

The same thing happens with gamma knife, with the new model of the gamma knife that comes out, the Gamma Part 1000. The vendor does the training for the AU and the AMP.

They will do their first case with the vendor representatives there with no previous authorized user or AMP approved for that model of the gamma knife. So this is a very similar situation.

And that was my point on having the vendor training daily going into a new site and training the AU, have them named on the license from the Mock Three trials. They've been doing the patient cases then, again, supervised by the vendor, because they're not going to get another authorized user from another facility to come in.

And as I pointed out, they're not going to be able to go to another facility. They will not have medical privileges to do that case at another institution.

CHAIRMAN PALESTRO: Thank you Mr. Sheetz. Ms. Shober, does that clarify things for you?

MEMBER SHOBER: I mean, I hear what people are saying. I just don't agree with it.

CHAIRMAN PALESTRO: Thank you. Dr. Ennis?

MEMBER ENNIS: Just to help. I think the difference Megan, is that one is just an intravenous administration, which you can watch someone do, or have someone watch you do.

And then you can have an authorized user doing that for you. As opposed to actually technically doing the procedure.

There's just no way to get that experience unless you're actually doing it. And having a physician there doesn't really gain you anything, because you actually have to do it.

So, I think there is a distinction to be made between procedure type of training necessary versus an intravenous administration.

CHAIRMAN PALESTRO: Ms. Martin?

MEMBER MARTIN: What type of experience are you looking for to add that physician, if any, to a license? Because it is sort of the cart before the horse.

You have to add the physician with no

experience to the license with some provision (audio interruption) --

CHAIRMAN PALESTRO: Could you repeat that, Ms. Martin? It was cut off at the end.

MEMBER MARTIN: I was just wondering what type of provision, or how is the process approved to add a license, following up on Megan's question.

To add a physician with zero experience to a license to perform these procedures? Because that's what you're doing.

If they're waiting for a manufacturer to train them, you're having to add them to your license with no experience in sort of good faith that they're going to have a manufacturer's representative come in there and train them.

Is that --

CHAIRMAN PALESTRO: Dr. Tapp?

DR. TAPP: Yeah. This is Dr. Tapp. And this alternate pathway is both in the draft and in the current guidance.

There is training requirements before these three cases. All those training requirements have to be completed before they're issued on the license.

Those are the T&E hours, similar to other

modalities. There are manufacture or other AU training on the device itself.

And if they do not have the three patient cases prior to the license, they have to have three mock cases. So, after the license, is only the three actual real live patient cases.

To actually run through the full thing with a patient. So that's what's proposed after the license.

And it's currently in guidance. And that's what's in the draft.

CHAIRMAN PALESTRO: Ms. Martin, does that answer your question?

MEMBER MARTIN: Yes.

CHAIRMAN PALESTRO: Thank you. Mr. Ouhib?

MEMBER OUHIB: I just want to switch gears to another area that was of concern to me. And that is the cremation component of these patients.

When I first thought about it, I thought perhaps that took practice guidelines. But the more I think about it, the more I feel like maybe not.

And looking at patient instructions, for instance, prior to the procedure, if, you know, with -- and patient instructions are the rules. You have to provide patient instructions.

That's when you submit your -- and I think, and I really feel like that perhaps in the patient instructions, that should be in there.

That you cannot be cremated for such a procedure. Because all, you know, the items can be listed there.

And then therefore the patient would know up front, prior to the procedure, that that is an absolute no no. If their wish is to be cremated, therefore they can make a decision prior to the procedure, and it's not to go forward with it.

I really wrestled with that. But, I think I came to a conclusion that perhaps that should be part of the patient instructions.

CHAIRMAN PALESTRO: Any comments on that? Ms. Martin?

MEMBER MARTIN: I would support Mr. -- the comments made already about cremation. Because serving as an RSO, it -- in an active hospital in Los Angeles, we've had a number of our encounters with the various crematoriums and funeral services of disposal of the bodies.

And it would have been so much more clear if the patient had already -- if the family had made that decision up front before the patient was treated.

CHAIRMAN PALESTRO: Mr. Green?

MEMBER GREEN: Just to echo this, the comments. Very supportive of these comments regarding pre-need patient counseling.

We've seen a published article recently out of Scottsdale, Arizona Mayo Clinic regarding lutetium-177 and 117m in a patient that was treated at hospital A, but then demised at hospital B.

And went on and was cremated. And actually had, you know, contamination of the crematory unit as well as the individual who performed the cremation.

So, it should be advised a part -- it should be part of the counseling to the patient that with a certain period of time for this half-life of this isotope, that other means of -- other then cremation should be considered.

CHAIRMAN PALESTRO: Thank you. Any other comments? Questions? Dr. Diabes, Figueroa?

DR. DIABES: Dr. Said Diabes. And Reg Guide 8.39, we added a section that addresses this specific issue on cremation of bodies. That -- of patients have been treated and bodies that are radioactive.

And it adds more information,

instructions, a very vast amount of data on this issue, which the Subcommittee will see soon, or is seeing. It's reviewing at this moment.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions? Just as an aside before we move on, the issue of cremation has also come up with another radiopharmaceutical, lutetium-177.

And it's my plan to address the issue of cremation and disposal of the seeds at some point later on in this meeting. I don't want to get sidetracked now.

But I think it's an important issue. And it's not just limited to yttrium-90 microspheres. All right.

Any other comments or questions from the Committee? Attendees in the room? Bridge line?

(No response)

CHAIRMAN PALESTRO: At this point Ms. Holiday, we're ready to vote on the Subcommittee's report.

MS. HOLIDAY: We are ready for the vote.

CHAIRMAN PALESTRO: All right. May I have a motion to approve the report?

MEMBER GREEN: I move the report be approved with the change of the word drug to device.

CHAIRMAN PALESTRO: All right. Second?

MEMBER O'HARA: I'll second.

CHAIRMAN PALESTRO: All right. All in favor?

(Voting)

CHAIRMAN PALESTRO: Any opposed?

(Voting)

CHAIRMAN PALESTRO: Any abstentions?

(Voting)

CHAIRMAN PALESTRO: Thank you.

MS. HOLIDAY: Okay. So for the record, Mr. Green made the motion to approve the Subcommittee report with the changing of the word drug to device. The motion was seconded by Dr. O'Hara.

And it was unanimously approved by the Committee. Thank you.

CHAIRMAN PALESTRO: Thank you Ms. Holiday. Next item on the agenda is the Lucerno Dynamics LARA infiltration detection.

And Mr. Lattanze will provide an overview about a product that can assist with detecting nuclear medicine injection infiltrations. Mr. Lattanze?

MR. LATTANZE: Good morning. And thank you for the opportunity to present. I'm Ron Lattanze. I'm the CEO of Lucerno Dynamics.

At Lucerno, we've developed the device called LARA that provides insight into nuclear medicine injection infiltrations, which are sometimes referred to as extravasations.

I'll be covering a lot of material in a short amount of time. So, I've prepared comments that describe infiltrations, their incidence, and patient impact.

I'll also share evidence that infiltrations can nearly be eliminated. And will conclude with a request that the NRC and the ACMUI reconsider a 1980 decision regarding infiltrations.

In anticipation of questions after my comments, I'd like to introduce Dr. David Townsend, who is attending this meeting by phone. David is Lucerno's scientific advisor, and receives no compensation.

He's the co-inventor of the PET CT scanner and a fellow of IEEE. He's received many awards including the IEEE healthcare medal, and the SNMMI Paul C. Aebersold Award.

Also in attendance is Dr. Dan Sullivan, the former NCI Associate Director, Division of Cancer Treatment and Diagnosis, and the former Director of the NCI Cancer Imaging Program. He's a science

advisor for the RSNA, and a founder of the Quantitative Imaging Biomarkers Alliance.

Dan does consult with Lucerno to review our scientific paper submissions. David and Dan are here to answer any questions related to infiltration effects on nuclear medicine imaging studies and on patients in this era of precision medicine.

Most nuclear medicine studies are based on the assumption that the radiopharmaceutical is injected as a bolus, where the entire dose is delivered in just a few seconds. The injection is usually followed by a saline flush, and an uptake period prior to imaging.

This process tends to ensure that by the time the patient is imaged, the low background noise and high counts in organs or lesions of interest results in a high sensitive study.

An infiltration results when some or all of the dose intended for a patient's vein is injected into the tissue near the vein. This not only exposes this tissue to unintended radioactivity, it increases noise, reduces effective counts, and reduces image sensitivity. And the image quantification is incorrect and understated.

Because the injected dose is an input to

the image quantification formula, quality control measures are in place to ensure dose accuracy. Clocks are synchronized in nuclear medicine departments to account for radioactivity decay.

And technologists after injecting and flushing the delivery syringe, measure the dose left in the syringe, and subtract this amount for a net injected dose. These QC measures increase accuracy of the net dose approximately 1 to 2 percent.

Despite the accuracy that QC provides for the net dose, there remains the assumption that the net dose is actually delivered into the patient's circulation.

Until recently there's never been a routine monitoring to confirm the delivery into the circulation. This is important, because an infiltration can dwarf the effects of any errors resulting from the residual or unsynchronized clocks.

To better understand the NRC position on infiltration, I've reviewed the historical records. And thank you for the folks who put the ACMUI information on the website. That was very helpful.

In 1980, the NRC published a final rule on misadministration reporting requirements. From a review of the supplementary information supporting

this rule, here are my interpretations of the NRC conclusions regarding this administration.

The NRC emphasized their role in protecting patients from unintended radiation exposure, and from compromised diagnostic procedures that could impact care.

They emphasized reporting is needed to identify root cause. And then prevent recurrence. And stated that referring physicians and patients should be notified.

Interestingly, and in apparent to these conclusions, the NRC reached their decision that an infiltration should not be considered a misadministration. Their decision was supported by the following justification: infiltrations frequently occur in otherwise normal intravenous and intra-arterial injections. And are virtually impossible to avoid.

In 2002 the term misadministration was replaced with the term medical event in the regulations. Additionally, reporting and notification conditions and limits for these events were established in Subpart M.

In 2008, a Boston VA patient was infiltrated, aware of Subpart M, the VA reported the

medical event to the NRC, based on their estimate that the infiltration may have exceeded the effective dose equivalent limit to the tissue.

The NRC requested that the VA retract the report, referencing the 1980 decision that infiltration should not be considered a misadministration.

NRC shared this decision with the ACMUI. And according to the December 2008 meeting minutes, the ACMUI supported the NRC decision and rationale, and passed a motion that "at this time, NRC should continue its policy of not requiring infiltrations of diagnostic dosages to be reported as medical events."

Few centers have ever shared their infiltration rates. But the limited available global data support the idea that nuclear medicine infiltrations can occur frequently.

In the last decade, St. Louis University, Ohio State University, and the University of Santiago in Spain, have conducted six retrospective studies of PET CT injection infiltration rates, by reviewing images for infiltration evidence.

As states in one of these studies, rates are likely under-reported, because as you can see here, the injection site, like this infiltrated site

shown by the arrow, are often outside of the routine PET CT imaging field of view.

These six studies retrospectively reviewed 2,804 patient images, and found a 15.2 percent infiltration rate. The studies ranged from 3 percent to 23 percent.

In Alberta, nine centers each retrospectively reviewed 25 consecutive nuclear medicine bone scans for infiltrations on two separate occasions.

In the first review of 225 patients, the centers had an average infiltration rate of 15 percent. The centers ranged -- rates ranged from zero to 28 percent.

The review of another 225 patient injections had an average rate of 20 percent. And the rates ranged from 8 to 44 percent.

From 2016 to 2018, Lucerno worked with seven prestigious U.S. PET CT centers, including MD Anderson, UCLA, Wake Forest Baptist, and UT Knoxville on a project called LARA QI.

This quality improvement project used LARA, our new monitoring device, to help clinicians determine infiltration rates by prospectively comparing the injection arm to the other arm for

excess radiotracer, rather than retrospectively reviewing images.

While this ensures infiltrations are not missed due to the field of view detection issues, the QI project results also likely under-represent real infiltration rates. That's because of the observer or trial effect.

Before beginning the infiltration rate measurement in LARA QI, all technologists were trained on the importance of high quality injections. They knew that their injections were going to be monitored for infiltrated radioactivity.

In the LARA QI measurement phase, 2,431 patients were monitored. Investigators found a 6.2 percent infiltration rate. Centers' rates ranged from 2 to 16 percent. Interestingly, technologists' rates ranged from zero to 24 percent.

These results were presented at the SNMMI annual meeting last June. During the closing session, a distinguished subject matter expert summarizes in what is known as the highlights lecture, selected significant general nuclear medicine presentations from the hundreds shared at that meeting.

The LARA QI findings were one of the 12 presentations highlighted last year. The highlight's

lecture was published in the October issue of the Journal of Nuclear Medicine.

Without an easy to use detection process, technologists do not receive injection quality feedback, are not aware of infiltrations, and thus can't improve their technique. And when infiltrations are identified, there are no reporting requirements in place that lead to root cause investigation, quality improvement, and reduction in occurrence.

In summary of this slide, the data we've gathered support the NRC position that nuclear medicine injection infiltration rates appear to be high. But, do infiltrations matter?

We do not believe that all diagnostic infiltrations matter acutely or to the ensuing patient care. But some do matter. And they can matter in many ways.

In 1980, the NRC stated that a misadministration of a diagnostic radiopharmaceutical could compromise the effectiveness of the diagnostic procedure. They were right.

A literature review since then has identified over 50 references that show how infiltrations can harm or have harmed patients. These references are cited in a letter that I sent to the

NRC yesterday.

Examples of how infiltrations may negatively affect patent care include missed disease that impacts staging and treatment, wrong quantification that adversely affects longitudinal assessment scans and treatment planning, false positive results that lead to unnecessary invasive procedures, and repeated imaging that increases patient radiation exposure.

I could show you many cases, patient cases, but due to time limits, I'll only share two. Here is a published report of a lung lesion patient with an infiltrated PET CT study, the left image with the infiltration circled in red.

That when repeated three days later with study parameters kept as constant as possible, the image on the right revealed a missed metastatic lesion shown by the arrow. In the infiltrated image on the left, only the lung lesion in the circle was identified.

To eliminate the impact of the streaking artifacts that you see emanating from the infiltration and obscuring the torso, the patient was reimaged with his arms over his head just 30 minutes after this infiltrated image was produced. With a clear torso

view, the reading physician did not identify any other lesions.

The day three non-infiltrated image on the right revealed that the standardized uptake value of the in -- or the SUV of the infiltrated image lesion, had been understated by 44 percent. More importantly, it revealed right adrenal metastatic disease.

With the infiltrated image guiding treatment, as is commonly done in many centers today, the patient would have received local regional treatment rather than treatment for metastatic disease.

Informed of the day three scan results, the patient chose to spend his last five months in hospice.

The next patient had two PET CT scans performed five days apart in a controlled test/retest study. Imaging parameters were controlled. Four metastatic lesions were quantified. And the results from the two scans were compared.

This example is also important. The first reason is the dramatic effect an infiltration can have on quantification.

As you can see from the far right column, the infiltration caused the SUVs of the four lesions

to be understated between 33 and 54 percent. And the infiltrated image metabolic tumor volume value calculations were understated between 32 and 70 percent.

Another reason this case is important is because without the device, no one would have known to order a repeat scan. The injection site was in the left hand, outside the imaging field of view.

In such a scenario, an infiltrated scan would provide the wrong information in assessing disease progression, or in developing treatment plans. This latest example is not unusual.

From our monitoring of over 14 thousand injections to date, we know injection site locations, and estimate that about 50 percent of injection sites are out of the routine imaging field of view.

A meaningful infiltration outside of the field of view like the example I just shared, or an infiltration that is seen, but not included in the radiology report, may result in compromised care. And patients and treating physicians would be unaware.

Not only can infiltrations negatively affect care, many exceed the NRC reporting limits similar to the Boston VA case.

One medical event reporting limit is 0.15

Sievert effective dose equivalent to the tissue. We've worked with physicists, measured visible infiltrations, and used Monte Carlo simulations to show how diagnostic infiltrations can exceed Subpart M reporting and notification limits.

In the letter that I sent to the NRC yesterday, I've also provided engineering reports to support these findings.

Example A is the actual case I just presented, where the hand was out of the imaging field of view. By knowing the injected dose and the tumor quantification changes, by estimating the reabsorption process, we can calculate how much infiltrated radioactivity was in the hand at the time of imaging.

And that conservatively, the infiltration resulted in an effective dose equivalent to the tissue that exceeded the reporting limit by approximately 23 times.

Example B uses actual infiltration data and is very interesting. It shows how the effective dose equivalent of an infiltration can be easily underestimated if one is just using static PET images.

In this example, at the time of imaging, 107 minutes post injection, there was a relatively low amount of activity left at the injection site.

Approximately 100 micro curies.

However, by using the infiltration resolution data with known infiltration volume data, we can estimate that an infiltration that may appear minor on imaging, can actually exceed reporting limits. Again, not all diagnostic radiopharmaceutical infiltrations will matter to patients, but some will.

Some infiltrations will exceed medical event reporting limits, and should be reported. And the referring physicians and the patients should be notified.

There is good news. Infiltrations are no longer virtually impossible to avoid. And infiltration rates can be dramatically improved.

Other healthcare injection processes monitor and report infiltrations. Over the last 40 plus years, quality improvement projects have monitored more than one million chemotherapy injections and infiltration rates have continued to decline.

A 2017 QI project involved nearly 740 thousand patients. And found a 0.18 percent infiltration rate for the peripheral IV chemotherapy injection. So that's an apples to apples comparison of PET CT.

Hundreds of thousands of contrast CT injections have also been studied. And because of monitoring and reporting, infiltration rates have continued to decline.

Another recent QI project monitored over 450 thousand CT injections, and found a 0.24 percent infiltration rate. The 1980 belief which was reaffirmed in 2008, is no longer accurate in 2019.

Infiltrations are not virtually impossible to avoid today. Now a device that uses sensors placed on the arms, and that adds just 20 seconds to the patient experience, can routinely help clinicians detect infiltrations before imaging.

As a result, centers can provide individual quality control for each injection with time activity curves, or TACs like this one, indicating no presence of excess radiotracers at the injection site after about 30 seconds post-injection.

Here you can see the injection arm sensor's black curve showing the bolus raise. And then quickly drop to the level of activity represented by the red arm, the referenced arm's red curve.

But not all TACs look ideal like this one. Unfortunately, many look like this. Where the injection arm's curve -- the injection arm's curve

never drops to the level of the reference arm, indicating the presence of excess radiotracers at the injection site.

Just as importantly, by using the device's quality assurance functions, centers can identify factors associated with their infiltrations. And then put improvement plans in place to correct them.

Following a QI -- following a QI process can lead to very low infiltration rates, as we've seen in other healthcare settings. In fact, four of the seven LARA QI centers tried to improve their infiltration rates.

As you can see by the columns highlighted in red font, each center improved. Their aggregated rate had a statistically significant decrease from 8.9 percent to 4.6 percent, with the p-value of less than 0.0001.

And even better news, measuring and improving results can be accomplished in approximately six to eight months. In fact now, some of these centers are in sight of 1 percent infiltration rates.

These results were also presented at the annual meeting last year. Their presentation was also one of the 12 that were selected for the highlights lecture.

It appears to us that addressing the infiltration issue is consistent with the goals of all interested parties. Minimizing infiltration seems consistent with the previously stated NRC goals of protecting patients from unnecessary radiation exposure.

As well as from compromised diagnostic studies of reporting determining causes and preventing recurrence. And of ensuring referring physicians and patients are notified of medical events that exceed reportable limits. Limits that I will add, that should be agnostic to whether the source is a diagnostic or therapeutic radiopharmaceutical.

Identifying and reporting infiltrations are also in the best interest of nuclear medicine and molecular imaging societies. As the NRC knows, the importance of patient safety was a consistent message throughout recent public comments received by the NRC with respect to the training and experience requirements for authorized users.

The societies are also focused on precision medicine. Infiltrations lead to imprecise medicine.

Societies are also aware that in the future alpha and beta therapeutic injections, with

their longer half-lives, will play an increasingly important role in medicine. And they know that the same personnel delivering diagnostic radiopharmaceuticals today, will be delivering radio therapeutics tomorrow.

And the SNMMI knows that infiltrations have no place in their quality of practice initiative. The goal of which is to ensure that members are known for high quality, value driven performance, and delivery of patient-centered nuclear medicine practice.

And when we deal with individual centers, the vast majority of technologists actually want feedback that they are doing injections properly. Physicists want reproducible imaging.

Safety officers want radioactive material used optimally and safely. And most interpreting and treating physicians we've spoken to, want the highest quality imaging to help treat their patients.

Finally, and most importantly, are the patients. It's their life and their care. We've met with them, their families, their friends, and patient advocacy groups. Their message is clear, and they all want the highest quality nuclear medicine injections.

On that point, let me share my last slide.

Now that there is awareness that infiltrations are avoidable, that they can harm some patients, and that they can exceed reporting limits, we are asking the NRC and the ACMUI to review the information I sent to the NRC yesterday, and reevaluate the 1980 infiltration policy.

Infiltrations that meet Subpart M reporting and notification criteria should be reported. This will lead to a reduction in infiltrations and to an improvement in patient care.

Thank you for your attention. And we welcome any questions you have.

CHAIRMAN PALESTRO: Thank you Mr. Lattanze. Any questions from the ACMUI? Dr. Dilsizian?

MEMBER DILSIZIAN: Thank you very much for the nice presentation. I guess I have several comments about your presentation.

But I'm going to start from agreeing with you. That QA/QC requires that you properly inject the dose.

And for the two examples that you gave, chemotherapy, and I'm going to talk about cardiology, when we're injecting radiotracers with exercise, we make sure that there's a blood return when you have an

IV line. Because you don't want to inject the radiotracer and you'll probably get peak exercise.

Also for absolute blood flow measurement, it's critical that when we're giving a bolus injection that it's going to the patient.

MR. LATTANZE: Absolutely.

MEMBER DILSIZIAN: So, but I would like to make the distinction between the type of examples that you gave. To routine imaging for bone scan that's a, where you direct inject the radiotracer to the vein, there's no IV line.

And so those are the type of things I think we're mixing the two information. But infiltration from radio diagnostic studies, whether it's common or infrequent to really reporting them as -- from the regulatory body, I'm just questioning that.

Now, let me address two of the things you have presented. The arm down patient that you made a big picture out of, --

MR. LATTANZE: Yes.

MEMBER DILSIZIAN: It would never happen in most institutions. The arm should never be next to it to miss that adrenal gland. It should have been up anyway.

Number two, so that's not really a good example. It's misleading. I mean, no one would accept that. If I saw that image, I'd say repeat the image with the arm up.

MR. LATTANZE: They did repeat the image with the arm up 30 minutes later.

MEMBER DILSIZIAN: Yes.

MR. LATTANZE: They had extended uptake in the SUV. And there was no evidence of that metastatically.

MEMBER DILSIZIAN: No, what I was saying, the first image, if they --

MR. LATTANZE: Yes. That -- that -- no --

MEMBER DILSIZIAN: They misproperly identified it. And the other thing you made a big deal about the SUVs and all.

You know, I read nuclear medicine studies every day. You gave a difference between seven versus 11, 28 versus 41, six versus 11. Clinically irrelevant. They're all hot.

It doesn't matter if I say to you it's seven versus 11, that doesn't change anything but therapy. So yes, it does affect SUVs. It doesn't change patient management. We're making a bigger deal than it is.

And the other thing, I'd like to caution you using the word can harm or have harmed patients. It's under some dramatic and exaggerated statements.

I agree with you that QA/QC we should do our best to give the dose that's necessary to the patient. I doubt it that it really has harmed or have harmed patients.

I mean, the examples that you gave are maybe rare, not common. And the percentages that you give, as an SNMMI incoming President, I agree with you. We should not do those.

But, I don't think that these are significant enough events that should be reported routinely, except when the whole dose for example, if I'm giving a thallium dose, --

MR. LATTANZE: Um-hum.

MEMBER DILSIZIAN: And everything went to the arm, I know that there's going to be skin issues. Those are reportable. But not the routine ones that we do every day.

MR. LATTANZE: So, is that done? Okay. So, the question about harm, when I sent the letter yesterday, I cited the 50 references that are peer reviewed. That they're the ones that state how patients have been harmed or can be harmed. So

that's, I'm just using what the references state.

The SUV use, and I hear this frequently, because I talk to oncologists as well as the nuclear medicine physicians. When oncologists are using the SUV, and it maybe not what nuclear medicine physicians want, in longitudinal assessment scans, they're making decisions often whether they're seeing a change in response.

And so according to the PERCIST criteria, a lot of these changes would actually be more than the PERCIST criteria. And they would make a decision that the patients have responded or not.

And so I think that while I understand very well the variability in the SUV measurements, the fact that the quality of the injection is not being reported to the physician, doesn't give them the opportunity to understand that they might have even more variability then they would normally expect.

So, the oncologist, and I do talk to a lot of oncologists, they are completely unaware that patients are being infiltrated.

Your comment about the -- the arms up, and getting an IV, getting blood drawn, all the centers that we go into, very few -- nobody does a straight stick anymore that we've seen.

They use the butterfly or the IV access. And every technologist will tell you, I look for blood in my return.

And we've been in cardiology centers as well, and have seen very similar infiltration rates in both stress and rest exams. That they will actually draw blood back in.

And they will tell you, I am sure that this is a good injection. And then when they look at the image, they'll see that they've infiltrated.

So, I understand what you're saying. I think it's actually my experience, we've been in some other centers as well, the occurrence is far more frequently than you think.

That's our experience.

CHAIRMAN PALESTRO: Any other comments or questions? Mr. Ouhib?

MEMBER OUHIB: Yeah. I have to apologize, this is certainly not my expertise. But listening to this presentation, it sounds to me like this is a practice of medicine more than anything else.

And society should be addressing that. Not a regulatory item.

MR. LATTANZE: Yes. I agree that the -- what we found is that the main difference between

chemotherapy injections for example, which is a very similar patient population to oncology PET CT patients, is that it's a practice of -- that you have trained clinical nurses that do chemotherapy injections for a living, and technologists don't.

But once they get the feedback, the technologists can get as good as those patients, or as those nurses. However, it's not a regulatory issue unless the dose that is affecting the tissue is so high that you're exceeding that Subpart M reporting limits.

So, by not reporting those doses that are very high to the NRC, you don't know when patients are being affected and when they're not.

Does that make sense? That's the regulatory piece. Not the -- not the training piece that can be fixed very quickly. Well, within six or eight months.

CHAIRMAN PALESTRO: Dr. O'Hara?

MEMBER O'HARA: There could be a regulatory piece as well, depending on how the firm advertises this product.

MR. LATTANZE: Absolutely. And I think we met back in December, Dr. O'Hara at the FDA.

And we're very conscious of, you know,

what the device does is it tells a clinician, it helps the clinician detect whether they have an infiltration or not. It does not tell them they have an infiltration.

CHAIRMAN PALESTRO: Any other comments or questions Mr. Ouhib? Dr. Ennis?

MEMBER ENNIS: My question isn't really directly related to your request, regulatory request. But, more of a, I guess curiosity about your product, if you'll indulge me.

MR. LATTANZE: Sure.

MEMBER ENNIS: So if you could explain why CT infiltration rates and chemotherapy -- you alluded to the chemotherapy one, are so low compared to what you seem to be seeing with nuclear medicine infiltration rates, A.

And B, why would a nuclear medicine department need your device if CT and chemo have figured out how to decrease infiltration rates without a chemo detection device, or a --

MR. LATTANZE: That's great.

MEMBER ENNIS: Contra-detection device?

MR. LATTANZE: That's great. The different -- the reason that chemotherapy and contrast CT rates are so much better then nuclear medicine

rates that we've seen so far is, for a lot of reasons.

One is -- the primary reason is the detection issue. So, when a chemotherapy patient is infiltrated, they know they've been infiltrated, because it's a vesicant and does an extravasation.

There's immediate feedback to the nurse that that patient has been infiltrated. In a contrast CT, the volumes are so large you actually see a swelling in the arm. So, there's feedback.

Unfortunately for nuclear medicine, there has been -- the technologists have never gotten the feedback, because they're injecting such small doses that they do not see that.

We have had one patient say that they felt a burning sensation. And it was a large dose infiltration. Larger than the one that I showed earlier.

But that's the only case we've ever heard of where a patient complained about a burning sensation. So, the patients don't know. The technologists don't know.

The injection sites are often out of the imaging field of view. And the other thing we've known is that infiltrations resolve during the time -- you know, during the 60 to 70 minutes of uptake time.

So when physicians do see them on the static pad image, they actually are seeing something that's much smaller than what it was during the uptake period. And so the detection issue is the main difference.

Your second question was well, once they can detect it and can solve their problem, do they need to continue to use the product? You know, is there a need for the product?

And that's an issue that the market will solve later. But what we've experienced in all the centers that have gone on to use the device, is because this is a human to human interaction, you know, you have this sophisticated PET CT technology that's so amazing, but it still relies on the human to human interaction between a technologist and the patient's arm, sometimes with very bad veins.

Is that if one of those humans, the technologist is not having a good day, they're -- we've seen actually where some of the best technologists at a center for over a year, will all of a sudden go and infiltrate 27 percent of their patients over the next nine working days. We've seen that example.

Some things happen because they're human.

And so, the centers have chosen to continue to use it as an ongoing monitoring process.

Also, because nuclear medicine is growing. And new technologists are coming in. And there is no training for this process.

The technologists are two year physicist students. They receive their training on the job from other technologists.

And so all the centers that have used the device continue to use the device, because they realize that there's a need to keep making sure that as people move around, that they're doing great injections.

CHAIRMAN PALESTRO: Any other comments or questions? Dr. Metter?

VICE CHAIRMAN METTER: Thank you for your presentation. It was very -- very informative.

One thing I would like to caution, is that the volume of CT studies are clearly far more, and performed 24 hours a day, usually in an institution, versus nuclear medicine, which is generally performed during the working hours of 8:00 to 5:00.

And so you're looking at perhaps like at a good day for example at our institution, maybe there are 30 studies in nuclear medicine, versus three

hundred or more for CT.

So if you looked at that, and if you look at a 25 percent infiltration rate, so you have, let's say, seven out of 30, versus 75 out of 300.

So, I caution you regarding that. Because the numbers, the smaller the numbers, an error in one area can raise that percentage.

MR. LATTANZE: Yes.

CHAIRMAN PALESTRO: Mr. Sheetz?

MEMBER SHEETZ: Thank you for an interesting presentation. I have -- was surprised by the infiltration rates that you presented on slide five. You don't have to go back to it.

But, it looks like you took a -- pulled the data and took a number of studies for different centers, took their infiltration rates, and then took the median value as your, you know, the reported rate as an average for those centers.

Did you look to normalize that for the end number for the actual number of patients? Because some centers may have had ten patients and had an infiltration rate of say 44 percent.

Another center may have had a thousand patients and an infiltration rate of two.

MR. LATTANZE: Yes.

MEMBER SHEETZ: And so by just taking the median value of those rates per centers, it could skew the percentage rates.

MR. LATTANZE: Yes. So, I like to often report, you know, that -- the -- both values. And so the -- we have seen that some centers are at the 2 to 3 percent rate. And they are usually the higher volume centers.

We've also seen some high volume centers have a 13 percent rate. And so, all that information will be in our -- once that LARA QI paper publishes, you'll be able to see all that data.

And you know, also sorry, one last comment. The other interesting thing is, oftentimes at a center, many of the technologists can be very, very low at the infiltration rate. But then you can have one that is a 25 or 24 percent infiltration rate technique, so.

CHAIRMAN PALESTRO: Ms. Martin?

MEMBER MARTIN: I would just comment following up sort of on what Dr. Metter said. Most facilities do not have anyone around that can make these calculations routinely to decide whether that infiltrate is at a dose of .5 Sieverts.

I was just wondering, who would make those

calculations routinely in a facility if it were required? Because that is not something that is routinely done by either nuclear medicine physicists, which are not necessarily on staff, unless you're a very large facility.

I don't see how that could routinely be happening.

MR. LATTANZE: So, I'm not sure how to answer that question. In the centers where we've had those calculations performed, the physicist involved actually has done the calculation.

MEMBER MARTIN: Um-hum.

MR. LATTANZE: But, you know, I get this question a lot when I go into centers that say well, you know, first they say I don't think I have an infiltration problem.

And then when they finally say, well maybe I do. And we start looking at it, their real concern is, well, if I'm infiltrating at 15 or 20 percent of the time and I have to reschedule these patients, then it's a problem.

And what I try to emphasize is that it's only a problem for a very short period of time. Once you start, like any quality improvement project, any time you want to improve something, if you start to

measure it, the improvements can happen very quickly.

And so, I would suspect that while the rates are high today, based on our experience in the centers that we've been in, the rates could be dramatically better very quickly if you begin to actually start detecting and reporting them.

Any time you put that process in place, it causes improvement. So then I don't think it's a big problem, because very few of the -- if you can reduce the infiltrations dramatically, then even fewer will be moderate or significant infiltrations what would require reporting.

CHAIRMAN PALESTRO: Any other comments or questions from the Committee? Mr. Green?

MEMBER GREEN: I think it was a very interesting presentation. You know, it's been, you pointed out and it's been --

MS. HOLIDAY: Rich, can you bring the microphone closer?

MEMBER GREEN: You pointed out, and it's been repeated by members of the Committee that not all nuclear procedures are quantitative. But PET with SUV are.

And I just wanted to point out that not all nuclear medicine and radiopharmaceuticals are

injected intravenously. There are now in the last five years, a drug which is indicative for intradermal administration, has also subcutaneous administration, and one that's intrathecal.

So, if we consider things that would require reporting, you know, not all drugs are intravenous. You know there are five that are oral, and two that are inhaled. But I'm excluding those.

But, via needle, not everything goes in a vein.

CHAIRMAN PALESTRO: Mr. Ouhib?

MEMBER OUHIB: Yeah. Just looking at your request here. So, moving forward with required reporting of infiltrations.

I guess I'm trying to understand, what do you think that will eventually achieve? People paying more attention?

And if so, wouldn't that be more like education and training and understanding that? Versus --

MR. LATTANZE: So the current NRC policy is that if a patient is injected and they're infiltrated, and the dose exceeds the reporting limits, is that that is not considered a misadministration, even though it could, you know, it

is a misadministration.

It's not considered one because there was the belief back in 1980 that they're virtually impossible to avoid. So, my request is, to the NRC, to say, well, we know now that they are not virtually possible to avoid.

They may have been back then. And when you go back and look at chemotherapy rates and contrast CT rates from the 1980s, they were significantly higher then than they are today, too.

So my request is, if you change your policy and say that if you misadminister an injection, and you expose a patient to above the reporting limits in Subpart M, that that should be a reportable event.

Whether it's a therapeutic infiltration, or a diagnostic infiltration, if it's receiving -- if a hand -- if tissue in a hand is receiving 11 Sieverts over a period of, you know, during a two-hour reabsorption process that should likely be a reportable event.

And if you do that, then people will start to monitor their injections. And they will actually improve their injections. Just like we've seen in every center that we've been in.

You know, until it -- you know, we've had

a lot of physicians tell me that, you know, we know we should be doing this, but we're not going to do it until we're told to do it. Until it's required to do.

And I think when you begin to monitor process, you'll see the results come down. And that will be better for patients.

CHAIRMAN PALESTRO: Mr. Sheetz?

MEMBER SHEETZ: I'm going to go back to my surprise on the infiltration rates. And I do want to point out that the gamma cameras and the PET scanners are very, very sensitive, so and a 15 millicurie injection, if only 1 microcurie or fraction of that leaks or infiltrates, you will visualize that.

So, I'm not sure, did you try to quantify any of your infiltrations? Or if you visualize it, it's an infiltration.

And I will say, it would probably not be uncommon to be able to visualize something. But, the actual amount of activity in a dose related to that would be inconsequential, of no real risk or harm.

Certainly if you extravasated the entire dose, that would be of concern. And you would want to be able to monitor, detect, or know that.

So, I'm not sure how you would try to quantify or evaluate whether this was a slight leakage

of a microcurie or so. Or we extravasated multiple millicuries.

MR. LATTANZE: Yeah. That's a great question. So, as Dr. O'Hara pointed out, you know, again we're not -- all our device can tell you is whether there is excess radiotracer. And then we leave it to the clinicians to determine how much is there.

Often times to your point, they'll see like a trace of a, you know, what appears to be a little bit of radiotracer. Our device would pick that up. But the time activity curve would be very, very low above the reference arm.

It's the ones that are like the ones that I've shown you before that were considered to be in sitting down with the physicians at the site. And when often times they had physicists, get involved and try to image the injection site if it was available, if the injection site was in the field of view. And in those cases, the clinicians determined that that was the infiltration.

But, I think the University of Santiago in Spain example, they had an 18 percent infiltration rate. And of those they found that they had a very small percent that were moderate or significant.

And you know, my point is, if you're only looking at a static image, all you're seeing is what was taken at 70 minutes. You don't know whether it was, you know, dramatically worse than that beforehand.

So you'd need to have some idea of what happened during the uptake period. If that makes sense.

CHAIRMAN PALESTRO: All right. Thank you. Any comments or questions from attendees in the room?

(No response)

CHAIRMAN PALESTRO: On the bridge line?

(No response)

CHAIRMAN PALESTRO: All right. At this point we're already running behind. And I'd like to end the discussion for the moment on this topic.

However, it's an interesting issue that's been raised. And it was last addressed by the NRC in 1980, which is almost 40 years ago.

And at that time I don't -- don't know if there were any intravenously administered therapeutic agents. There certainly are several since then.

And the vast majority, if not all of the intravenously administered diagnostic agents were technetium based. And now we've got indium-based

agents, iodine-based agents, and so forth.

So, with that in mind, I'm going to form a Subcommittee to reevaluate the 1980 NRC decision. And you may come away with the same conclusion.

I have no idea. And this has nothing to do with the device that Mr. Lattanze is talking about. That's not part of this.

And so I'd like the Subcommittee to charge -- the Subcommittee is to reevaluate the NRC's 1980 infiltration position. And to report back to us at the September meeting.

I'm going to ask that Ms. Martin chair this Committee, Subcommittee, excuse me. And members will include Mr. Green, Ms. Shober, Mr. Sheetz, and Dr. Dilsizian.

MR. LATTANZE: Thank you very much.

CHAIR PALESTRO: Thank you. And at this time we will take a short break and resume -- let's try to resume at five to 11:00 so we can get ourselves back on schedule. Thank you.

MR. EINBERG: But excuse me, before we break, Dr. Palestro, would you like to have a patients' rights advocate on the subcommittee also? Because I think this has impacts for patients as well.

MS. HOLIDAY: Mr. Einberg, Ms. Weil's term

ends in August. So she will not be here for the September meeting.

However, I do recognize that the Subcommittee would start their work prior to the September meeting. Just to throw that out there for consideration.

MR. EINBERG: To the extent that she can participate while the deliberations are going on, I would recommend that.

CHAIRMAN PALESTRO: I think that's an excellent suggestion. I appreciate that. Ms. Weil?

MEMBER WEIL: Yes.

CHAIRMAN PALESTRO: You will?

MEMBER WEIL: I will.

(Laughter)

CHAIRMAN PALESTRO: Thank you. Okay. We're adjourned for ten minutes.

(Whereupon, the above-entitled matter went off the record at 10:44 a.m. and resumed at 10:56 a.m.)

CHAIRMAN PALESTRO: I'm going to call the session to order, please, to resume, so we can try to get back on schedule.

MS. HOLIDAY: Dr. Palestro just requested that ACMUI members return to your respective seats.

We're getting ready to restart.

CHAIRMAN PALESTRO: All right, and we're going to resume with item number six on the agenda for today, a summary of the changes to 10 CFR Part 35, and it will be presented by Ms. Lisa Dimmick from the NRC. Thank you.

MS. DIMMICK: Thank you, and good morning, everyone. So I guess I can thank the meeting planners for not putting this talk after the lunch break because I know, the regulation changes, how exciting is that? So anyway, we'll go ahead and get started.

So this presentation will kind of quickly step through the final rule changes, largely for 10 CFR Part 35, and there were some changes impacting Parts 30 and 32, but largely Part 35.

So the objective today is to present to you a summary of the rule changes that became effective January 14, 2019. Just to note that Part 35 was last amended in its entirety back in 2002, so this rule change or set of changes really encompasses a number of clarifications that needed to be made for that 2002 rule.

So this was really a long term rule in the making. There's a lot of history with this rule. There's a lot of involvement with ACMUI on this rule

change, especially in the area of permanent implant brachytherapy and the medical event definitions.

The major changes to the rule do address impacts for permanent implant brachytherapy, medical event reporting, and notification. The rule also now names an associate radiation safety officer or officers on a medical license.

There are generic changes to training and experience requirements for all individuals, and there is now a new frequency for reporting of, well, a new frequency for testing the Moly breakthrough in your Moly/Tech generators, as well as the reporting of failed generators.

So those are the major changes that most people are aware about. However, there are changes throughout the rule, and so in that sense, the rule changes were substantive because there were a lot of changes.

So we can kind of break down our talk this morning on the rule changes in 11 broad areas of the Part 35 regulation, so we're going to touch on the generator changes, the changes or the new associate RSO, as well as the ophthalmic physicist.

There were some changes impacting emerging technologies, changes in notifications, and some of

the rule changes or areas of interest are actually found in the notification section of the regulation. We have changes to manual brachytherapy, training and experience.

There are some changes in diagnostic medical uses, also in the 10 CFR 35.300, radiopharmaceutical requiring a written directive, sealed source and device registry, vendor training, and Gamma Knife.

So we're going to talk just basically about some of these rule changes, and in some areas, I'll try to give a little bit more perspective or insight as to why that rule was changed.

Okay, so for generators, the breakthrough for the Moly/Tech generator is now to be required for each generator elution. Before, the rule required just the first elution of the day with that generator, but now it's for each generator elution the Moly/Technetium ratio needs to be checked.

Also, if the breakthrough limits for the Moly/Tech generators, as well as the strontium rubidium generators, and we also carry this into the 35.1000 guidance for the germanium/gallium generators, if you have a breakthrough in excess of the limits, there is a requirement now to report that as a failed

generator to both the NRC and the distributor.

So the rule change basically changes the frequency for testing the Moly/Tech breakthrough, and then there is the reporting requirement for failed generators.

So the reporting requirement for the failed generators is a telephone report within seven calendar days, and that telephone report needs to include the manufacturer, model number, and serial number or lot number of the generator, the results of the measurement, the date of the measurement, and whether the dosages were administered to patients or human research subjects when the distributor was notified and the action taken.

A follow up 30-day report is also required to note any actions taken by the licensee, also the patient dose assessment and the methodology used to make that dose assessment if the eluate was administered to the patient.

So when we were talking earlier about the strontium rubidium generator and the breakthrough, so now we have a new regulation that will help filter or provide a path to report those situations that wasn't maybe previously present in the regulations.

The regulations now define an Associate

Radiation Safety Officer. Here, it will be ARSO, and we also identify an ophthalmic physicist. So these terms are defined in the regulation. These are new definitions in the regulations.

There are some changes to preceptors for the ARSO, and also some other requirements for the ARSO that I'll mention here in a moment, and it provides some clarifications for the licensee, the radiation safety officer, and the ARSO.

So the changes in the regulations are found, some of the changes here are found in 35.50, 10 CFR 35.50. It now includes training requirements for the radiation safety officer and associate radiation safety officer.

The changes made clarify the basic training and experience requirements are basically the same for the RSO and the ARSO. The regulations also permit the ARSO to provide written attestation.

So for example, the ARSO authorized for maybe 10 CFR 35.100 uses on a license and that license is authorized for 35.100 and 35.200 uses. That ARSO could provide the attestation for another ARSO or a radiation safety officer for the 35.100 uses because that's the uses for which that ARSO is authorized. So the message here is that the ARSO can provide written

attestation for another RSO or ARSO.

This regulation also fixed a few issues in the previous regulation. It does now permit -- so if an individual is seeking to be a new authorized user and a radiation safety officer on a new license, that can occur.

Previously, when a new license was issued, you could not make the individual both an AU and an RSO at the same time. Now with the rule, that can happen for those new licenses where the AU will also be the RSO.

The regulation, the new regulation also fixes and permits authorized individuals to use authorized status to be an RSO on a different license for the same use for which the individual is authorized.

Previously, the authorized individuals had to be listed on the same license for which they are seeking RSO status. So the rule made some clarifications and provided some flexibilities that weren't previously found in the rule.

The ophthalmic physicist, this is a new role, and there are specified tasks for the ophthalmic physicist, as well as certain training criteria that needs to be met for the ophthalmic physicist. The

rule also clarifies the expected duties for the authorized medical physicist and that of the ophthalmic physicist.

Emerging technologies, so with regard to 10 CFR 35.1000, which is the other uses of byproduct material, we often refer to this as emerging medical technologies, there is a link to 35.1000 to 35.12. So 35.12 clarified information for the 35.1000 medical use applications.

So now, in addition to the regulations in 35.12, an application for a license or amendment for medical use of byproduct material as described in 35.1000 must include any additional aspects of the medical use of the material that are not addressed in or are different from other parts, the other subparts of 10 CFR, including general information, administrative requirements, technical requirements, records, and reports, also the identification and commitment to follow the applicable radiation safety program requirements that are appropriate for that new technology that are found in the other medical modalities, in addition, if there is specific information that should be included regarding radiation safety precautions and instructions for those uses under 35.1000 or the methodology for dose

measurement for doses to be administered to patients or human research subjects, as well as calibration, maintenance, and repair of instruments. So the regulation makes the link between 35.1000 and 35.12 more clear.

So notifications is an interesting section of the regulations because this is where it describes what amendments or notifications are required, so in this section are some of the areas that we've already mentioned regarding, for example, the ophthalmic physicist.

So for the ophthalmic physicists was added to the amendment section in 35.13. The section of the regulation now allows the licensee to allow an ophthalmic physicist, in addition to an AU, AMP, or ANP to work without an amendment request provided the individual is already listed as an ophthalmic physicist on a license.

Also in the notification, the ARSO was added to the amendment section. This section of the regulation requires the licensee to submit and receive approval for an amendment before it permits anyone to work as an ARSO or before the RSO assigns duties and tasks to that ARSO that differ from those tasks for which the individual is authorized on the license.

The notifications also permit the licensee to receive a sealed source from a different manufacturer or to receive a different model number than authorized by its license. So if the sealed source is used in manual brachytherapy, it's listed in the SS&D and is in a quantity for an isotope already listed by the license.

So this rule uses the provisions of the notification process to give manual brachytherapy licensees the flexibility to change manufacturers or models of a source for which they're authorized, or a radionuclide for which they're authorized without having to wait for an approval of an amendment.

The notifications, there's also, in this section, the regulations were revised to remove the requirement for preceptor attestation for board certified individuals. The regulation continues to require submission of a copy of the board certification and documentation of additional training of clinical case work for authorized users under 10 CFR 35.300 or the additional training for an AU or ANP under 35.600.

And then last, I wanted to note that with regard to exemptions regarding Type A specific licensee of broad scope, the broad scope licensee is

exempted from certain notification processes such that it can name its own users and an ophthalmic physicist as a new user under that broad scope licensee, that the broad scope licensee can name them without notification.

Manual brachytherapy, so the ACMUI had raised concerns that the NRC's regulations that were issued in 2002 did not properly address the needs of the manual brachytherapy authorized users and patients. Physicians were beginning to perform manual brachytherapy procedures in real time in the operating room and using image guided techniques, and as such, they were finding they might need to adjust the doses or the dose that was going to be delivered to the patient, and they were not able to calculate the radiation dose to the patients. So they believed the written directive requirements and medical event reporting requirements prevented them from providing the best care to patients.

So as a result, and a long process, 35.40 was amended to clarify some components of the written directive.

With the written directive, it still includes an authorized user's signature and dating before the administration, but instead of requiring a

dose, it now requires the total source strength in the pre-implantation portion of the written directive to be recorded, and what it does do is it does delete the dose, so again, it's only using source strength.

So in the pre-implantation portion of the written directive, the source strength to be administered or delivered is recorded, and then upon completion of the procedure, the actual source strength that was delivered is what gets recorded.

And it does require and it introduces a new term that the source strength that was delivered is to be reported on the post-implantation of the written directive before the patient leave the post-treatment recovery area.

And what we mean by that, and it's got a specific meaning in the regulations, the term post-treatment recovery area in 35.40 means the area or place where a patient recovers immediately following the brachytherapy procedure before being released to a hospital intensive care unit or patient room, or in the case of an outpatient treatment, released from the licensee's facility.

So the other change in the manual brachytherapy, it revises the definition of a medical event for permanent implant brachytherapy. So the new

requirements or the new criteria for reporting a medical event in permanent implant brachytherapy says that licensees shall report any event as a medical event except for an event that results from patient intervention in which the permanent implant brachytherapy, for the permanent implant brachytherapy, the administration of byproduct material or radiation from byproduct material results in a total source strength administered differing by 20 percent or more from the total source strength documented in the post-implantation portion of the written directive, or the other, going on, the total source strength administered outside of the treatment site exceeding 20 percent of the total source strength documented in the post-implantation portion of the written directive, or the administration that includes any of the following, the wrong radionuclide, the wrong individual or human research subject, a sealed source implanted directly into a location discontiguous from the treatment site as documented in the post-implantation portion of the written directive, or a leaking source resulting in a dose that exceeds 0.5 Sv or 50 Rem to an organ or a tissue.

And another term was introduced in the regulations being discontiguous, and what does that

mean with regard to 10 CFR 35.40? Discontiguous in general terms is used to describe things that are not contiguous in space, things that are not adjacent or touching, and things that have a gap between, or disconnected, or separate.

As it relates to medical event criteria in 35.3045 for permanent implant brachytherapy, discontiguous means a location that is not physically adjacent to or touching the treatment site.

The other component to manual brachytherapy is requiring licensees to have procedures to determine if medical events have occurred, and the procedures must have determined within 60 days.

So the requirement now has that the procedures need to determine for permanent implant brachytherapy within 60 calendar days from the date that the implant was performed, the total source strength administered outside of the treatment site compared to the total source strength documented in the post-implantation portion of the written directive unless a written justification of patient unavailability is documented, and that's what I just referred to.

So concerning training and experience,

this rule did address some generic training and experience changes. Primarily this rule removed the written attestation and board certification pathway requirements.

It revised the written attestation when one is required to say in one portion of it that the person who is being attested to is able to independently fulfill the radiation safety-related duties as, for instance, an authorized user, as an authorized medical physicist, or authorized nuclear pharmacist.

This regulation change also permits residency program directors to provide written attestation under certain conditions.

So one area I wanted to note was that in 35.51, this is for the training for the authorized medical physicist. This section was amended to clarify that the AMP who provides supervision for meeting the requirement of this section must be certified in medical physics by a specialty board whose certification process has been recognized by the NRC or an agreement state.

Under the T&E, there were some grandfathering conditions that were incorporated into the rule as a result of some previous petitions in

this area. The rule grandfathered -- so grandfathered RSOs and AMPs must meet the requirements in 10 CFR 30.50 and 30.51 for materials or uses that they were not previously authorized for.

The grandfathered individuals who were board certified on or before October 24, 2005 by boards listed in the regulation for materials and uses performed before this date. So there was some grandfathering as a result of what we know as the Ritenour petition. For those of you, that petition came in several years ago.

There were a few clarifications made under diagnostic medical uses. There was concern that the sources authorized under 35.65 for calibration, transmission, and reference sources were being used on patients without licensees recognizing these uses required by an authorized user.

There was also some concern that the sources that have an individual maximum activity were being bundled to produce a source that exceeded the maximum value in the regulation, so clarifications were made in that regard, and so the regulations also clarify when these sources do not have to be listed in the license.

Continuing with diagnostic medical uses

for the T&E, for use of sealed sources and medical devices for diagnosis, this section was restructured and expanded to clarify that both diagnostic sealed sources and devices authorized under 35.500 for use of sealed sources for a diagnosis are included in the T&E requirements of the section.

A new paragraph was also added that recognizes the individuals who are authorized for uses listed in 35.200 or equivalent agreement state regulations are also authorized for use of diagnostic sealed sources or devices under 35.500.

So there were amendments made under 35.300, radiopharmaceuticals requiring a written directive, and so the points I wanted to make here was that under 35.300, there was a change that clarifies that a licensee's authorization of the radiopharmaceuticals requiring a written directive is only for those types of radiopharmaceuticals for which the authorized user has documented training and experience.

This section was also amended for the 35.390, training for unsealed byproduct material for which a written directive is required. This section of the regulation was revised to identify a single category of parenteral administrations of a

radionuclide.

Parenteral administration of any -- and that changes parenteral administration of any radioactive drug that contains a radionuclide that is primarily used for electron emission, beta radiation characteristics, alpha radiation characteristics, or photon energy of less than 150 keV for which a written directive is required.

And just to note, in 35.300 and under 35.396, training for parenteral administration of unsealed byproduct material requiring a written directive, the change concerning the parenteral radiation characteristics was carried over in this section to be the same as 35.390.

And I also wanted to note that under 35.396, that this is a training and experience section that does still require an attestation for board certified individuals.

I have several slides that, after looking at them, are probably a little bit confusing. So they're included. It's not advancing, so -- that talk about the previous rule, the current rule through 35.300, but I believe they're a little bit confusing and they kind of restate what I just said in regard to the 35.300 and 35.390 and 396 descriptions in the

regulations that were amended, so we're going to skip ahead through these for clarification purposes.

35.400, use of sealed sources for manual brachytherapy, so this section is expanded to allow for sources that are listed in the sealed source and device registry for manual brachytherapy to be used for other manual brachytherapy uses that may not be explicitly listed in the sealed source and device registry.

The paragraph in the regulation was amended to allow sources that are listed in the sealed source and device registry for manual brachytherapy medical uses to be used for manual brachytherapy medical uses that are not explicitly stated in the sealed source and device registry provided that these sources are used in accordance with the radiation safety conditions and limitations described in the sealed source and device registry.

These radiation safety conditions and limitations described in the sealed source and device registry may apply to storage, handling, sterilization, conditions of use, or leak testing of the radiation sources.

The NRC recognizes that the medical uses specified in the sealed source and device registry may

not be all inclusive, so the final rule permits physicians to use manual brachytherapy sources to treat sites or diseases not listed in the sealed source and device registry.

For example, the sealed source and device registry may specify that the sources are for interstitial use, but the final rule change allows physicians to use sources for a topical use. It does not have to be explicitly stated in the SS&D that topical use is a condition of use.

So the NRC determined that flexibility should be afforded to physicians to use at their discretion in the practice of medicine brachytherapy sources in this way.

Coming down the pipe, vendor training, so there was an amendment to 35.610, safety procedures for instructions for remote afterloader units, teletherapy units, and gamma stereotactic radiosurgery units. This section was revised and restructured to add a new training requirement for the use of afterloaders, teletherapy units, and gamma stereotactic radiosurgery units.

This amendment requires all individuals who operate these units to receive vendor operational and safety training prior to their first use for

patient treatment of a new unit or an existing unit with a manufacturer upgrade that effects the operation and safety of the unit. Again, this is a new requirement in these regulations.

This training must be provided by the device manufacturer or by an individual certified by the device manufacturer to provide that training. This training is also required when software upgrades are made by the vendor or the manufacturer that effect the operation or safety of the unit.

This section was also revised to clarify that the training required by this paragraph on the operation and safety of the unit applies to any new staff who will operate the unit or the units at the facility.

And the last regulation change I wanted to mention is in the area for 35.655 for Gamma Knives specifically, and this is now the full inspection servicing for teletherapy and gamma stereotactic radiosurgery units.

The section title was revised to delete the five-year inspection and insert full inspection servicing to more accurately reflect the requirements in this section for inspection and servicing of teletherapy units and gamma stereotactic radiosurgery

units.

The regulation was revised to extend the full inspection and servicing interval between full inspection servicing for gamma stereotactic radiosurgery units from five to seven years to assure proper functioning of the source exposure mechanism.

The interval between the full inspection and servicing for teletherapy units remains the same, so it's not to exceed five years. So it was changed for GSRs to seven years and remain the same for teletherapy units at five years.

And that, real quick, were the changes to Part 35, and if you have any questions, my colleague, Donna-Beth Howe -- yeah, I don't know if you want to hold questions now, or if there are any questions, or --

CHAIRMAN PALESTRO: Thank you, Ms. Dimmick, for a very concise review of a very comprehensive document. We have time for one or two brief questions or comments from the committee.

MS. DIMMICK: Let me -- I'll take questions, but just, we are having -- we've had several public meetings on the Part 35 changes and they last anywhere from about four hours, then with a lunch break, almost five hours.

So they are fairly comprehensive and take a deeper dive into why the rule areas were changed. We also talk about inspection changes that were made to look at various areas of the regulations and inspection.

Our next public meeting will be on April 24. It will be on our public meeting notice website, so, and Donna-Beth Howe and Maryann Ayoade have been the presenters of those webinars and they've been very well received.

So if anyone wants to spend a couple of hours listening more about Part 35, you are more than welcome to call into that webinar.

CHAIRMAN PALESTRO: Thank you very much. Mr. Sheetz?

MEMBER SHEETZ: I actually participated in the last webinar and I thought it was absolutely excellent, and I think it's a must for any medical RSO.

MS. DIMMICK: Yeah.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions? Comments or questions from attendees here in the room or on the line?

All right, if not, then we will move onto the final topic of this morning's session, the

Germanium-68/Gallium-68 Subcommittee Report which will be presented by Ms. Shober.

MEMBER SHOBER: Good morning. I will wait for the slides to come up, I guess. Okay, yes, my name is Megan Shober and I'm going to be presenting the discussion from the ACMUI subcommittee on the Germanium-68/Gallium-68 generator licensing guidance. Next slide.

The subcommittee members, as we heard earlier this morning, most of them are Dr. Metter, Mike Sheetz, and myself, and our NRC staff resource who is very helpful is Dr. Diabes. Next slide, please.

Okay, so just to kind of go through some of the features of the existing guidance that was published in 2017 -- you can click. The current guidance expressly names the Eckert and Ziegler brand of the generator. It also includes a specific breakthrough limit that's particular to that generator.

It has some instructions for what to do if the generator hasn't been eluted within 48 hours. It requires notification to the NRC operations center if the eluate exceeds the breakthrough levels, and it requires wipe tests on each day of use. So that's

what has been, that is functionally in place now, and if you can go to the next slide?

So when the proposed guidance was published, there were several things the NRC was trying to move forward with in these future versions of the guidance, and one of those is to make the guidance brand neutral as there's already one additional generator and several others that are coming down the pipeline.

So the proposed revision removes the reconditioning requirements for generators that are not eluted within 48 hours, and there were some revised breakthrough reporting requirements in the proposed guidance that talked about multiple failures, and so those are just some of the higher level changes with the proposed licensing guidance changes. Next slide.

Okay, so the subcommittee had a few recommendations that I would like to highlight today. So the guidance in its draft form had an alternative pathway training option for an authorized user, but not for an authorized nuclear pharmacist. So to make it consistent, we suggested adding an alternate pathway training option for the authorized nuclear pharmacist.

As I mentioned earlier, the breakthrough limit that is in the proposed guidance revision does have a brand-specific breakthrough limit, and it's my understanding that some of the other generators that are developed or being developed may have different breakthrough limits for those products, and so our recommendation was to remove the brand-specific breakthrough limit from the licensing guidance.

And then we, as the subcommittee, wanted to reject the proposed breakthrough failure reporting requirement, and in lieu of that, we recommend conformance with the recently published 10 CFR 35 that we just heard about. Okay, next slide.

Okay, so one of the things that we had a lot of discussion about in the subcommittee is at what point the breakthrough is considered a generator failure, and this is because unlike with other generators that are commonly in use in nuclear medicine, the breakthrough testing for these germanium/gallium generators, it does take a couple of days to actually get to the point where you can determine whether the generator has breakthrough.

And so the question that we have that we weren't really able to resolve with the current licensing guidance is when does that failure happen?

Is it when you elute the generator to take the test?

Is it when you measure that after all of the gallium has decayed? Is it later, some day later when you actually calculate what that breakthrough number is? And so we just were wanting some clarification on that point at which that breakthrough is considered failed.

And then with the last recommendation to highlight today, we recommended revising the survey requirements to allow increased flexibility in how those are performed.

So the guidance currently specifies wipe testing, but, for example, kit preparation areas, they could be adequately monitoring with meter surveys.

And then the other comment about that is that the guidance currently requires generator storage areas to be surveyed quarterly, and that conflicts with the existing guidance in NUREG-1556 Volume 13 for radiopharmacies, which requires weekly contamination surveys of storage areas.

So those are the recommended changes from the subcommittee and that's all I had for this part of the presentation.

CHAIRMAN PALESTRO: Okay, thank you for your presentation, Ms. Shober. Any comments from

other members of the subcommittee? Mr. Green?

MEMBER GREEN: I think this is a very nice report, a very thorough report, and it does nail down some of the unique characteristics of germanium generators.

One artifact of the germanium generator is it does not have a United States Pharmacopeia breakthrough percentage. The analog, the Moly/Tech generator has a USP limit of 0.15 microcuries of Moly per millicurie of Tech at the time of patient administration.

There is no USP analog for that for germanium/gallium because the raw trichloride is not FDA approved for human use in raw form. You use that as an API to label a kit that's FDA approved. So there's no USP limit for the breakthrough percentage.

The manufacturer, Eckert and Ziegler, has a 0.001 percent breakthrough limit that they've adopted and that's the European Pharmacopoeia breakthrough limit because in the European Pharmacopoeia, they do have a standard for it, and so generator manufacturer number one has that European limit, so does generator number two. The Galli Eo has the same 0.01 percent.

There's another manufacturer coming out

that's got a unit that's in the pipeline that has a 0.05 percent, so it's a value five times higher than the other two manufacturers.

There is no U.S. limit to point to. We're kind of hugging and holding the European limit for those two manufacturers. Is the NRC, is the committee comfortable with saying don't exceed the manufacturer's limit, but two manufacturers have a value that is one-fifth of the other? Just a question.

CHAIRMAN PALESTRO: Any other comments or questions? Mr. Sheetz?

MEMBER SHEETZ: I actually have a question or a clarification from the NRC related to the licensing guidance document which was not addressed by our subcommittee.

There was a memorandum issued on July 13, 2017 creating a technical basis for the exemption from the decommissioning funding plan for licensing of a germanium/gallium generator, but I was curious and I've had questions from several licensees to me on what the rationale was for still requiring the financial assurance element?

If the requirement is for the licensee to have to return the generator to the vendor or to the

manufacturer, what was the need or rationale for still requiring the financial assurance?

Because the decommissioning funding plan requires manpower to develop the plan, but the financial element actually costs the licensee money, and so if we could provide clarification on that, I know that would because I know I have gotten questions on that. Thank you.

MR. EINBERG: Lisa, can you address that question, or Said?

DR. DIABES: Said Diabes. Thank you for the question. So before I answer any of your questions, let me clarify something. So a licensee has the option of pursuing a DFP or pursuing the medical exemption, so they have either one, or, you know, whatever is in their best interest.

The whole point of providing the medical exemption was to relieve a licensee from the actual DFP because early on, the same rationale of being expensive, too onerous, too complicated was brought up to the committee and to staff as well, so the whole point of initiating discussions of the medical exemption were under that basis.

So going back to your question on what's the point of financial assurance. When we initiated

discussions as we exempted the DFP, there had to be a mechanism that provided a pocket of money or basically finances to assure that in a case of bankruptcy or a case of an emergency, there was funding somewhere to work with decommissioning, and that was the basis.

I don't know if Lisa would like to provide further information or our legal side. Okay, thank you.

CHAIRMAN PALESTRO: Mr. Sheetz?

MEMBER SHEETZ: Thank you, and I understand that rationale should the licensee go bankrupt, but in the guidance, in that memorandum, it left it open to agreement states because it's a health and safety compatibility level.

And so the agreement states would have the option of not requiring financial assurance, and that's exactly what's happening across the country. Some agreement states are requiring it, other ones are not, and so it makes it difficult for the licensees having a double standard.

CHAIRMAN PALESTRO: Mr. Einberg, could I ask you to respond to that?

MR. EINBERG: Yes, so the agreement states are co-regulators, and as such, they have the latitude to establish the financial assurance requirements for

their particular state.

As such, again, what we find acceptable, the agreement states may have more stringent requirements, and as such, it seems like what you're calling out is happening across the country or in certain states, that they have additional requirements that they want to impose, and so that's a part of the compatibility that we have agreed with the agreement states.

Our agreement state representative, Megan Shober, do you have anything to add regarding that?

MEMBER SHOBER: So the thresholds at which financial assurance is required, those are uniform across the country, and I think the difference is that what you're mentioning is with the amount of financial assurance or whether or not there's an exemption.

So agreement states or the NRC can exempt licensees from any rule or requirements on a case by case basis, and so I don't have a lot of -- I know that there was a lot of question originally when this first version of the guidance came out as far as what actually is being exempted.

And so, and we were receiving requests from licensees to use these products before they showed up at a lot of NRC facilities, and so straight

out the gates, agreement states often have -- we encounter these products first.

We have to make these decisions early on, and it took quite a while to get the memo out originally about what NRC's position about financial assurance was.

And so I think in the period of months to a year, or however long it took between when these products first show up versus when the NRC policy statement came out, that's the time period where the various states are making the best decisions they can with the information that we have, and I think that's where some of those gaps tend to show up, and then once those exemptions have been granted, it's difficult to go back and then require the financial assurance from a licensee.

CHAIRMAN PALESTRO: Mr. Green?

MEMBER GREEN: I understand the confusion at first when the products first came on the market, and so there was the document to allow an exemption for the decommissioning funding plan and that's great, but it still left open for debate in different agreement states the financial assurance's warranty bond.

I can assure you that the roughly $100

cost to Federal Express a generator back to the manufacturer or distributor is far outweighed by the annual cost of the quarter-million dollar financial assurances' warranty bond. For the generator, it's just overkill.

For under 100 bucks, I can FedEx a package and make it go away, and have a proof of delivery receipt that that generator is back at the manufacturer, but a quarter-million dollar financial assurances' warranty bond with an annual payment of one or two percent of that bond to keep that bond there far exceeds $100 for FedEx.

CHAIRMAN PALESTRO: Other comments or questions? Ms. Shober, I'd like to go back for a moment. It was an issue, I think, raised by Mr. Green, and then we got off on the financial assurance, regarding the difference in the breakthrough levels.

Does the subcommittee have any concerns about the fact that one company is allowing a breakthrough about five times as much as two other vendors?

MEMBER SHOBER: We, I think absent a value that's in the regulations, I'm not sure that as a subcommittee, I'm not sure that we want to recommend a particular number, and then just looking, especially

as we look forward, I don't know what those future products are going to look like. I'm not sure that it's appropriate for us to specify a number.

CHAIRMAN PALESTRO: Thank you. That answers my question. Other comments or questions? Mr. Ouhib?

MEMBER OUHIB: Yeah, I think it only makes sense to have some sort of a number that any company should be below that. They don't have to meet that, but they have to be somewhere below a certain number.

MEMBER SHOBER: So are you suggesting a maximum that may not agree with any of the vendor recommendations?

MEMBER OUHIB: Correct, but something that's meaningful, you know, based on some data.

CHAIRMAN PALESTRO: The question to that is are those data available? And absent those data, it would seem at least for the moment to be the more appropriate course is what the subcommittee had adopted. Mr. Green?

MEMBER GREEN: I'm aware of one published study that shows the actual effective dose equivalent from, you know, minuscule micro, submicrocurie quantities of germanium in gallium, and the argument could be made that even the manufacturer's level of

0.001 percent is gross overkill, but that's votes.

We have the European Pharmacopoeia, which two manufacturers have adopted, but it really doesn't bear any semblance to reality as far as level of patient harm.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions from the subcommittee or the committee? Comments or questions from attendees in the room? Comments or questions from the bridge line?

MS. JAMERSON: Yes, we have two individuals. Mr. Mattmuller, I will unmute your line.

MR. MATTMULLER: Yes, hi, this is Steve Mattmuller. As they often say, long time listener, first time caller on the radio.

But I certainly appreciate the comments on the financial assurances because I really think while they're needed, I think at the current level, they're inappropriate, inappropriately high.

And as an example, we recently are in the process of replacing our cyclotron, so we've had to figure out how much it would cost to remove and have our old cyclotron disposed of, and the costs and the effort are in sharp contrast to what would be needed for a gallium generator.

I mean, for a cyclotron, you have a high

energy accelerator that serves as a source of protons for the radionuclide production versus a gallium generator. It's a final product. It produces -- the generator itself is produced under an FDA GMP and it serves as a source of gallium-68 or radiopharmaceutical used in a patient.

The math of the two items, the cyclotron, its utility cabinets, its water recirculation system, its shielding all adds up to a total of 66 tons versus 31 pounds for the EZ generator.

If you consider the radionuclides, the cyclotron components and concrete floor underneath the cyclotron contain activation products from its operation, and the exact level and quantities are really unknown at this time versus the generator where you know exactly how much is in it from the calibration label.

When it comes to disposal sites, our cyclotron will go to two different sites in the U.S., one in Idaho and a second one in Texas for the cyclotron itself and the shields, whereas for the generator, it gets returned to the manufacturer.

So what are the current costs for all of these activities? To decommission and remove our cyclotron, it will cost less than $400,000 versus

what's currently recommended by the NRC is if you have less than or equal to 100 millicuries, $225,000, and if you have more than 100 millicuries of germanium, $1.125 million.

So I think as highlighted or was hinted in some of the previous comments by other members, the FA amounts are really inappropriate for a gallium generator.

And I would say when the NRC staff first considered the FA amounts for the licensing guidance, one really couldn't fault them for erring on the conservative side, but we've now had several years of experience with the generator in the field with no incidents.

And as compared to other radionuclides that require financial assurances, it should be emphasized that this is a final product. It is a completely known entity. Its product, gallium-68, is used in patients, and its disposal is very, very simple.

So I think it would be wonderful if the same subcommittee could make a recommendation to assign more reasonable levels of financial assurances for the generators. I think $10,000 per generator would be more than sufficient and appropriate. Thank

you.

CHAIRMAN PALESTRO: Thank you, Mr. Mattmuller. Any other comments or questions from the bridge line?

MS. JAMERSON: Yes, we have Mr. Rubin. Mr. Rubin, I have unmuted your line. Mr. Rubin?

CHAIRMAN PALESTRO: All right, while you're trying to connect with Mr. Rubin, I see that Ms. Weil had a comment or a question.

MEMBER WEIL: I do have a comment just in support of Mr. Green and Mr. Mattmuller's comments. This is one of those instances where -- you can't hear me -- one of those instances where an unnecessarily stringent regulation may be creating a barrier for patient access to a necessary piece of treatment and diagnosis.

And I would strongly suggest that we revisit this financial assurance question because there are, you know, smaller institutions who don't have broad scope licenses that make adding this generator easy, financially easy, and it's an unnecessary barrier in my opinion.

CHAIRMAN PALESTRO: Other comments or questions? Mr. Sheetz?

MEMBER SHEETZ: Another point to consider

is that the Appendix B Part 30 limits are based on the Appendix B Part 20 limits, and so as one looks at the rationale on how those limits are established from inhalation and exposure rate at 10 centimeters, the limit for germanium-68 would be 10 microcuries, and then it would be exempt from the financial assurance.

CHAIRMAN PALESTRO: Other comments or questions? Dr. Diabes?

DR. DIABES: Said Diabes. I want to add that we're currently working on a petition for rulemaking that is addressing financial assurance all across, not only for germanium/gallium, but how we implement financial assurance for every single case, and that is currently under review and we're working on it, and it will address many of the issues that we're discussing here today.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions? Sorry, Ms. Martin?

MEMBER MARTIN: I was just wondering if he could elaborate on what they were looking at for the germanium-68 because obviously these are significant costs now, or to follow Mr. Sheetz's recommendation to allow them to be exempt by changing the limits.

CHAIRMAN PALESTRO: Dr. Diabes?

DR. DIABES: Said Diabes. So let me see

what I can say here since we're currently working on this petition, but with respect to germanium and gallium, we're trying to find a way that we don't even have to apply the exemption anymore.

So it's going to be based more on a risk assessment approach per isotope and it will be applied in the same manner all across, but it's still -- we're working on it. I cannot expand more, but I'm going to pass it to our colleague here from the legal side.

MS. HOUSEMAN: Hi, my name is Esther Houseman. I'm an attorney in the Office of the General Counsel and I just want to make a quick point about the process.

So the staff is currently in the deliberative process of reviewing the petition for rulemaking. They're going to develop a paper to send to the commission to make a recommendation on how to disposition that petition, and the commission will of course vote on it.

So what Dr. Diabes is explaining now is that process that we're going through, but do keep in mind that commission approval is necessary to move forward with that proposed rulemaking.

CHAIRMAN PALESTRO: I have a question. In terms of that proposal, can we get a sense, and I know

it may be difficult, of a timeline?

MS. HOUSEMAN: The paper to the commission should go up to the commission in the next several weeks to a few months. Again, that depends on upper level management review, so that's the point we're at in the process. How long it will take the commission to vote on that paper is highly variable and we can't commit to a timeline on that.

CHAIRMAN PALESTRO: Thank you. Any other comments or questions? Mr. Green?

MEMBER GREEN: As we get limited opportunities to meet with the commissioners directly, I think it would be worth the committee's time to plant the seed that they will be hearing about the decommissioning funding plan, financial assurance warranty bond changes.

And they met with us one or two years ago when we first showed them a generator and they developed this exemption process. They will be getting a document from the staff as we just described, either we have the opportunity to meet with the commissioners very soon.

And I think it would be worth the time to plant the seed that we're very supportive of the forthcoming financial assurance's revisions to

facilitate generator use in the medical community.

CHAIRMAN PALESTRO: We are on the agenda for a meeting tomorrow with the commission, but that program is already set and it's not going to include the Geranium-68/Gallium-68 generator, nor is there, and correct me if I'm wrong, Mr. Einberg, nor is there leeway to make alterations in these programs.

MR. EINBERG: Yes, Dr. Palestro, you're correct. There is no leeway to make alterations in the agenda right now.

So, but having said that, and in listening to the dialogue here, maybe, Esther, will the ACMUI have an opportunity to review the SECY paper at some point or would that be appropriate for them to be able to review the SECY paper that's going up to the commission on decommission funding?

MS. HOUSEMAN: I don't believe that process is built into the schedule because this rulemaking, this proposed, would affect far more than just medical uses.

If the commission were to see the paper and if the paper recommends that we undertake this rulemaking and they agree, and they vote to initiate the rulemaking process, perhaps at the draft proposed rule stage and the final, the draft final rulemaking

stage, there might be an opportunity for ACMUI review at that point.

Again, I say might because I'd have to go back to the project manager and management in the rulemaking division and the lead office on such a rulemaking to confirm that.

CHAIRMAN PALESTRO: Any other comments or questions? Bridge line?

MS. JAMERSON: Mr. Rubin, I'm going to unmute your line.

CHAIRMAN PALESTRO: Is he on mute?

MS. JAMERSON: Is your phone on mute?

MR. RUBIN: Hey, it's Joe Rubin. Can you hear me?

MS. JAMERSON: Yes, we can.

MR. RUBIN: Oh, good, sorry about that. I'm clearly having audio problems. Mr. Joe Rubin on behalf of the United Pharmacy Partners. We're a group of 80 nuclear pharmacies. I just wanted to echo the concerns about the financial assurance --

MS. JAMERSON: Mr. Rubin?

MR. RUBIN: -- for the gallium generators. We'll be submitting more formal comments, but I wanted to echo the concern and thank the ACMUI and the commission for taking steps to try and address this

problem, so thank you for your consideration.

CHAIRMAN PALESTRO: Thank you, Mr. Rubin. All right, at this time, I'll entertain a motion for approval of the --

MS. JAMERSON: One more.

CHAIRMAN PALESTRO: One more?

MS. JAMERSON: Mr. MacDougall, I'm unmuting your line.

MR. MacDOUGALL: Yes, can you hear me?

MS. JAMERSON: Yes.

MR. MacDOUGALL: This is Rob MacDougall and I'm the project manager for the petition for rulemaking that Esther just spoke of, and I can at least attest that if the commission does approve the staff's recommendation and the rulemaking goes forward, we have already built in additional time for review, both during the proposed rule stage and the final rule stage.

CHAIRMAN PALESTRO: Thank you. All right, at this -- Mr. Einberg?

MS. DIMMICK: Hi, it's Lisa Dimmick, medical team leader. I just wanted to add that UPPI did send in a letter to the ACMUI to discuss their issues and concerns with the financial assurance for germanium/gallium generators, so you will have a

letter appended to the meeting for their concerns.

CHAIRMAN PALESTRO: Any other comments or questions? All right, at this point, I'll entertain a motion for approval of the subcommittee's report. Dr. O'Hara is second, Mr. Sheetz. Any discussion? All in favor? Any opposed? Any abstentions? All right, thank you.

All right, that ends this morning's session and we will resume promptly at 1:00.

(Whereupon, the above-entitled matter went off the record at 12:03 p.m. and resumed at 1:03 p.m.)

CHAIRMAN PALESTRO: All right, we're going to call the afternoon session to order.

But before we begin with presentation on medical related events, my haste to assemble a subcommittee to review the NRC's viewpoint on infiltrated doses, I neglected to add a staff resource.

And that staff resource will be Maryann Ayoade. And I appreciate her willingness to participate.

So now we're going to move on to the first item on this afternoon's agenda, Medical Related Events. And this will be presented by Dr. Howe. Dr. Howe.

DR. HOWE: Okay, welcome everybody back from lunch. And this will be such an exciting one that nobody is going to be napping. I know that.

So, I'm going to be talking about the medical events that happened in the Fiscal Year 2018. Which would have been October 1st, 2017 through the end of September in 2018.

And medical events, we always put this disclaimer. The number that's presented on this slide at 150,000 therapeutic procedures is a ballpark. I don't really have a reference for it but it's about a right number.

So, the message here is that, as you see, we will have very few medical events for the fiscal year compared to the number of patients and treatments that are being provided.

And previously, the ACMUI has asked for a perspective on how the medical events for this year compare with last year. So, I'm going to just run very quickly through the, I got about the previous five years and then this years.

So, you will see that the total medical events for 2013 to 2015 range from 43 to 57. If you look at the table, you'll see most of the medical events are down in 35.1000.

And as in all of those years and in this year, most of those medical events are going to be with the TheraSpheres and the SIR-Spheres.

And to be more up to date, I've got 2016 through 2018. And I've got a couple typos on there so that should be '16, '17, '18.

And in this slide, I've got 50 medical events reported in 2018. In fact, I went back and counted, and I really only have 48.

And as you can see, we have very few diagnostic medical events. We've had zero for the last few years.

We didn't have very many radiopharmaceutical therapy events. We have a fair number of manual brachytherapy. That number is incorrect, it should be 11 and 13.

And the parenthesis is the total number of patients that were affected by medical events in that particular category.

And once again, most of the medical events, over half of them are occurring in 35.1000. And most of those are in the Yttrium microspheres.

So now I'm going to start looking at medical events by modality. And as you saw before, there were no medical events in the diagnostic

radiopharmaceuticals.

And we had two in the radiopharmaceuticals requiring written directives. We had one for I-131 MIBG and we had one for Radium-223.

The MIBG case was an interesting one. In this case, part way through the administration of the MIBG, the patient needed to use the restroom facility, so they disconnected the patient from the pump, and when they came back and they reconnected it, they didn't realize that they had not connected it correctly at the Spiros connector.

And so, at the end of the procedure, they ended up with a high activity of I-131 on the patient's clothing and the bed linen.

And even at this point, they didn't do any additional testing to see if they had a medical event. And so, it wasn't until two days later that the patient reported discomfort and reddening of skin on the upper right thigh and erythema lesion that went to desquamation the next day. So that was a fairly hefty dose that they had not expected.

And why did it happen? Well, for one thing, the activity levels for the I-131 were quite high. They did not decontaminate the patient until signs of the erythema.

And it's clear that they could have done some surveys to see that they had an I-131 skin contamination. Even though they thought it would be difficult to measure because of so much I-131 in the patient.

And what did they do for corrective measures? Well, for corrective measures they decided that they will no longer disconnect the patient, unless it's a medical emergency. So that they don't have the issues with connecting and reconnecting.

That they will always use absorbent pads underneath the administration line, so if there is a leak on the administration line it will be absorbed into the pad and not onto the patient.

And they will develop patient specific decontamination procedures. Because with the I-131 MIBG, they would have had to use a different type of decontamination than you would use from a water-soluble isotope.

And so, the other case was a radium dichloride. And in this case, we have one of our medical events where the, a medical event is when you depart from the written directive. In this case, the written directive asks for something.

It asks for an oral administration of

radium-223, which Radium-223 is never given orally. And the technologist just must have been in autopilot because she administered it intravenously, which is the way it should have been administered. So the patient got what they were supposed to get, but the treatment was not in accordance with the written directive.

And so, as a corrective measure, the licensee is going to implement new written directive procedures so that it is clear what mode of administration you're going to have. I think they looked at the, I guess they normally did sodium iodide oral administration and they just clicked the wrong boxes. And they're going to do a current review of their policy and procedures.

So that takes us to the manual brachytherapy procedures in 35.400. And this is where I have some mistakes on my slide.

We had a total of 11 medical events involving 13 patients. We had an eye plaque medical event and then we have an unknown procedure.

And then for the prostate we had non-medical events with 11 patients.

So, what happened with the eye plaque, the licensee was using a new eye plaque and they hadn't

really focused on, was there a difference between their old plaque and their new eye plaque. And it ended up there was a difference.

And so, the isodose curves differed in the brachytherapy plan and the dose, because of how the new eye plaque was made, put the dose deeper into the tissue. So they had prescribed 8,000 centigray and they only received 6,500. So that was their corrective action.

Now, I've got an unknown procedure. And you should expect that if the licensee doesn't provide enough information in the NMED report, we're not going to know much about this procedure. And I hope this is one of the areas that will be talked about in the next talk.

So, about all we got from this particular NMED report was that it was only 70 percent of the intended dose. I think I could guess that it's probably going to be a prostate brachytherapy one, but I don't have any information to confirm that.

So we'll have to go back to the regulator and get additional information, okay?

So now we move on to the largest category under manual brachytherapy, and those are the prostate dose administrations.

And it was pretty interesting here because we had one licensee that had three different reports of medical events with prostate brachytherapy. The inspectors went out and inspected the licensee and found a medical event in 2018.

And as part of that inspection process, the licensee went back and did a historical review. And during that historical review, they identified two more medical events.

So the first report has three separate patients within it, and then we're going to have two more events that were reported later. So they did not determine a root cause, but they attributed it to human error.

They did not expand on what human error was involved. It appears that some seeds may have migrated post-implant.

So the first patient received 63 percent of the prescribed dose, the second patient received 132 percent of the prescribed dose, the third patient received 130 percent of the prescribed dose for the prostate.

So that was the first report for that particular licensee. And then subsequent to the 2018 medical event that was reported, they discovered two

more medical events in 2018.

And so, in Report Number 2 it was an underdose to the patient. And in Report Number 3, it was also an underdose to the patient. And not a lot of additional information was provided at this point.

So moving on to other prostate implant brachytherapy therapy. We had a patient that received roughly 53 percent of the dose.

This was a stranded implant. And part of the seeds in the strand were implanted into the bladder. And so when the licensee removed those seeds, immediately then the dose to the treatment site was much less.

And they attributed it to human error. And for a corrective action, they're now going to have a new written directive procedure.

They're going to use more needles and more independent seeds and they're going to do less aggressive sparing of the urethra. And they're going to stop using pre-loaded strand seeds so that improperly planted seeds can be individually placed.

And the next licensee, let's see, 15, okay. They received 50 percent of the prostate, received no dose at all.

They were using the ultrasound volume of

the prostate. And it was smaller on the ultrasound pre-implant scan, than the CT post-implant scan. So the prostate appeared to be much larger in the CT post-implant.

And the real-time implementation didn't allow them to really get a good idea of how big the prostate was. And so, it didn't permit visual identification of visual errors that they had during the procedure.

They attributed the medical event to human error. For additional corrective actions they're going to have additional training to personnel and improved supervision.

And they're going to terminate the seed implant program due to low patient volume. So they have essentially given up their manual brachytherapy program.

And now we've got two different reports on this slide. And the first one the patient received 56 percent of the dose they attributed to human error. And they use, the corrective actions they're going to improve their imaging techniques.

In the next one, they received 73 percent of the dose. And they attributed it to the lack of dose being given to the prostate as an 18 percent

increase in the prostate size when compared to the pre-plan.

And the plan, they also planned and intentionally cooler coverage near the rectum. So they're going to provide additional training to their personnel.

Okay. So now we've got a pretty interesting medical event. In this case, they intended to give 12,500 centigray, but they only gave about 1,000 centigray.

They were using a Foley catheter, and they should have inflated the balloon in the urethra, but they inflated the balloon in the prostate. So, 32 of the 54 seeds were placed outside the prostate and three seeds couldn't be seen at all.

And they expect the risk of radiation damage to the, they expect risk of the radiation damage to the rectum and to the surrounding tissue because of where the seeds ended up.

So they, part of the problem was they failed to locate the Foley catheter, and that compounded, was compounded by using a magnification factor that didn't allow them to get a full view of the treatment and relevant anatomy.

So, this licensee, for this particular

case, the physician and the medical physicist will now audibly concur on image quality before procedure. This on their corrective actions.

Their manufacturer was asked to re-set the default magnification value so that the initial view would be of the relevant prostate anatomy. And then once the first seed is implanted, they're going to use the fluoroscopic image to make sure that they have the relative location of the seed and the Foley catheter where it's expected to be.

Okay. So now we've got a patient that was, received about 77 percent of the prescribed dose. They had three seeds in one needle but the seeds didn't remain in place.

They considered the contributing factors to be the AU's preference for peripheral loading. The potential rotation of the prostate during the needle insertion and pressure effects when using a hydrogel to separate the prostate from the rectum.

So, as a result of the medical event, they're no longer going to implant the needle between the urethra and the rectum, they're going to use two needles offset on an axis. And they're also going to use stabilizing needles during surgery so that the prostate doesn't move as much.

And that brings us to the end of the manual brachytherapy medical events.

And moving on to the 35.600, which are the therapy devices. We had ten medical events. And they were all with the HDR unit.

We had one skin, two breast and seven gynecological. And as you'll see, we had a device malfunction. We had a wrong site in the human error.

So, let's look at the first one, and that was the skin. In this case, the patient was prescribed to get eight fractions of 500 centigray for each fraction to the temple area, but they only received 350 centigray on the first two fractions.

So, the problem here was, the first physicist used an incorrect setup. There is an accuform that should have been in place to give the proper distance from the sources to the temple area. But they didn't use it.

And then the second physicist used the correct setup. So, the first physicist did the first two fractions and then the second physicist came back on the third fraction, used the correct setup and then they proceeded from there.

So, there was a gap between the treatment device and the patient's skin.

So, what did they do for corrective action? They lacked a policy for custom and mobilization devices for skin treatment. They're going to develop that now.

And the therapist present at the first treatment, and anytime, will be present at the first treatment anytime there is a new physicist. So there will be a continuation of information going from one treatment to the next.

And another thing that contributed to it is, when they had the patient setup and they were running the HDR sources out, the patient orientation was such that they could not really see where the sources were and they couldn't see whether the accuform was in place or not.

And so they're going to now take a photograph at setup. With and without the patient to show how the accuform should be used. And then they're also going to check that when they do have a patient.

And they're going to use a barcode scanning system to track custom setups using their devices.

So now we have a breast medical event. And in this case, we had 1,200 centigray to the

lateral breast skin.

This is similar to other medical events that we've seen with the HDR in the breast implants, in which the physicist used the tip end instead of the connector end in the treatment plan. And so, the dose was not delivered to the treatment site but out close to the skin and created problems.

So, corrective actions are going to be additional training to personnel.

We had a second breast medical event, wrong site. In this case, the first one we didn't identify whether there was a, what applicator was being used, but in the second case it's a Savi applicator.

And in this case, there are six struts and two and six were mislabeled. So that changed the orientation of the applicator and the direction of the radiation field.

So, the corrective actions are that the second physicist will independently verify that the catheter struts are in the treatment plan and there will be an HDR review checklist and they'll verify digitization of the struts in the treatment plan.

And they're going to add an HDR review, plan review, to their monthly audit so that they can

pick these things up. And they're going to provide additional training to their personnel.

So now we move into the largest category for 600 medical events, and that is the gynecological treatments.

In the first one we have a device malfunction. The patient was to receive 1,500 centigray during three fractions in 13 dwell positions but the HDR malfunctioned at Dwell point nine and the treatment stopped at that point. And then after the device was repaired, then they continued with the treatment.

We had another one that was device malfunction. The device failed to fully retract at completion of the treatment fraction, so that you had a dose of 100 centigray to the patient thigh.

The source was five centimeters from the cylinder guide to connector. And the source wire was bent at the source.

And then was a delay in removing the source from the vicinity of the patient and reporting the event to the RSO. So they compounded the issues that they had.

If they had been a little faster on identifying the sources outside of where it was, they

might not have had a medical event.

Then we have catheter movement. And in this case, the connector locking nut was too loose and that allowed the catheter to slide out. And the event was discovered by skin reaction progressing to moist desquamation.

The dose to the skin was between 5,000 and 8,500 centigray. The corrective action was to retrain the medical staff and the AU.

The AU will now double check all connections and placements before and after each treatment to make sure they were intact during the treatment. And they've purchased a new cylinder with a new design that they believe won't have this connection problem.

The next medical event there were six fractions of 350 centigray each. But the first fraction received 2,100 centigray.

So the total treatment time was incorrectly entered into the treatment planning system. It was human error and poor decision making.

They started the first treatment after hours. And there should have been two physicists checking, but the second physicist wasn't available. So the second physicist put the information in and it

wasn't correct.

So, their corrective actions are now to have the second physicist independently verify the treatment plan and the physicist to check if the plan was exported correctly to the treatment console.

Okay. The next one is a pretty interesting one. It was a wrong site. The patient's pelvis had extensive damage due to uterine cancer, not cancel.

There were two dwell positions that shifted to deliver the dose to the non-target small intestine bowel in the first three fractions. So the treatment plan was modified for the next two fractions so they could give treatment to the treatment site.

And the licensee originally thought it was not reportable because, in the process they gave the dose to the treatment site that was asked for.

But NRC determined that it is reportable because the licensee did not take into account that the fact that the fractional dose was greater than 50 percent. And that the dose was delivered to the wrong treatment site. They were focusing only on the treatment site.

So, we have another wrong site. In this case, the dose was delivered 5.5 centimeters outside

the treatment site. It received 500 centigray in a half centimeter volume.

And this was a digitization issue. We had digitization issues earlier. In this case, Channel 12 was digitized twice with no digitization of Channel 13.

And so, there were no dwell positions in 13. The treatment plan was displayed. There was plenty of opportunity for the physicist and the AU to see that there was no dwell positions in Channel 13, and no one picked it up.

So, the physician approved the plan and the physicist, neither one of them picked up that there was a problem here. So, they attributed the fact that they were rushing.

The patient was in discomfort with a full bladder. They had tried to start the procedure. They had the patient on the table and they tried to do the procedure, while the patient was there, and the patient was discomfort so they rushed to get the plan and export it into the treatment console and they overlooked their errors.

The corrective action is there will be a second check by the physicist that did not prepare the plan. And then each channel will be carefully

reviewed, and the patient won't be brought to the treatment area until the plan has been checked and exported to the console.

Another wrong treatment. So, in the first three fractions they digitized the catheter as linear instead of a single curve catheter.

So, the physicist failed to recognize the incorrectly reconstructive catheter shape in the planning software. And treatment length was 15.7 centimeters instead of the nine centimeters.

Okay. And they didn't discover the problem until the second fraction. So, one of the things they attributed it to was that the treatment plan was not enlarged enough, so the physicist couldn't see the dwell points that were overlapping in that incorrectly digitized Channel 12.

And the corrective actions are to enlarge each treatment plan in which the physicist signs off and to use a formalized checklist. And that concludes our 35.600 medical events.

And now we move into the emerging technology or the other medical uses. We had 25 medical events. We had one for the Perfexion, one for intravascular brachytherapy, one for radioactive seed localization and then we had 22 for the Yttrium-90

microspheres.

For the Perfexion, the device malfunctioned. The device recorded an error, the backup power was low, so the sources were returned to the shielded position and they had to get the device repaired. So, only one-third of the prescribed dose was delivered.

For intravascular brachytherapy, they were using an extra-long delivery catheter and the source would not go out to the treatment site. So they retracted the source safely, they exchanged the long treatment catheter for another extra-long treatment catheter and the source still wouldn't go out to the treatment site, but the source could not be returned to the intravascular brachytherapy unit. And all the catheters were removed.

The hydraulic return mechanism failed to return the source, and no dose was given to the treatment site and 39 centigray was given to the surrounding tissue. And they looked at it and determined there was a deformation of the delivery catheter that was the root cause.

Okay. We had one radioactive seed localization. In this case, the patient was given a seed and was scheduled to come back for surgery six

days later.

And in the middle of this process, after the seed was implanted, but before the seed could be removed, the insurance company rescinded the approval. And it required about, it required three medical opinions before they would continue to okay the surgical removal of the seed.

So the surgery wasn't performed until approximately 64 days after the implant. So the surrounding tissue from the implant was supposed to get 12 centigray and the patient received 99 centigray.

And now we're going to move into the Yttrium-90 microspheres. We have 25 of them. And the first two, they did not identify the manufacturer.

So you can imagine if they didn't identify the manufacturer, you're not going to see a lot of information on the first two.

So they got, in the first one they got 77 percent of the intended dose. No other information.

The second one the patient received 60 percent of the prescribed dose. And no other information.

And now we'll move on. I'll always divide these up to TheraSpheres and SIR-Spheres because the

devices are not exactly the same and some of the root causes are not the same.

So this year I'm doing the TheraSpheres first. We had 13 medical events involving 14 patients. We had an overdose, catheter obstruction, bubbles, backflow to contrast and a human mistake.

So, let's take a look first at the overdose. They prescribed 13,670 centigray, but they received 29,400 centigray.

They picked up the wrong dosage. They measured it, they compared what they saw with what was on the shipping box and not what was in the written directive. So they had a shipping box that was for next week's patient, and they picked that up and they administered that to this week's patient.

So, the post-administration calculations identified the medical event. And so, as a corrective action, they're going to add a dose verification step in the interventional radiology department.

And now we're going to see a lot of cases where the dose didn't end up in the patient, it ended up in the waste jar. Or in the catheters or in some other place, but not in the patient.

So they prescribed 12,000 centigray, but they only administered 1,700 centigray. Fourteen

percent of the intended dose.

They thought the equipment didn't function as designed, and most of the dosage was found in the waste jar. The manufacturer was unable to determine a root cause.

On the next medical event we had two patients. And both of them received less dose than prescribed.

So the first patient was prescribed 72.6 millicuries, but they received 15 millicuries. And the inspector that went out and looked at this case thought the expansion tubing resulted in turbulent flow triggering suspension issues.

The second patient was also prescribed 72 millicuries but received 36.7 millicuries. And the inspector thought the lack of adequate agitation prior to administration, or that the issues were with a quality sizing of the microspheres.

So, as a result, the licensee is no longer using extension tubing, and the manufacturer supported the inspector's findings.

The next case, they were prescribed 122 millicuries but received 46 millicuries, 38 percent of intended dose. The device components were sent to the manufacturer, and no cause of the blockage was

determined.

There was an obstruction blockage located in the micro-catheter in the outlet tubing to the E junction. The manufacturer recommended handling micro-catheters with extra care in looking for kinks.

So, we have another 12,000 centigray but only received 2,000 centigray. The licensee attributed it to a malfunction in the administration set.

Significantly less pressure was noted than usual when pressing the syringe. Saline accumulated in the overflow valve.

And only, they were supposed to return the whole unit to the manufacturer. All the tubing and everything but they only returned a portion of the administration set that infused the dose into the patient, to the manufacturer. So they didn't get to see what the real problem was.

It could have been a kink or obstruction in the treatment catheter, but it wasn't conclusive. So their corrective actions, next time they have one these, they're going to send everything back to the manufacturer.

So we've got now one licensee with two reported medical events. In Report Number 1, they

were scheduled 64 millicuries, they only got 41, 65 percent of the activity.

Air bubbles were noted in the overflow tube. So they connected a three-way stopcock between the overflow tube and the micro-catheter, aspirated bubbles to the syringe with a stopcock close to the patient. And I believe they decided to stop the treatment at that point.

And they re-surveyed the delivery kit, showed residual activity.

And Report Number 2, they prescribed 46 millicuries but only received 27. Or 59 percent of the activity.

They used the left radial artery with a 5-French Sarah Radial catheter with a coaxial micro-catheter. They didn't see anything unusual. They didn't have any radioactive contamination. But then they found the dose was in the catheter, the gauze, the dose vial and the other waste.

This one received about 64 percent of the dose. There was a backflow of microspheres into the contrast line and syringe. There was significant contamination in the contrast syringe, the flushing syringe, the contrast tubing and the associated y-adaptor.

Though, they thought that the contrast syringe and tubing were made of materials that bind the microspheres more than the administration kit. And so they're going to look for things that are, have the same materials as the manufacturer's recommended administration kit. And they are now going to use a clamp and a one-way valve.

This one was, received about 32 percent of the activity. There was a blockage in the delivery apparatus. They imaged the administrative set and saw most of the undelivered activity near where the plunger connects to the dose vial.

So they, in this case, they're going to send the administration kit and procedure waste to the contract. To the manufacturer.

And this one received 16 percent of the activity. The microspheres were coagulated in the tubing. There was unexpected activity remaining near the Touhy-Borst connector.

And the manufacturer thought the cause, by issues with the micro-catheter. Their remedy will be to flush the micro-catheter immediately prior to connecting it to the administration kit. They think that might help in getting the micro-catheters through the, getting the microspheres through the micro-

catheter.

This patient received 65 percent of the dose. The first vial was administered without incident.

They primed the second vial and they prepared it, but they saw a train of bubbles in the line between the dose vial and the patient. So the AU stopped the procedure.

They didn't want the bubbles to cause the flow to reflux to the gastric artery and cause permanent damage to the stomach. And they couldn't pinpoint a cause for the bubble, so they limited, they now limit the number of staff trained to prime and do the setup, to ensure enough are available on treatment day.

The next patient received 53 percent of the dose. They did a CT scan to verify the dose was administered to the correct location, but the remainder of the dose hung up in the catheter despite flushing, and the catheter tube met the manufacturer's specification. So no root cause was identified.

In this case, the patient received 71 percent of the dose. And this particular licensee used three different written directives to fractionate the delivery.

So they thought the small activity prescribed in one of those fractionated doses contributed to the underdose because of the typical loss of microspheres in the valve and the tubing.

They are now going to order higher dosages for any administration below ten millicuries, and they're going to amend the license to go to a different manufacturer. So they're switching manufacturers.

That brings us to the end of the TheraSpheres and we're now moving into the SIR-Spheres. We had seven medical events with SIR-Spheres.

You'll see that we have wrong site, measurement unit error, written directive error, high activity clogging, and low activity clogging.

So the first one was a wrong treatment site. And the post-treatment scan appeared normal with the small uptake in the bowel, but the patient experienced pain in the abdomen and erythema on the abdomen.

They thought the dose was above 55 centigray but less than 1,000 centigray. And they thought one-third of the dose migrated up a venous ligament and lodged in the abdominal wall.

I think this is one of the first ones that we've seen with erythema on the abdomen. Or microspheres.

So, they attributed their issues to difficultly visualizing the arterial access to the tumor. That the micro-catheter was not advanced far enough into the correct artery.

And this particular patient had a preexisting kidney impairment that precluded use of more contrast, so that was attributed to why they didn't get a good visualization.

And they're going to add a second monitor to refer to the original arteriogram without switching task and to improve the confidence and correct location. And they're going to take prophylactic measures for future patients with impaired kidney function.

This is another wrong site. They prescribed it to the left lobe of the liver, but they delivered twice as much to, they prescribed it to the right lobe of the liver but they received about two to three times more dose to the left liver.

They attributed it to human error, and they placed the catheter in the left hepatic artery instead of the right hepatic artery.

This was an interesting one. This was a measurement unit error. They prescribed .91 gigabecquerels but they received 8.9 millicuries.

They ordered it, even though it's prescribed in gigabecquerels, they ordered it in millicuries. They marked the wrong box in the computer. And when they went to measure it, they didn't multiply the measurement dose value by a correcting factor of ten.

So they didn't identify it until the post-procedure check, so they are going to revise their worksheets to be all in SI units. And the written directives will also be in SI units, and the dose preparation and post-procedure forms will be in SI units.

So they had issues going back and forth between SI units and other units. So they're going to make uniformity. Uniformed changes there.

Okay. This is a written directive error. They prescribed 1,500 centigray to the right lobe of the liver, but they delivered about 1,500 centigray to the left lobe.

The written directive was prepared incorrectly. The AU wanted to treat the left lobe. And it was identified after completion of the

procedure.

It also indicates that the AU didn't indicate the correct treatment site on the written directive, and the AU didn't fall with the pre-treatment information to the RSO. So the clinical staff failed to identify the discrepancy between, during their patient time-out just before the implementation.

So, we've had a number of licensees that use time-out as a corrective measure, but time-out doesn't always work.

So now we have a high activity clog where 19 percent of the dose was received. The micro-catheter clogged due to an unusually large number of microspheres being used, according to the licensee.

The prescribed activity was at the high end of the treatment range and the patient was administered, the administration was delayed a day, and because it was delayed a day and it decayed, then they had to increase the number of microsphere volume roughly by 25 percent.

And so, in the future they're going to use smaller aliquots and do a slower infusion rate.

And we have a device malfunction. In many of the things, licensees are now attributing most of

their problems to device malfunction.

So they received 25 percent of the activity. They say the device malfunctioned and ceased to deliver the microspheres. I think this is another way of saying clogging.

The manufacturer's representative was present, but the cause of the malfunction was unknown. They'll return the delivery device to the manufacturer for technical analysis and root cause determination.

This patient received 51 percent of the activity. They had planned to deliver the activity in two split dosages. The written directive was not properly reviewed.

So they split one dose into two, instead of providing two separate doses. The radiation oncologist failed to check the drawn dosages prior to injecting them. And the identification was after the injection, when the remainder of the doses was delivered. Discovered.

So, they attributed this to lack of comprehension of the dose draw worksheet, a miscommunication failure to review the written directive and a failure to perform a safety pause and properly review the dosage to be administered against

the written directive prior to administration.

And that concludes my list of 48 medical events for FY 2018. Are there any questions?

CHAIRMAN PALESTRO: Thank you, Dr. Howe. Comments or questions from the ACMUI?

MEMBER SCHLEIPMAN: I have a question. It's more just a process.

Who adjudicates, some of the corrective actions seem quite appropriate, some seem, perhaps, not enough. Who adjudicates whether those corrective actions are sufficient and how are they followed up and by whom?

DR. HOWE: What normally happens is, if you have a medical event there's normally an inspection. These medical events happen throughout the agreement states in NRC.

And then on inspection time and reviewing their reports, they give corrective actions. And it's up to the regulator to say, yes, that appears to be reasonable. And we generally will sign off on retraining of people.

The licensee comes up with their own corrective actions.

CHAIRMAN PALESTRO: Any other comments or questions?

Comments or questions from attendees here in the room?

On the bridge line? Mr. Ouhib?

MEMBER OUHIB: Yes, I just have a question. I know this has been brought up in the past regarding the units, which the SI units many times. Any hope, any chance, any plan for that down the road?

DR. HOWE: Normally our SI unit problem, that's been brought to our attention is, the problem with the manual brachytherapy seeds being air kerma or some other unit.

And in this case, it was a licensee that appeared to have multiple different kinds of units from one document to the next and didn't have uniformity. So they were just kind of, it was really something that was kind of asking to have an accident between ordering in SI units and ordering in millicuries and then making measurements.

So, it wasn't the normal type of unit problem we have, it seemed to be kind of unique to this particular licensee.

CHAIRMAN PALESTRO: Any other comments, questions? Ms. Weil.

MEMBER WEIL: I have a question. Not necessarily for Dr. Howe but maybe for the group.

If the NRC were to take the suggestion that these high level infiltrations, where the dose to an unintended tissue reached the regulatory limit, how much would that increase, do you think, the number of medical events that are reported?

Is there any way of thinking about that?

DR. HOWE: I don't think we know at this point. I would suspect we would get, we do have cases where they report infiltrations with therapy drugs and we don't call them medical events because of our prior.

And so we have ones and twos of those. But I think if there was more focus on it, we might see more, I'm not sure.

It would also depend on whether we kept the same, if we were to go to calling them medical events, whether we kept the same criteria in place or we developed a different criteria that might be a little bit higher to take account for capturing things that might have a significance for the patient. But we have an able team that's going to look at that.

CHAIRMAN PALESTRO: Any other comments or questions? Thank you very much, Dr. Howe. I'm sorry.

DR. HOWE: No, you get the --

PARTICIPANT: Oh, it's working now?

DR. HOWE: No.

MS. BLANKENSHIP: Hi. Bette Blankenship, AAPM. I had a question on the SIR-Sphere medical event.

Typically, you can only order three gigabecquerel and receive three gigabecquerel from the SIR-Sphere's folks. So I was curious as to why they would indicate that they had received 8.9 millicuries because you can only order in gigabecquerel, receive a gigabecquerel, that amount, and then draw from that what your physician orders or prescribes.

So I was just curious on, their reporting is even further confusing because they didn't receive 8.9 millicuries because Sirtex can't ship anything other than three gigabecquerel. So they only work in SI units.

DR. HOWE: And that's the one where they confused all the SI units and --

MS. BLANKENSHIP: Yes. It basically says prescribed .91 gigabecquerels but received 8.9. So that, just that language there kind of confused me, because they can only ship in one --

DR. HOWE: So, they were supposed to get .91 gigabecquerel, they wrote it out for .91 millicuries.

MS. BLANKENSHIP: Okay.

DR. HOWE: And then when they made the measurement, they didn't multiply by ten, so they stopped, thought they were still down in the level they were supposed to, and it wasn't until later that they discovered that they were --

MS. BLANKENSHIP: Yes.

DR. HOWE: -- way off.

MS. BLANKENSHIP: Yes, I just, thank you.

DR. HOWE: Yes. I can't explain any more than that.

CHAIRMAN PALESTRO: Mr. Sheetz.

MEMBER SHEETZ: In response to that, some licensees will receive SIR-Spheres from a radiopharmacy and they'll get a unit dose, so the three gig vial will be sent to the radiopharmacy, the radiopharmacy will then follow-up and then dispense into the dose vial what the licensee has required. Or requested.

MS. BLANKENSHIP: Okay.

CHAIRMAN PALESTRO: Any other comments or questions? All right, thank you very much. Dr. Howe.

Next topic on the agenda is the Appropriateness of Medical Event Reporting Subcommittee Report, will be presented by Dr. Ennis.

MEMBER ENNIS: Good afternoon, everyone. Thank you, Chairman Palestro.

And I couldn't have asked for a better introduction. Especially the case where we didn't know what site was implemented.

Okay. So, we formed a subcommittee looking at the appropriateness of medical event reporting that came out of the growth of Donna-Beth's presentations over the last few years, as well as mine.

And just take a look at the pictures on the bottom, and you'll see a better representation of what we're doing here, than we saw this morning.

Next slide. Okay. So, our charge was to review the appropriateness of required elements of medical event reporting, the adherence to these requirements and recommendations to improve reporting.

Next slide. So I want to thank the subcommittee members, this was really an excellent subcommittee. A lot of involvement of all, and activity of all the members, including Dr. Dilsizian, Ms. Martin, Mr. Ouhib, Ms. Shober and Ms. Weil and myself.

Next slide. So starting, it's worth reflecting on what is the purpose of reporting. And

using some of the NRC documents that describe the event reporting requirements and schedules for them.

I will highlight for you what are relevant aspects of the requirements for a higher subcommittee. And that this information of medical events should be used to assess trends and patterns, recognizing inadequacies of unreliability of specific equipment or procedures, and will significantly aid in understanding why events, an event occurred and then find any actions necessary to improve the effectiveness of NRC and agreement state regulatory programs.

Next slide. These are the documents that we reviewed in helping us make our determination of what is required. Currently in the medical event reporting and what is available to the public.

Next slide. In the end, the events that are reported are collected into a database. The nuclear materials event database, otherwise known as NMED.

It does include information for both agreement states and the NRC. It's managed by an office within the NRC, the Office of Nuclear Materials Safety and Safeguards.

And there is a contractor that is

responsible for coding and quality control of the information under the oversight of the NRC NMED project coordinator.

Of note, access to NMED is limited. And the general public does not have access to that. Rather they have access only to an annual report that is available publicly.

Next slide. Issues that our subcommittee identified in NMED are as follows. We felt that frequently the narrative was inadequate for an ACMUI reviewer to understand the event, its cause and contributing factors, and the adequacy of the corrective action.

At times, there appear to be a disconnect between the narrative and the chosen cause from the cause pick list.

Just a point of clarification, there is a drop-down menu within NMED for causes and for corrective actions that lists many of the most common causes and corrective actions with a word or phrase.

But that chosen corrective action or cause, from the drop-down menu, often does not appear to connect well to the description within the corrective action or cause parts of the NMED database.

Next slide. In addition, NMED lacks

information from some inspections that have been conducted by NRC or agreement states, like the example we talked about a minute ago.

We did a brief audit of a couple of issues and, for example, of all the medical events in Fiscal Year 2017/18, 23 percent of them, there was either no cause or no corrective action identified in NMED as of a month ago.

In addition, of all medical events reported in 2017, 11 percent are still incomplete and an additional 11 percent are listed as pending additional information, and, again, this is as of a month ago.

And as alluded to before the public, including authorized users, RSOs, physicists, authorized physicists, only have access to an annual report, not to the actual data that we can see in NMED.

Next slide. As such, our subcommittee is in the process of finalizing recommendations to improve and address the issues laid out in the first part of this presentation.

Those that we are moving towards a full recommendation on include the following, that the root cause and corrective action sections in NMED, in

addition to the pick list, there should be a required narrative and searchable section.

Currently there is the narrative section itself of the NMED is searchable, but there's only one place for a narrative section. It's not specifically asked that there be a narrative part for the root cause and corrective action aspects.

Currently, whoever is entering the data can just do a drop down menu for those aspects, which really are the crucial ones to really understanding an event and helping the ultimate goals of these that we discussed on the first couple of slides.

We also are leaning towards a recommendation that the root cause and corrective action sections always need to be completed. (Sound system interference.)

PARTICIPANT: Sorry.

MEMBER ENNIS: We are looking at requiring that information gathered from any investigations be added to NMED as that is not necessarily the case at this point.

We are looking to require that a report may be fully completed within 12 months. We are looking to require ACMUI and NRC staff annually promulgate the findings of the ACMUI subcommittee on

medical events to the medical community and the medical physics community.

Currently, while that report does go up on the website, we might recommend that additional ways of promulgating that be done on an annual basis in order to educate the medical community about what can be learned.

Next slide. Further things we are considering but haven't totally come to a conclusion on include requiring that the report use additional guidelines that we might develop to assure more complete and useful information is provided.

So, more specifically, what is required of a root cause analysis, how can we structure the requirements of causes and root cause analyses and the connections between them, can we come up with ways of structuring those and advising licensees that when they are reporting what is required in more detail so that we get better reports.

Another aspect we were looking at is requiring that the report eventually gets submitted and reported within NMED be initially written by the authorized user and their physicists and then reviewed by the inspector as opposed to being written by an inspector, having in mind that the authorized user and

medical physicists tend to have a deeper understanding particularly of the medical aspects of what is going on.

Require that the inspector interview all involved in a medical event, to do a more in depth evaluation of each medical event, require the report from a manufacturer be included in the report if the event reported involved the device to assure adequate responsiveness from the manufacturers and input from them, and then, again that gets reported within NMED so that we can all learn from those individual events and the manufacturer's thoughts about it.

We are also looking at a notion that a corrective action be explicitly defined to include medical aspects as well as technical aspects because some of these solutions or the improvements of that nature and could be helpful to other authorized users to be aware of these, but would be missed if not specifically required, and to require that the final report, even if drafted by the physicist and the authorized user, be signed off by all involved, meaning the authorized user, the physicist, and the inspector.

I think that's the end. Next slide. Ah. So in conclusion we believe, our subcommittee

believes there are significant opportunities to enhance the utility of the medical event reporting, the NMED database specifically, and promulgation of the information to user community.

The subcommittee asks that it be able to continue evaluating these issues in more detail with the goal of creating a set of specific recommendations. Thank you.

CHAIRMAN PALESTRO: Thank you, Dr. Ennis. Comments or questions from the subcommittee?

(No audible response)

CHAIRMAN PALESTRO: From the ACMUI?

(No audible response)

CHAIRMAN PALESTRO: Dr. Ennis, I have two questions. One, in your recommendations you say that you recommend that a report in NMED be completed within 12 months. That seems like an awfully long time.

MEMBER ENNIS: This is trying to be strict. The point is as a previous slide shows that about a quarter were opened two years or so. If you could go back a couple slides. There we go.

So 2017 we reviewed all the events of 2017, 11 are still incomplete, 11 percent, and another 11 percent are still pending additional information,

so we are trying to make it a little bit stricter by requiring a year.

I certainly wouldn't disagree that that might be generous, but for a starting point at least we thought that would be a good place to start.

CHAIRMAN PALESTRO: Are there time requirements in place now?

(Off microphone comment)

CHAIRMAN PALESTRO: All right. Yes, I'm sorry, Mr. Einberg.

(Off microphone comment)

PARTICIPANT: Your mic is the one that died.

(Off microphone comment)

MR. EINBERG: Dr. Palestro, yes, there are no time requirements. However, the agreement states and licensees report these to the agreement states and the agreement states have to report into NMED and NRC licensees report to us and we put it into NMED.

And then during the IMPEPs, which are the Integrated Materials Performance Evaluation Program, where we go out and evaluate agreement states, we look at whether they have been entering their NMED reports in a timely fashion.

CHAIRMAN PALESTRO: Thank you. But

without any time requirement how do you define timely?

MR. EINBERG: Well whether they have been entering the reports at all.

CHAIRMAN PALESTRO: Okay. Thank you.

MS. HOLIDAY: Dr. Palestro, this is Sophie. I would also like to follow up to say that there have been times where medical events come in and members on the medical team specifically reach out to a staff member actually in our branch who is called the regional coordinator and we ask that she reach out to the NRC regions or to the respective RSAOs, which are the Regional State Agreement Officers, to ask them for additional information.

Yet at the same time we are asking for the information doesn't mean that we the medical team can force them to provide us that information, but we as a medical team often do reach out and ask for additional information.

CHAIRMAN PALESTRO: I have another question for you, Dr. Ennis. Excuse me. Where you said that you require the final report must be signed off by the AU, physicist, and inspector, what about the RSO?

MEMBER ENNIS: I wouldn't disagree with that. That may have been an oversight on our committee.

CHAIRMAN PALESTRO: Mr. Sheetz?

MEMBER SHEETZ: That was going to be one of my comments, yes.

CHAIRMAN PALESTRO: Any other comments or questions from the ACMUI?

(No audible response)

CHAIRMAN PALESTRO: From attendees in the room?

(No audible response)

CHAIRMAN PALESTRO: Bridge line?

(No audible response)

CHAIRMAN PALESTRO: All right. Now this is an interim report so we don't have to take any action on that, am I correct, Ms. Holiday?

MS. HOLIDAY: Correct. That was going to be my next comment. While what you guys see on the slide says recommendations under consideration, as I think I have alluded to previously these are not the formal recommendations being put forth by the subcommittee at this time.

These are just things that they have thought about and that they are considering. When they have finished their deliberations they will come forth with a draft final report for vote.

CHAIRMAN PALESTRO: All right. Well, I'm

certainly happy to extend the term of the subcommittee, Dr. Ennis, and we look forward to another report from your group at the fall meeting.

MEMBER ENNIS: Thank you very much.

CHAIRMAN PALESTRO: Thank you.

MEMBER ENNIS: If anyone has any other ideas to add we're open to hearing suggestions.

MR. EINBERG: And, Dr. Palestro, is there a staff resource for this subcommittee?

MEMBER ENNIS: Yes, Lisa Dimmick.

MR. EINBERG: Lisa, okay. Thank you.

MEMBER ENNIS: I apologize for not mentioning that, Lisa.

CHAIRMAN PALESTRO: Actually, you know, Mr. Einberg, you made a good point. I think we tend to be negligent when we put up the members of the subcommittee that we should acknowledge the staff resource, because not only because they are important contributors but we should know who they are as well.

MR. EINBERG: Yes. And that was not my intent to call out Lisa, but Lisa does great work and I just wanted to make sure that you were getting the support that you needed.

CHAIRMAN PALESTRO: Thank you. I wasn't suggesting it was, but I think it really should be

done.

MR. EINBERG: All right.

CHAIRMAN PALESTRO: Any other comments or questions?

MEMBER GREEN: Dr. Palestro?

CHAIRMAN PALESTRO: Any other business -- I'm sorry. Mr. Green?

MEMBER GREEN: Going back to the timeframe of completing the medical event report, it's a long time to write regulations and do rulemaking, but could we recommend that, could the subcommittee recommend that that get written into the regulations and then, you know, some years later it will be adopted by the agreement states, but right now it's just open-ended?

CHAIRMAN PALESTRO: The answer is, number one, this an interim report so we are not approving or, not approving or rejecting any recommendations today.

And while I am not initially thrilled with the idea of a one year lag time, given the fact that there is no time limit at the present time I think that's a step in the right direction and then assuming that eventually gets written into the records that it could potentially be shortened. Any other comments or questions?

(No audible response)

CHAIRMAN PALESTRO: All right. I have an item that I had hoped to bring up earlier this morning, but we ran out of time in the open forum and rather than waiting until tomorrow I would like to bring it up now if I may.

It's an issue that came up regarding cremation of a patient or patients who had received lutetium-177 dotatate for treatment of neuroendocrine tumors.

Apparently, and I actually went back and I very quickly checked through the NRC website and looked under cremation, deaths, tried to come up with a variety of terms, and maybe I wasn't looking using the right terms or looking thoroughly enough, but the only thing that I could find was a statement in NUREG-1556 about the explantation of plutonium-powered pacemakers prior to cremation.

And so the issue arises is there a policy, is there recommendations or are there recommendations by the NRC for the handling of decedents, particularly with respect to cremation when they have radioactivity on board?

DR. DIABES: Said Diabes. We are currently working on patient instructions and part of

those patient instructions is instructions for family members, caregivers, on cremation and what should that entail.

That was directed by the Commission on a patient release project and we are currently working on that data and that was part of the updated data on Reg Guide 8.39.

There is a whole section on cremation and instructions related to cremation and what information shall be provided. We are currently working on other initiatives, a brochure, and more information that will come available later.

CHAIRMAN PALESTRO: So let me ask you a question and, Mr. Einberg and Ms. Holiday, is this an appropriate time to form a subcommittee to work with you on that or for you to consult?

MR. EINBERG: This would be, but I think Katie, Dr. Tapp, here, wants to add some additional information as far as what we require at this time.

DR. TAPP: Yes. Just adding on to Dr. Diabes, so patient release regulations in 10 CFR 35.75 do have the limits for release of patients and then you have -- the release should have instructions if it's likely to exceed 100 millirem.

So we do right now require licensees to

consider situations where the release of that patient could possibly expose members of the public to over 100 millirem.

That's how we go back to Reg Guide 8.39 and adding in some instructions for licensees to follow that will help them for cremation in the future.

We also are adding to NUREG-1556, Volume 9, in the Draft Revision 3 that is going out final hopefully here in the summer, a reference to NCRP-155, and NCRP-155 right now has guidance for cremation.

But you can form a subcommittee to address more of Reg Guide 8.39, I wasn't trying to stop that. But I am saying right now we are going to reference NCRP-155 in the near term soon to kind of have a stop gap.

CHAIRMAN PALESTRO: Thank you. Do you want to --

VICE CHAIRMAN METTER: Thank you. Also, you know, usually when you talk about cremation you also talk about autopsies and I really think that should also be included in this investigation.

DR. TAPP: Yes. NCRP-155 discusses cremation and autopsy. One other thing to mention is Dr. Zanzonico, a former nuclear medicine physicist,

did have a talk with the ACMUI I believe in 2015 on cremation, so there was a presentation from him where he looked at gaseous plumes and had some follow-up items just for consideration as you go forward.

CHAIRMAN PALESTRO: Mr. Green?

MEMBER GREEN: A question for Dr. O'Hara. Would it be conceivable that the NRC, the FDA, can ask the manufacturers when they revise PIs or submit PIs for new NDAs that they include information on graded pharmaceuticals on autopsy and cremation?

MEMBER O'HARA: The labeling that the FDA looks at is by definition draft labeling, so we can ask for that in the labeling and the manufacturer can change that.

And then where it becomes, when it becomes an issue is when an inspector goes to a manufacturer and sees that that has been changed, but it can be a long drawn out process, yes, but that is a safety consideration that I think that we can at least propose.

MEMBER GREEN: With the number of new therapies, you know, we're changing nuclear medicines, changing from a primarily diagnostic modality to a much more robust therapeutic modality with the theranostics that are coming our way, you'll have many

coming across the FDA desk where maybe that's an ask you make for these new therapies and we'll catch up the other ones later.

But I think it would be great to have a resource to the prescriber and to other practitioners that is actually in the labeling for the product on autopsy and cremation.

MEMBER O'HARA: I will pass that on to the drug side of FDA as well because the theranostics they usually get the call on those.

CHAIRMAN PALESTRO: Any other comments or questions? Ms. Holiday?

MS. HOLIDAY: Dr. Palestro, as Dr. Diabes was mentioning, and Dr. Tapp as well, you do have an existing subcommittee that is looking at the draft Regulatory Guide 8.39, which they both mentioned.

Just to remind you guys of who the members are on that subcommittee as they, those subcommittee members, were provided with the draft Reg Guide last week.

The members are Dr. Dilsizian, Ms. Martin, Dr. Schleipman, Ms. Shober, Ms. Weil, and Mr. Sheetz is the Chair of that subcommittee. The NRC staff resource is Dr. Diabes and in particular there is, as Dr. Diabes mentioned, a section in the Reg Guide that

is related to patients who are deceased after undergoing radioactive administration.

So I don't think that you have to amend the charge of the subcommittee as their charge is to review the Reg Guide in its totality and provide comments to the NRC staff.

CHAIRMAN PALESTRO: Thank you. Mr. Sheetz?

MEMBER SHEETZ: As the Chair of that subcommittee and actually I was wondering if this topic was going to come up, I was going to bring it up also later, because the JAMA article did get a lot of media attention, I do think it's an issue that needs to be evaluated further.

While there are NCRP-155 guidelines I am not sure how practical they are. It's a very difficult and sensitive situation when someone dies, you know, whether they are to be cremated or not, they may have pre-arrangements. It's very difficult to stop that process to go with alternative plans.

So I think it does warrant for the study, you know, is there a potential risk to workers and the general public from the radiation, what's the magnitude of the risk, how prevalent is the event, although cremation is now over 50 percent of all burials in the United States, what guidance can be

provided to reduce or mitigate that, and so these are the questions we will certainly look at.

CHAIRMAN PALESTRO: Thank you. Is the -- Is Ms. Weil on that subcommittee? I'm sorry, okay. Yes, I would think that would be appropriate, especially appropriate for the patient rights advocate.

MEMBER SHEETZ: Thank you.

CHAIRMAN PALESTRO: Mr. Ouhib?

MEMBER OUHIB: Yes. I just have -- I think, and maybe Ms. Shober can answer this question, this is not just addressing like the concern with the authorized uses and all that, but this goes to the cremation centers and all that that if in the event there is a -- How would you determine that a patient has radioactive material or not, you know, when they come from cremation?

I guess the question is does the state get involved with these cremation centers at all, is there any communication?

MEMBER SHOBER: This is Megan Shober. So I can only speak for my experience. We have been involved with cremation centers in the past. Usually we find out about that from the licensee where the decedent had been previously treated.

And so it's not clear how that information comes. You know, like there is not a process for that. But as soon as our licensee found out about it they followed up with us.

And I am not sure how else you can regulate that, but it is a huge -- By the time you find out about it it's happened and it's happened a while ago usually.

CHAIRMAN PALESTRO: Thank you. Any other comments, questions?

(No audible response)

CHAIRMAN PALESTRO: Mr. Sheetz, are you comfortable with the subcommittee that is already formed?

MEMBER SHEETZ: Yes. Yes, I am.

CHAIRMAN PALESTRO: All right. Thank you. All right, then the afternoon session, the open session is adjourned and Ms. Holiday --

MR. EINBERG: Wait.

CHAIRMAN PALESTRO: I'm sorry, Mr. Einberg.

MS. HOLIDAY: And we'll resume at 8:30 in the morning tomorrow. Mr. Einberg?

MR. EINBERG: Yes. Actually before we close this with the creation of a new subcommittee for cremation does this possibly merit a separate

subcommittee because of the extensiveness of the issue?

For 8.39 we are looking for a fairly rapid turnaround on the review of that Reg Guide. We are asking for a 60-day turnaround on that. Would additional time and a separate subcommittee give you the opportunity to explore this issue in more detail or --

CHAIRMAN PALESTRO: I will defer to Mr. Sheetz on that.

MEMBER SHEETZ: Why don't you allow our subcommittee to look at that and if we need further time on that particular topic we could come back and do that.

MR. EINBERG: Okay.

MEMBER SHEETZ: I would like to stay involved in that. I have an interest. I grew up in that business from my father and so I am interested in seeing this through.

MR. EINBERG: Okay. Thank you.

CHAIRMAN PALESTRO: Any other comments, questions?

(No audible response)

CHAIRMAN PALESTRO: This session is adjourned. Thank you all.

MS. HOLIDAY: Thank you.

(Whereupon, the above-entitled matter went off the record at 2:27 p.m.)

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April 2, 2019

Hon. Kristine L. Svinicki
Chair, U.S. Nuclear Regulatory Commission
Mail Stop 016-B33
Washington, DC 20555-0001

Cc: Andrea Kock
Director, Division of Materials Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards

Re: Extravasations of diagnostic radiopharmaceuticals and Medical Event Reporting

I am writing to respectfully request that the Nuclear Regulatory Commission (NRC) and the Advisory Committee on the Medical Use of Isotopes (ACMUI) re-evaluate the 1980 decision regarding extravasations and begin requiring Medical Event reporting of diagnostic radiopharmaceutical extravasations that exceed Subpart M-Reporting and Notification limits. This request supports my presentation to the ACMUI on April 3, 2019 regarding this same topic.

NRC and Extravasations

In 1980, the NRC amended the Misadministration Reporting Requirements. Details regarding this change can be found in the Federal Register Vol. 45, No. 95, Wednesday, May 14, 1980 Rules and Regulations 31701, Supplementary Information. The Supplementary Information included details regarding public comments and the NRC responses. In responding to comments, the NRC expressed several fundamental tenets regarding misadministrations:

- The reporting of misadministrations is clearly consistent with NRC regulatory responsibilities and a necessary part of an effective nuclear medicine regulatory requirement.
- Misadministrations should be reported so that causes can be identified to enable corrections and to prevent recurrence. Seemingly isolated incidents at individual medical institutions could reveal a generic problem when compared nationally.
- The significance of a diagnostic misadministration goes beyond radiation exposure to the patient if it results in misdiagnosis. Diagnostic misadministrations are of serious clinical concern because they can clearly compromise the effectiveness of the diagnostic procedure.
- The goal of the NRC is to protect patients and patients have the right to know about the risks associated with their diagnostic procedures. When patients are involved in a serious misadministration, they should be informed.
- Referring physicians should also be informed of misadministrations.

Several public comments questioned whether an extravasation should be considered a misadministration. An extravasation is the inadvertent injection of some or all of the radiopharmaceutical dose into the tissue surrounding a vein or artery. Extravasations can happen when a catheter punctures or erodes the venous wall or when the injection pressure damages the venous wall.(*1*) An extravasation results in some of the dose not being administered through the prescribed route of administration (i.e., a bolus injection into the venous system). Instead some of

the dose is administered into the tissue surrounding the vein and slowly clears through the lymphatic system. The NRC reached the decision that an extravasation should **NOT** be considered a misadministration. Their decision in 1980 was supported with the following justification: "**extravasations frequently occur in otherwise normal intravenous and intraarterial injections and are virtually impossible to avoid".**

A 1980-2002 review of the NRC position on misadministrations of radiopharmaceuticals found consistent emphasis on the importance of patient safety and a focus on the implementation of quality management programs to try to reduce misadministrations. A change to reporting thresholds was implemented (the 5-rem total equivalent dose was increased to 50-rem) as well as the introduction in August 1994 of the *Quality Management Program and Misadministration Rule*.

In 2002, the NRC amended its regulations regarding the medical use of byproduct material. Below are some discussions related to extravasations.

- The term "misadministration" was replaced with the term "medical event" (ME). In the Supplementary Information supporting the changes to the regulation, the NRC stated the misadministration term was replaced because some believe the term had "negative connotations implying negligence on the part of the physician or other hospital workers". Furthermore, "the term 'medical event' more correctly and simply conveys that the byproduct material or radiation from the byproduct material was not administered as directed by the AU".
- The Supplementary Information also described the importance of retaining "radiation protection-related requirements because of their contribution to risk reduction" as part of the 2002 Final Rule. The NRC used quality control tests for radioactivity of patient dosages as an example of a retained requirement because QC would help ensure that the dosage administered to the patient is as prescribed by the Authorized User.
- Support for notifying patients about a medical event was reinforced when the NRC stated, "We continue to believe that patient notification enables patients, in consultation with their personal physicians, to make timely decisions regarding any remedial and prospective medical care. This approach also codifies existing medical ethical standards obligating physicians to provide complete and accurate information to their patients."
- Support for requiring Authorized Users to notify referring physicians of medical events was emphasized. The NRC stated, "It is important that a referring physician is aware of medical events involving individuals. The referring physician knows the individual and his or her medical history and is likely to be in the best position to make a decision about whether informing the individual about the medical event would be harmful. That physician may also need to evaluate any follow-up actions relative to the individual's overall health history. Although notification of referring physicians may represent the "standard of care," that practice may not be uniformly followed. Therefore, the NRC retained the current requirement for a licensee to notify the referring physician about a medical event."
- The reporting and notification requirements for medical events were moved to Subpart M.
- The 50 rem or 0.5 Sievert (Sv) reporting limits were shown to correspond to the annual occupational dose limits in Part 20 and the level for reporting overexposures of workers to NRC. The Commission stated, "We believe that applying these same thresholds to reporting exposures to patients is reasonable."

In January 2008, the Boston VA hospital reported an extravasation as an ME to the NRC because the effective dose equivalent to the tissue caused by the extravasation may have exceeded the ME reporting limit of 50 rem. The NRC staff reviewed the May 14, 1980 Supplementary Information that had determined that extravasations should not be considered as misadministrations and,

therefore, concluded that the VA extravasation did NOT require reporting as an ME. As a result, the January 2008 Boston VA hospital extravasation report was retracted. Later in 2008, the NRC consulted with the ACMUI for their opinion on this NRC decision. As recorded in the ACMUI meeting minutes, both Dr. Vetter and Dr. Nag agreed that extravasations of diagnostic radiopharmaceuticals should continue to NOT be considered as misadministrations. The motion that "at this time, NRC should continue its policy of not requiring extravasations of diagnostic dosages to be reported as MEs" passed unanimously.

Today, with the help of new technology, there is evidence that nuclear medicine extravasation rates can be significantly reduced with minimal time, effort and cost, while reducing the risk of diagnostic misadministrations. This new evidence should be considered in conjunction with the long-held NRC beliefs about misadministrations and the information about extravasations that is presented in the sections that follow.

Extravasations negatively affect nuclear medicine studies

PET/CT and gamma camera images are derived from the radioactivity injected in the patient. Patients are injected with a prescribed radiopharmaceutical dose for a pre-defined uptake period to allow the radiopharmaceutical to disperse throughout the body and collect in tissue or organs before imaging begins. Imaging begins after the uptake period and when the patient is positioned with respect to the imaging equipment. When imaging begins, the detectors in PET/CT and gamma cameras start recording the gamma radiation and its distribution within the body. Computer algorithms (software) reconstruct the gamma rays into images based on the anatomic location where the rays originated and the quantity of radioactivity detected. Capturing the absolute quantification of the radiopharmaceutical distribution is one of the most valuable clinical strengths of PET imaging. This biological quantification is important for current patient care, important for precision medicine, and is a unique aspect of PET as compared with other clinical imaging modalities (e.g., CT, ultrasound, or MRI).

To create high-quality images and quantitative results, the reconstruction algorithms require manually-entered inputs, including precise information regarding the amount of radioactivity administered to the patient and the size of the patient. For nearly all procedures, clinicians require this dose be administered quickly and all at once (i.e., a bolus administration). The exact amount of uptake time the radiopharmaceutical is in circulation between the bolus and the creation of the image is also critical to image quality, quantification, and analysis. An extravasation results in radioactive dose that remains in the arm. This extravasated dose can leak back into circulation during the uptake period, degrade image contrast and quality, and contribute to inaccurate quantification. Additionally, collecting every gamma ray matters. The more counts available to the reconstruction algorithm, the better the image and the more accurate the quantification. Certain nuclear medicine scans require very low levels of injected radioactivity. Even small extravasations of these injections can have a meaningful negative effect on image quality, since the extravasated amount can represent a high percentage of the administered dose. When some of the prescribed radioactive dose is not delivered into the patient's circulation, the radiation from the undelivered dose cannot contribute to the accurate formation of images and quantification. And because the algorithm assumes the entire radioactive dose was delivered, extravasations negatively affect the resulting images and quantification results.(*2-4*) At this time, there is no way to account for, correct for, or fix an extravasation.

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Quality control (QC) exists, but not for extravasations

QC procedures for PET/CT and gamma camera scans are mandated by regulation in Europe and Australia.(*5*) In the US, QC is not mandated by regulation but is encouraged by medical societies (*6-9*) and multiple guidelines have been created for how to conduct nuclear medicine procedures. Many of these guidelines are focused on minimizing biological and behavioral factors that might adversely impact image quality and quantification. For example, in PET/CT imaging the accuracy of the dose calculations is essential for the proper reconstruction of the image. The goal of the QC steps shown in the table below is to ensure precision in the amount of dose that has been delivered into circulation and that is available for uptake. The table also describes how an extravasation affects this QC goal.

Quality Control or Protocol Process	Impact	Importance	Extravasation Effect
Measuring the residual dose left in delivery syringe after saline flush	The residual dose measurement is subtracted from the dose injected to provide a "net administered dose". The residual information affects the accuracy of the administered dose, which is an input into the PET/CT scanner and in the calculation of the Standardized Uptake Value (SUV).	Research from Osama Mawlawi, PhD at MD Anderson showed that the residual typically accounts for a 0.25% to 5% inaccuracy in the image quantification.	Same effect. Depending upon the severity of the extravasation, the quantification can be impacted from 0.25% to nearly 100%.
Entering the net administered dose into the PET/CT scanner	An incorrect entry negatively affects the calculation of the SUV.	The accuracy of the dose is critical for the quantification of the image.	Same effect. An extravasation ensures that the administered dose that is entered into the PET/CT scanner and that is used in the SUV calculation is wrong. Depending upon the severity of the extravasation, the quantification can be impacted from 0.25% to nearly 100%.
Synchronizing Clocks	Radiotracer doses are measured prior to the patient injection. The time of measurement is important in ensuring the proper decay calculation of the radioactive isotope. This impacts the accuracy of the dose and the calculation of the SUV.	Not recording the proper time that the dose was administered negatively affects the SUV.	Same effect. An extravasation results in some of the dose being delivered at a later time than intended, if it is delivered at all. This results in an understated SUV.
Delivering the dose as a bolus in first 30 to 60 seconds of the injection	A delayed or continuous injection reduces image quality and accurate quantification.	If the dose is being administered continuously throughout the uptake period then the dose remaining in the vascular system at the time of imaging is at a higher concentration than if the dose had been delivered as a bolus. This reduces the contrast and thus the image quality and sensitivity. It also negatively affects quantification because the tumor has not been exposed to the full dose for the full uptake period. This also impacts longitudinal image comparisons.	Same effect. An extravasation ensures the dose is not delivered as a bolus.

Quality Control or Protocol Process	Impact	Importance	Extravasation Effect
Uptake time from Injection to Imaging	Insufficient or inaccurate uptake time negatively affects quantification and image quality	It is essential in the comparison of two longitudinal images that the time between injection and imaging be as consistent as possible to ensure the tumor exposure to the dose is consistent. Changes in tumor uptake should be based on tumor characteristics, not on time of exposure to the dose. In addition, the length of uptake time is important to tumor uptake. The reporting of the uptake time allows clinicians to understand the implications to tumor quantification.	Same effect. An extravasation completely confounds quantification and scan comparison. When the dose is not delivered as a bolus, one cannot calculate with any accuracy the time between injection and imaging. The SUV will be understated.

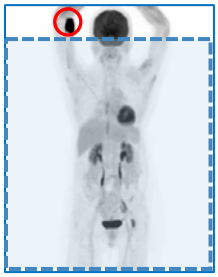
Current QC guidelines are important, are recorded, and help inform physicians regarding the quality of the diagnostic test. But current QC guidelines are missing a crucial step, ensuring that the entire administered dose enters the patient's circulation. Extravasations, which have no current QC guidelines, can have a far greater negative effect than the errors that the current QC steps are intended to address. And because extravasations often go undetected,(*10*) clinicians may unknowingly make patient management decisions using compromised images.(*11*) The only adequate solution is for a clinician to know when an extravasation happens and determine if the scan results should be used or if the scan should be repeated on a different day.

Extravasation detection

Historically, nuclear medicine extravasations have been difficult to detect during injection or upon review of the produced images. These detection difficulties are likely the result of:

- Nuclear medicine scans usually use small injection volumes of non-vesicant radiopharmaceuticals that do not cause immediate, visible changes to the overlying skin near the injection site, nor immediate pain to the patient.

- During clinician interpretation of the PET/CT images, the injection sites are often outside of the limited imaging field of view (FOV).(*10*) Area outlined by dashed blue line is the typical FOV.



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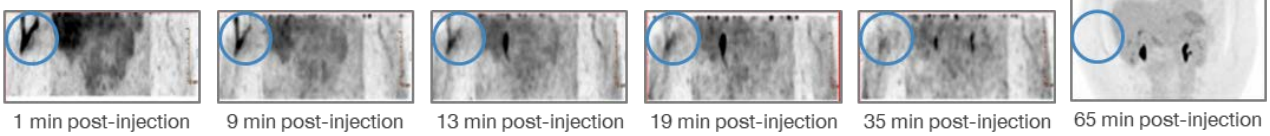
- Extravasations may have resolved (sometimes completely, see images below and right) after injection and before the image is obtained. In these situations, clinicians may not see any evidence of an extravasation on the image even when the injection site is included in the imaging FOV.(*12,13*)



Dynamic PET image acquisitions of injection site, taken during the uptake period, capture a resolving extravasation. Standard routine PET/CT image (far right) of the same patient provides no evidence of extravasation from uptake period.

Nuclear Medicine Extravasation Incidence

While not many nuclear medicine centers have reported their extravasation rates, a few have. These published and presented results support the NRC belief that diagnostic radiopharmaceutical extravasations frequently occur in otherwise normal intravenous and intraarterial injections.

- Published results – In six studies, St. Louis University, Ohio State University, and the University of Santiago in Spain have attempted to understand the magnitude of the extravasation issue by retrospectively reviewing routine static PET/CT images that were taken after the uptake period, approximately 60-90 minutes after injection. These clinical studies involved 2,804 patients and found 425 extravasations (15.2%). The PET/CT centers' extravasation rates ranged from 3-23%.(*10,14-18*) These rates are likely underestimated, due to the fact that the imaging FOV often does not include the area of the injection.(*10*)
- Soon-to-be-published Lara Quality Improvement Project - MD Anderson Cancer Center, UCLA, University of Tennessee Medical Center, Wake Radiology Services, Carilion New River Mobile, Wake Forest University, and Carilion Memorial Hospital, using Lucerno technology prospectively throughout the uptake period will report an aggregate of 2,431 patients and 150 extravasations (6.2%), with centers' extravasation rates ranging from 2-16%. Extravasation rate by technologist ranged from 0-24%.(*19*) These results likely underestimate the true extravasation rate due to the "observer" or "trial" effect, where technologists were trained on the importance of injection quality and knew that all of their injections were being monitored.
- Unpublished, presented project - All nine nuclear medicine sites (three hospitals and six centers) in Edmonton, Alberta contributed to a quality improvement project involving 450 Tc-99m MDP SPECT bone scans. They reported 79 extravasations (17.5%). The centers' extravasation rates ranged from 0-44%.(*20*)

Lucerno's early clinical work also supports the NRC belief that extravasations frequently occur. Assessments in three centers using Lucerno technology throughout the uptake period involved 393 patients and found 152 extravasations (38.7%). The centers' extravasation rates ranged from 18-40%. Extravasation rate by technologist ranged from 0-44%.

Extravasations can matter in many ways

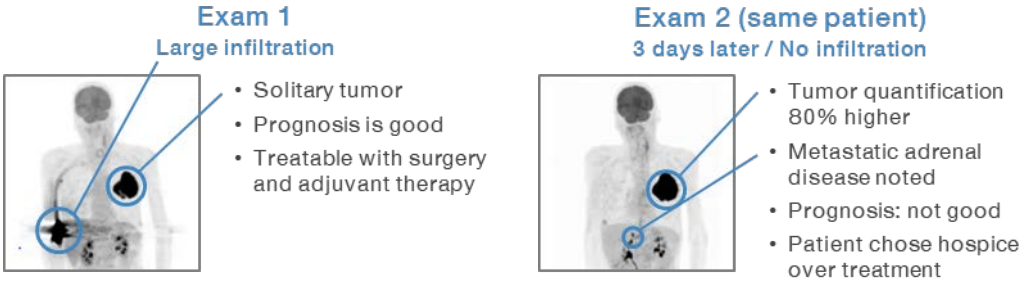
As previously noted, the NRC recognizes that the significance of a diagnostic misadministration goes beyond radiation exposure to the patient; diagnostic misadministrations are of clinical

concern because they can clearly compromise the effectiveness of the diagnostic procedure. While not all extravasations will matter acutely or to ensuing patient care, many will.

Of the three million PET/CT procedures each year in the US, over 90% are used to help oncologists diagnose, stage, choose therapy, plan treatments, assess tumor response, or longitudinally monitor cancer patients.(*21-29*) A few years after PET/CT scan reimbursement was approved by CMS, data from 40,863 PET/CT procedures performed at 1,368 centers were reported in the National Oncologic PET Registry (NOPR). The impact of PET/CT was assessed for 18 cancer types in patients with pathologically confirmed cancer. When intended management was classified as treatment or nontreatment, PET/CT images caused clinicians to change their intended management for 38% of patients. The NOPR demonstrated that PET/CT scans are a very sensitive imaging modality with respect to cancer,(*30,31*) and that the scan results play an important role in therapeutic decision-making.

Importantly, extravasations have a negative effect on the sensitivity of PET/CT. The clinical implications of an extravasation on a PET/CT study for the management of cancer patients include:

- Under-staging the disease. Leads to unnecessary (ineffective) surgery and its associated morbidity and cost, and delays initiation of necessary systemic treatment (e.g., a lung cancer patient's metastatic disease is missed (*3*) and the patient receives unnecessary surgery for what is thought to be a single lung lesion). The ways in which under-staging can occur include:
  - Failure to detect metastatic disease due to degraded PET/CT image quality and inaccurate quantification results. Due to low count rates, some metastatic disease may not be seen, or if visible, may be considered to be benign.(*11,32-35*) See example below.



  - Masked metastatic disease caused by significant extravasation artifacts in image.(*36*)
  - Misinterpreting metastatic disease, identified near an expected injection site location, as an extravasation.(*37*)
- Over-staging the disease. Leads to treatment for metastatic disease, which withholds potentially lifesaving regional therapy from the patient (e.g., an incorrect finding of metastatic disease in a lung cancer patient with a single lesion results in systemic treatment for metastatic disease rather than regional surgery or radiation therapy). The ways in which over-staging can occur include:
  - False positive lymph nodes with no obvious evidence of extravasations (due to the transport of extravasated radiopharmaceuticals through lymph channels to regional lymph nodes) may result in unnecessary invasive procedures like fine needle aspiration cytology (FNAC) or changes in chemotherapy regimens.(*32,36-54*)
  - False positive bone scans.(*55,56*)
  - Spurious lung lesions caused by radioactive clots from extravasations; such spurious lesions may require investigation by diagnostic CT and sometimes rescanning to ensure there is not a lung lesion.(*34,36,46,57-59*)

- Therapeutic procedure planning errors. Several oncologic treatment procedures rely on accurate PET/CT scans to correctly plan the therapy. For example, to plan potentially curative radiation therapy, the precise extent and location of the tumor must be known. Accurate PET/CT procedures can be crucial for the radiation oncologist to determine the patient's "planning treatment volume." Defining the gross tumor volume is the single most important step in the planning process and all other planning steps depend upon it. If the tumor is not well imaged and the gross tumor volume is not well-defined, then the entire treatment process may be futile. Oncologists use PET in target volume delineation due to its higher sensitivity and specificity compared to CT, the standard structural imaging modality. Numerous published papers show that including PET/CT information in the planning process alters treatment volumes that were originally based on CT information alone. Additionally, when patients undergo PET/CT just for radiation treatment planning, very small doses of radiopharmaceutical are used.(*60*) As previously described, small doses can be especially affected by even small extravasations. Specific examples of extravasation implications on planning include:
  - In visual assessment of the gross and clinical tumor volume, contrast of the image is very important. An extravasation can negatively affect image quality and underestimate the size of a tumor, resulting in inaccurate radiation treatment planning.(*60*)
  - In quantitative assessment of the gross and clinical tumor volume, an extravasation alters thresholds (because of lowered count rate) and therefore provides an incorrect planning treatment volume.(*60*) See patient example below where in a controlled test-retest study of results from a PET/CT scan with an extravasated injection (Day 1) and from a scan five days later with an ideal injection. The metabolic tumor volume (MTV) for four metastatic lesions were quantified.

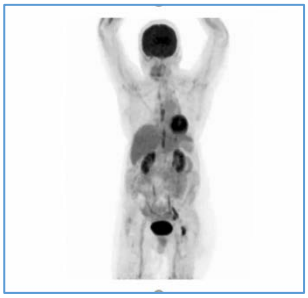
	Day 1 MTV Extravasated Injection	Day 5 MTV Ideal Injection	Understated
Lesion 1	7.43	11.34	34%
Lesion 2	5.57	10.66	48%
Lesion 3	27.77	41.07	32%
Lesion 4	0.88	2.93	70%

- Therapy assessment errors, due to understated quantification of baseline or follow-up scan.(*14,35,58,61-70*) For example:
  - An extravasated baseline study, compared with a properly injected follow-up study, may falsely indicate disease progression. Treatment may be working, but the images do not reflect this improvement. See example below. The patient was extravasated in the left hand (Day 1) and as part of a test-retest study received a second PET/CT scan 5 days later with study parameters controlled to assess the impact of the extravasation on SUV measurements of four lesions.

	Day 1 SUV Extravasated Injection	Day 5 SUV Ideal Injection	Understated
Lesion 1	5.27	10.49	50%
Lesion 2	3.97	5.94	33%
Lesion 3	7.17	11.46	37%
Lesion 4	2.62	5.73	54%

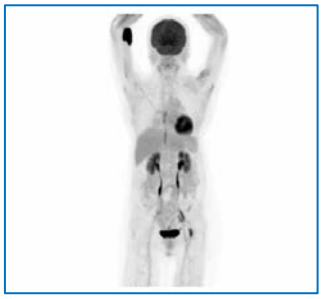
  - An extravasated follow-up study, compared with a properly injected baseline study, may falsely indicate response to treatment. Treatment may not be working, but the images suggest tumor response. See hypothetical treatment assessment example using an actual extravasated patient below:

Exam 1
No extravasation at baseline



Left pelvic lesion with SUVmax – 7.1 and an SUVmean – 4.1

Exam 2 (same patient)
Extravasation at follow up



Left pelvic lesion with SUVmax – 5.63 (21% decrease) and an SUVmean – 3.28 (20% decrease)

- Ambiguous results, caused by extravasations, unnecessarily subject the patients to invasive procedures or repeat scans, with additional radiation exposure.

PET/CT for indications other than oncology. Approximately 10% of PET/CT procedures are performed to assess myocardial perfusion, neurological function, and other physiologic processes.(*28,71*) Extravasations in these procedures can also have negative patient management implications. For example:

- A myocardial perfusion study. An extravasation on either the rest or stress exams can directly lead to either a false positive or false negative misinterpretation of the study with serious consequence for patient management.(*11,72-74*)

- An FDG neurological function study. An extravasation limits the FDG uptake in the brain and would adversely affect the reported results.(*75*)
- Amyloid plaque imaging for Alzheimer's disease and dementia diagnosis. An extravasation can cause poor image quality due to low counts and can lead to study misinterpretations.(*76*)
- Fever of unknown origin (FUO) study. FUO cases have mortality rates between 12-35% and more than 50% of these cases cannot be diagnosed using conventional imaging. PET/CT imaging shows relatively high sensitivity and specificity and can be used to improve diagnosis.(*77*) However, an extravasation may compromise imaging sensitivity and diagnostic capability.

Gamma camera. There are 15.5 million gamma camera procedures each year in the US. Extravasations of these procedures have similar implications to those found in extravasated PET/CT procedures: misinterpretation of results may lead to patient harm, unnecessary invasive procedures, and additional exposure to radiation from repeat scans. Below are some examples from published literature of gamma camera procedures and the possible implications of an extravasated injection. These examples are not intended to be comprehensive, but rather a means to illustrate the pernicious effect that extravasations can have on the quality of the resulting images and patient care.

- Kidney function. A renal scan/glomerular filtration rate (GFR) study quantifies kidney function. Extravasated injections cause false-positive findings, require repeat procedures,(*45*) invalidate GFR studies, and may not be visible in the imaging FOV.(*78,79*)
  - GFR tests are used to determine kidney donor eligibility; a falsely low GFR calculation rules out donation.
  - GFR is used to modify chemotherapy regimens based on kidney function; an affected GFR can lead to inappropriate cessation of chemotherapy treatment.
- Cardiac function. Tc-99m Sestamibi studies assess cardiac ventricular ejection fraction. An extravasated injection may compromise the study in three ways.(*72*)
  - Because less radiopharmaceutical is taken up by the myocardium, counting statistics are lowered, resulting in a scan with poor-quality images.
  - If the extravasated injection occurs during the second phase of a same-day study, the resultant second scan will be confounded by activity from the first injection. Thus, ischemia induced during a stress study may be masked—a significant error.
  - An extravasation can lead to altered distribution of the radiopharmaceutical, such as uptake in lymph nodes. Visualization of lymph node activity on the cine (dynamic) raw data images may inappropriately lead to an investigation for malignancy.
- Chemotherapy monitoring. Multigated Acquisition (MUGA) studies of the heart also assess left ventricular ejection fraction and can be used to assess the impact of a patient's chemotherapy treatment on myocardial function. An extravasation during the administration of the stannous ion compound or Tc-99m pertechnetate will result in suboptimal radiolabeling of blood cells with corresponding increased amounts of residual, unreacted free pertechnetate.(*80*) A false positive interpretation can lead to inappropriate cessation of chemotherapy treatment.
- Neurological assessment. Dopamine transporter imaging studies assess Parkinson's disease, only image the brain, and use a slow, 20-second IV injection of Ioflupane I-123. An extravasation of Ioflupane I-123 can confound the dopamine transporter study results.(*81*) In a study of 224 patients, 30 injection issues were documented.(*82*)
- Pulmonary embolism diagnosis. Ventilation Perfusion (V/Q) studies are used to diagnose the presence of pulmonary embolisms (PE), a particularly dangerous condition.
  - A V/Q scan compares two views of the lungs. The ventilation (V) image is created by breathing in air that includes a radioactive substance. The perfusion (Q) view is created by

injecting a radioactive substance with a different gamma-ray energy in an arm vein. The injection arm is out of the imaging FOV.
    - An extravasation creates the opportunity for false negative interpretations (*83*) with potential serious patient implications. In pregnant women for example, undiagnosed PE (e.g., false negative) has a mortality rate as high as 30%, which falls to 2–8% if the condition is diagnosed and treated appropriately.(*84*) If an extravasation is suspected, the study is repeated the next day with additional patient radiation exposure.(*85*)
- Bone evaluations. Planar bone scanning is one of the most common gamma camera procedures. The study requires a sharp, single-peaked bolus injection and the benefits of the study are greatly influenced by the quality of the image. A bone scan that has been compromised by an injection issue has several clinical implications:
    - Misinterpreting an extravasation for pathologic findings
    - False positive lymph node uptake
    - "Compton scatter" caused by the extravasation, leading to misinterpretation of significant breast abnormality (*86*)

In addition to the negative patient effects caused by compromising diagnostic studies, extravasations can affect patients in other ways. Using Monte Carlo simulations and actual PET data, we have concluded that some diagnostic radiopharmaceutical extravasations can exceed the Subpart M Reporting and Notification limit of 50 rem or 0.5 Sievert (Sv) effective dose equivalent to the tissue.

We investigated three radiopharmaceutical extravasation scenarios: (A) hypothetical size with activity based on tumor SUV change, (B) both size and activity based on patients' PET measurements, and (C) hypothetical size and activity. In these three simulations, no activity was modeled in the rest of the body – only the activity within the extravasation. Thus, the dose calculated is due only to the extravasation.

In example A, we simulated an actual case where the hand was out of the imaging FOV and the tumor quantification was understated by 30-74%, as observed in a controlled test-retest study designed to assess the effect of infiltrations. By knowing the injected dose and the tumor quantification changes, and by estimating the reabsorption process, we calculated how much radioactivity was extravasated into the hand. The estimated effective dose equivalent to the tissue was 11.5 Sv. In example B, we used patient data to represent how the effective dose equivalent of an extravasation can be easily underestimated by using only static PET images. In this example, by the time of imaging (107 minutes post injection) ~100 micro Curies of activity was left at the injection site. However, by monitoring this extravasation after the injection and before imaging, we know the rate at which the extravasation was resolving during the uptake period. That information, combined with an extravasation volume based from PET data, leads to an estimated effective dose equivalent to the tissue of 2.26 Sv. In example C, we created a simulation that we believe is representative of many of the extravasations we have monitored. We simulated an extravasation of 1 mCi at time of imaging with a reabsorption time of 166 minutes. The estimated effective dose equivalent to the tissue was 3.41 Sv. The engineering report that details these calculations is attached as Appendix A.

	Time between injection and imaging	Estimated extravasation activity at time of imaging	Estimated effective dose equivalent to the tissue from injection to reabsorption time
A	57 minutes	4.55 mCi	11.5 Sv (~23x limit)
B	107 minutes	0.11 mCi	2.26 Sv (~4.5x limit)
C	60 minutes	1.0 mCi	3.41 Sv (~6.8x limit)

Therapeutic radiopharmaceutical extravasations can cause severe patient injury near the injection site (*32,39*) and can also exceed Subpart M Reporting and Notification limits. Using Monte Carlo simulations to model the effects of a Lutetium-177 radiotherapeutic extravasation, we have concluded that even a small (5%) extravasation of the 200 mCi infusion can expose the tissue and skin to effective dose equivalent amounts that exceed reporting limits. The engineering report that details these calculations is attached as Appendix B.

Finally, in addition to the harm that extravasations can cause by compromising diagnostic procedures and by unnecessarily exposing tissue and skin to effective dose equivalents that exceed NRC reporting limits, known extravasations can cause patients to undergo repeat diagnostic studies, where they receive additional radiation exposure and increase costs for patients and payers.

Extravasations are avoidable

There is substantial and current evidence supporting the NRC statement: “extravasations frequently occur in otherwise normal intravenous and intraarterial injections”. In addition, there is substantial evidence that supports the NRC belief that extravasations can negatively affect diagnostic procedures and thus patient care. ***However, the NRC belief that extravasations are “virtually impossible to avoid” is incorrect***.

In injection processes for patient populations similar to nuclear medicine patient populations, monitoring and reporting requirements have led to continual quality improvement efforts, and extravasation rates have declined to low levels over time. Despite this improvement, clinicians continue to make large scale efforts to drive these rates even lower.(*87*) Chemotherapy extravasation rates in the 1980s and 1990s ranged from 3-6%.(*88,89*) A recent attempt to create a national benchmark of the chemotherapy extravasation rate assessed 739,832 patients. The overall extravasation rate was 0.10% with peripheral IV and central venous access methods contributing estimated extravasation rates of 0.18% and 0.01%, respectively.(*90*) Similar efforts to reduce non-ionic iodinated contrast medium extravasation rates have also proven successful. CT extravasation rates from 1991-2007 were 0.45%. In 2015, A National Data Registry and Practice Quality Improvement Initiative involving 454,497 CT scans showed that rates had improved to 0.24%.(*91,92*)

Low extravasation rates can also be accomplished in nuclear medicine injections. Four of the centers that participated in the Lara QI project designed quality improvement plans based on extravasation contributing factors specific to their centers and improved their extravasation rates (see table below). Their aggregated rate had a statistically significant decrease, from 8.9% to 4.6% ($p<0.0001$). These results were accomplished in approximately six to eight months from the time the centers began measuring their baseline extravasation rates. In fact, two of these centers are now approaching 1% extravasation rates.

Site	Measure Phase Rate	Standard Error	Improve Phase Rate	Standard Error	Change
A	13.3%	2.1%	2.9%	1.0%	-78%
B	15.7%	4.0%	6.0%	2.6%	-62%
C	12.8%	1.5%	8.7%	1.3%	-32%
D	2.1%	0.6%	1.9%	0,6%	-10%

Extravasations will matter even more in the future

Prevention of extravasated radioactive injections will become more important for US patients in the future for three reasons:

- Procedure volumes will increase. PET/CT and gamma camera procedures are expected to grow in volume and importance as precision medicine initiatives increase.(*28,71,93-97*) As a result, more patients will be extravasated.
- Per-procedure doses will decrease. As part of an effort to reduce radiation exposure for patients, clinicians are being asked to administer doses that are “as low as reasonably achievable” (ALARA). US clinicians currently use significantly higher doses (~2x) of PET/CT radiopharmaceutical than those in Europe and Asia. Extravasations of lower administered doses will have a greater negative effect on image quality and quantification. An extravasation of a 1 mCi dose may only have a 5% impact to a nuclear medicine study using a 20 mCi dose. However, that same 1 mCi extravasation of a study using a 5 mCi dose will result in a 20% impact to the scan results. Moving forward with the ALARA principle will result in a higher proportion of cases where extravasations potentially affect patient management.
- Use of alpha and beta emitting therapeutics is growing. As radiotherapeutics enter the US market, the stakes rise in yet another way. Radiation from alpha and beta emitters is different (half-life and distance traveled) than gamma emitters and can be more dangerous when extravasated. Even a small extravasation of an alpha or beta emitter can provide a significant effective dose equivalent to the skin (as simulated in Appendix B) and destroy the tissue at the injection site.(*98,99*)

Interested parties

Addressing the extravasation issue appears consistent with the goals of all parties involved in nuclear medicine.

Identifying, and then reporting extravasations that qualify as a medical event, and reducing the incidence of extravasations, seem consistent with NRC goals:

- To protect patients from unnecessary radiation exposure, as well as from compromised diagnostic studies.
- To receive reports, determine causes, and prevent recurrence.
- To ensure referring physicians and patients are notified of medical events that have exceeded reportable limits.

Correcting the extravasation issue is also consistent with nuclear medicine and molecular imaging societies' policies. These societies are focused on patient safety, as evidenced by their consistent public comments during the NRC's latest request concerning the training and experience levels of Authorized Users. These societies also understand that radiotherapeutic extravasations will cause acute patient harm and that the technologists extravasating diagnostic doses today will be the same technologists responsible for therapeutic injections tomorrow. Additionally, societies believe that nuclear medicine can play an important role in the practice of precision medicine; extravasations result in imprecise medicine. More specifically, the Society of Nuclear Medicine and Molecular Imaging has created an initiative focused on the "Quality of Practice". This initiative has created a goal to ensure that Society members are known for high-quality, value-driven performance and delivery of patient-centered nuclear medicine practice. Extravasations have no place in the "Quality of Practice".

Improving extravasation rates is also consistent with the goals of the personnel involved in nuclear medicine. Technologists are very interested in ensuring they are delivering ideal injections to their patients. Physicists are interested in ensuring reproducible and repeatable nuclear medicine studies. Radiation safety officers want to minimize unnecessary radiation exposure to patients. And physicians want to ensure their patients get the best care.

Certainly, patients want the highest quality nuclear medicine studies since these studies are important to their care. Patients do not want the risk of additional radiation exposure as the result of extravasations. And no one—patients, payers, or employers—wants to pay providers for compromised diagnostic studies, unnecessary procedures, or the wrong care.

Extravasation Summary

Extravasations negatively affect nuclear medicine studies. The significance of extravasations is increasing each year. While QC exists today to address some processes that may affect study outcomes, no QC exists for the critical injection process to ensure the entire administered radiopharmaceutical dose is actually delivered into the patient's circulation. Historically, detection of extravasations has been difficult, and no reporting requirements existed. As a result, extravasation rates are not only high, but approximately 60 times greater than contrast CT rates and 84 times greater than chemotherapy rates. Nuclear medicine extravasations can matter in many ways. They can negatively affect care by compromising patients' diagnostic procedures and the ensuing care. They can cause repeated imaging procedures that expose patients to unnecessary radiation exposure. And extravasations can exceed the NRC reporting limits of effective dose equivalent to the tissue. Because extravasations often go undetected or unreported, patients and their treating physicians are unaware; this can lead to misinformed care decisions. However, the current NRC policy does not consider diagnostic radiopharmaceutical extravasations reportable as medical events even when they exceed current reporting limits. This policy is based on a 1980 decision that suggested that extravasations are virtually impossible to avoid. But today, there is evidence that nuclear medicine extravasations rates can be significantly and quickly reduced by using new, low-cost, QC/QA technology seamlessly integrated into current workflows. Such an effort appears consistent with the goals of all parties involved in nuclear medicine. A suggestion for an injection-monitoring QC procedure is included as Appendix C.

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Request

To help protect nuclear medicine patients, the NRC should modify their 1980 policy based on new evidence that many extravasations can be detected, and ultimately avoided. In the future, nuclear medicine injections should be monitored and any therapeutic **or** diagnostic radiopharmaceutical extravasation that meets the medical event reporting requirements of 10 CFR Part 35.3045 Subpart M should be reported and notifications made.

Sincerely,

Ron Lattanze
Chief Executive Officer

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Appendix A: Equivalent Dose due to Diagnostic Radiotracer Extravasation—a Monte Carlo Investigation

Background

An intravenous extravasation is when an injected substance leaks into surrounding tissue instead of remaining within the vasculature as intended. It can be caused by improper placement of the IV, erosion or degradation of the vessel wall, or failure of vessel integrity*(1)*. When a diagnostic radiopharmaceutical is extravasated, a percentage of the activity remains at the injection site instead of circulating throughout the patient's body. This reduces the net available activity for uptake and changes the kinetics of uptake for subsequent imaging*(2-6)*.

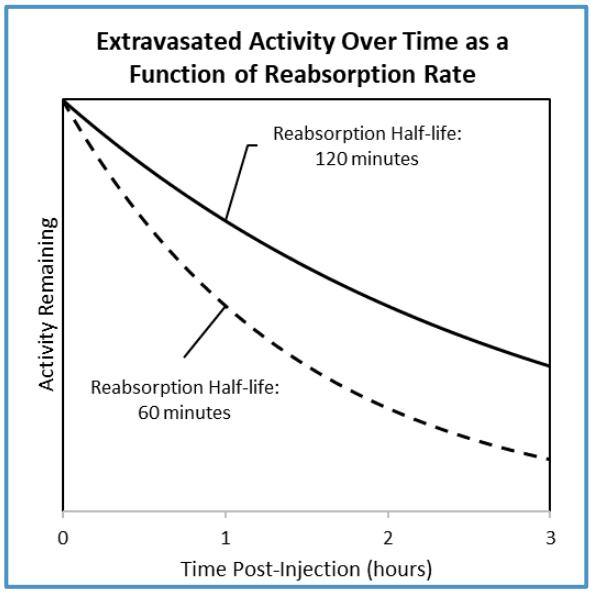

Figure 1. Representative graph of the way in which extravasated activity changes over time. Imaging time would typically occur at 1 hour post-injection.

Because diagnostic radiotracers are administered as a bolus, the extravasation can be modeled as an initial value that is reduced over time due to radioactive decay and biological reabsorption. For this work, we modeled reabsorption as a mono-exponential function. The time needed for resolution of the extravasated activity depends on the combination of radioactive and resorptive half-lives and the extravasation may or may not fully reabsorb by the time of imaging. Figure 1 depicts the way in which two hypothetical extravasations with differing reabsorption half-lives may resolve over time.

Clinical qualitative analysis of extravasations is not routinely done. However, it is possible to do so using single photon emission (SPECT) or positron emission tomography (PET) data. This creates a quantifiable snapshot of the extravasated activity at the time the image was acquired*(7)*. In order to quantify the overall significance of the extravasation throughout the uptake time and beyond, clinicians must know the rate of biological reabsorption.

There is technology (Lara®, Lucerno Dynamics LLC, Cary NC) which can monitor the injection site for excess radioactivity during and after the injection. These topical scintillation detectors generate time-activity curves (TACs) for both the injection and reference arms (Figure 2). TACs show the relative amount of local radioactivity over time.

In this investigation, we sought to understand the impact of a diagnostic radiotracer extravasation from the perspective of radiation safety and determine the amount of radiation dose likely to be deposited in tissue around the extravasation. Additionally, we investigated whether topical injection quality-control sensors could provide information about the rate of reabsorption for more accurate estimation of absorbed dose.

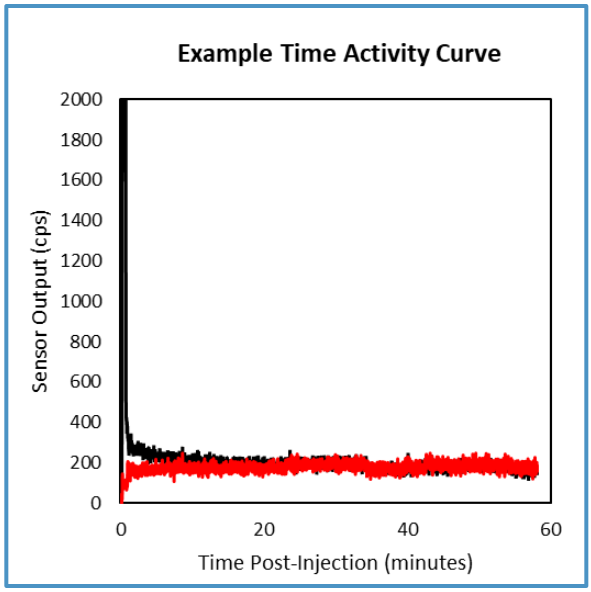

Figure 2. Example TAC graph generated from Lara® sensor data.

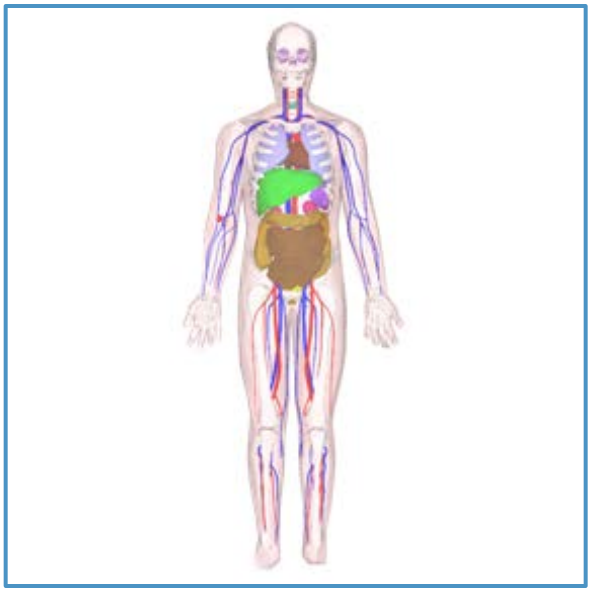

Figure 3. Example of the anthropomorphic model.

Methods

We used the GATE Monte Carlo framework* along with anthropomorphic 3D models † of a human (Figure 3) to simulate three extravasation scenarios.

The model was sized to represent an adult male with weight of approximately 69 kg. Internal organs were modeled using realistic material properties for tissue, bladder, brain, heart, intestines, kidneys, liver, lungs, skeleton and spleen. Throughout this analysis, extravasation activity at the time of imaging is used as a reference point, but total dose is calculated over the entire extravasation time based on the combined radioactive and biological reabsorption half-lives.

Where available, PET data was used to improve the simulation assumptions.

Table 1 details the activity, volume, and experimental basis for each simulated extravasation. Simulations of 1 second were run five times each and averaged. Each simulation was itself subdivided into 64 parts to assure randomness of the numerical particle generator. Equivalent dose was recorded in each organ as well as the extravasation site itself using 1 cm^3 voxels to calculate total organ doses in Sv/sec. In each example, total dose over time was calculated by integrating throughout the extravasation time period—defined as the time required for the extravasated dose to reach 5% of its initial value.

Simulation Identifier	Extravasation Activity at Imaging Time	Extravasation Volume	Reabsorption Half-life	Basis
A	4.5 mCi	5.5 cm^3	60 Minutes	Based on a clinical extravasation example with PET-measured SUV change.
B	0.11 mCi	2.0 cm^3	Based on Sensor TACs	Based on clinical extravasation examples with PET measurement of activity and volume. Reabsorption based on sensor TACs.
C	1 mCi	5 cm^3	60 Minutes	Hypothetical activity, volume, and reabsorption.

Table 1: Details of extravasation scenarios simulated.

* Geant4 Application for Emission Tomography. www.opengatecollaboration.org

† BodyParts 3D, ©2008 Life Science Integrated Database Center licensed by CC Display - Inheritance 2.1 Japan

Simulation A

Simulation A was based on a clinical example of ^{18}F-FDG extravasation that resulted in an approximately 50% reduction in tumor SUV relative to a non-extravasated repeat PET scan 5 days later. The injection site was outside of the PET field of view, so we made assumptions for extravasation shape (semi-planar volume located in dorsal hand) and volume (5.5 cm^3). The initial extravasated injection consisted of 13.72 mCi and PET imaging was performed 57 minutes post-injection. The repeat, non-extravasated injection was performed 5 days later and consisted of 14.5 mCi with PET imaging occurring 65 minutes post-injection. These parameters are within published guidelines for quantitative PET test-retest*(8,9)*. We can assume the tumor metabolism was unchanged*(10,11)* between the two PET scans.

According to compartment modeling of tumor glucose uptake, we know that the tumor uptake (SUV) at the time of imaging is related to the concentration of radiotracer in the blood throughout the uptake time*(12)*, referred to as the arterial input function (AIF):

$$\boldsymbol{SUV \approx AUC \times K_m + \overline{V}_r} \qquad [1]$$

Where $\boldsymbol{AUC}$ is the area under the AIF curve, $\boldsymbol{K_m}$ is the tumor's metabolic rate, and $\boldsymbol{\overline{V}_r}$ is the variability of the distribution volume. Because the two PET studies were only 3 days apart, $\boldsymbol{K_m}$ and $\boldsymbol{\overline{V}_r}$ are assumed to be constant. Thus, [1] becomes simply:

$$\boldsymbol{SUV \approx AUC} \qquad [2]$$

The $\boldsymbol{AUC}$ is the integral of the activity of ^{18}F-FDG in arterial blood. In the case of an ideal injection, it depends on initial activity as well as uptake into tissue and organs. In the case of an extravasated injection, however, reabsorption of the radiotracer over time dynamically alters the blood activity; it resembles a reduced height bolus followed by a slow infusion.

In order to calculate the change in SUV due to differences in the injection, Equation 2 becomes:

$$\frac{\boldsymbol{SUV_{ideal}}}{\boldsymbol{SUV_{extravasated}}} \approx \frac{\boldsymbol{AUC_{ideal}}}{\boldsymbol{AUC_{extravasated}}} \qquad [3]$$

Our overall methodology for Simulation A is based on linear system theory as described by Muzi et al.,

> *"PET tracers are assumed to behave in a linear, time-invariant fashion at the local tissue level, and can be described by an impulse response function." (14)*

When considering tissue uptake as a linear system, a bolus injection would be the impulse and the normal AIF curve would then be the impulse response. We used arterial blood sample data reported by de Geus-Oei, et al.*(13)* as a model of the normal AIF (Figure 4).

In the case of an extravasated injection, however, the AIF is a convolution of the normal impulse response with the altered input signal consisting of decreased initial impulse (bolus) followed by prolonged decaying exponential (reabsorption).

We used this approach along with an assumed reabsorption rate to determine the magnitude of an extravasation that would produce a 50% change in the SUV.

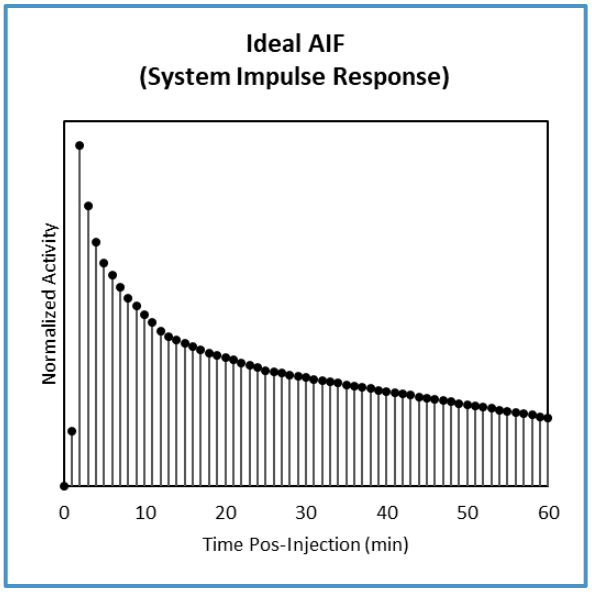

Figure 4. AIF curve for an ideal injection. This is the impulse response for the linear system.

Figure 5 shows the general form of the model for an altered input signal due to extravasation. It consists of the combination of a reduced height impulse followed by a decaying exponential signal due to reabsorption.

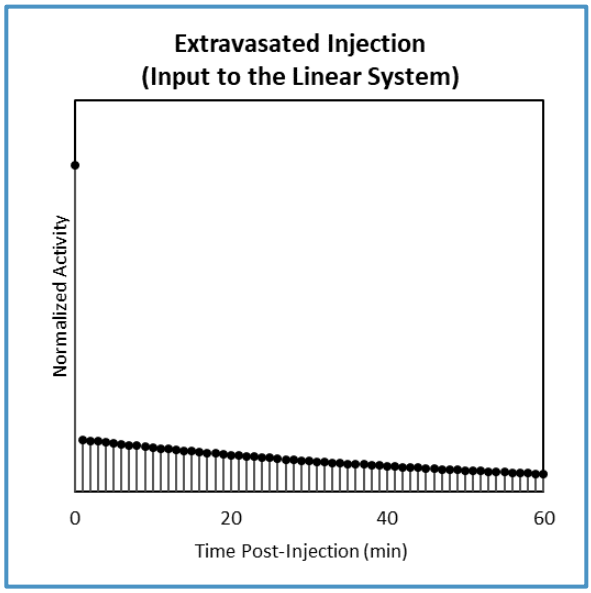

Figure 5. Example of the linear system input caused by an extravasation – impulse at time=0 followed by decaying exponential due to reabsorption.

This model can be used to describe the altered input for any extravasation given the initial extravasated activity and the reabsorption rate. To obtain the resulting blood concentration curve, we convolved this signal with the impulse response.

Finally, we used a least-squares approach to determine the specific extravasation magnitude that would result in a 50% reduction in SUV. Using a reabsorption rate with a 60-minute half-life, this magnitude was found to be 92% (Figure 6). The total injected activity of 13.72 mCi means the initial extravasation activity for Simulation A was 12.6 mCi.

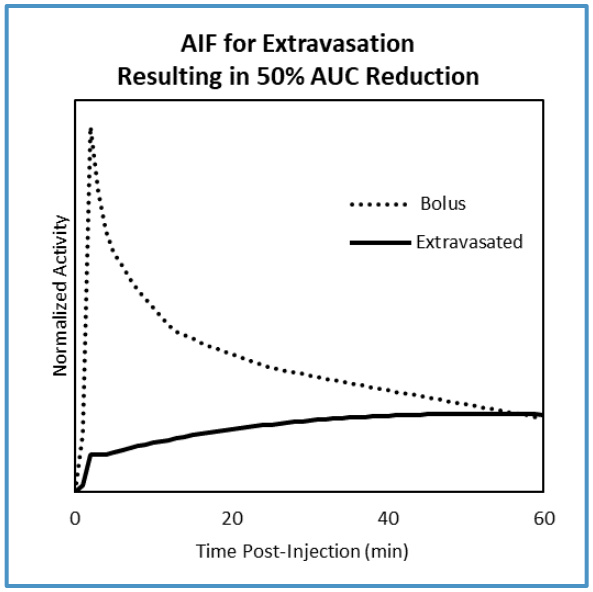

Figure 6. Comparison of AIF for an ideal bolus injection vs an extravasated injection. The resulting difference in AUC is 50%.

Simulation B

For simulation B, the extravasation volume (2.0 cm^3) and activity (0.11 mCi) both resulted from actual PET data measurements using regions of interest defined by isocontours with a threshold of 30% of SUV_{max}.

Additionally, topical injection quality-control sensors data was used as a measure of radiation near the injection site. Whereas the rate of reabsorption was assumed in Simulation A, we used the sensor TAC data to estimate the relative rate of reabsorption in Simulation B.

Sensor TAC data from the reference arm was subtracted from the injection arm data to remove "background" counts from the patient's torso. After the time of sensor removal (81 minutes post-injection), an exponential fit of the last 30 minutes of TAC data was used to extrapolate to 5% of the initial TAC value. Figure 7 shows the TAC data with extrapolation.

For the rate of reabsorption, we used the actual TAC data for the time period available, and then the extrapolation.

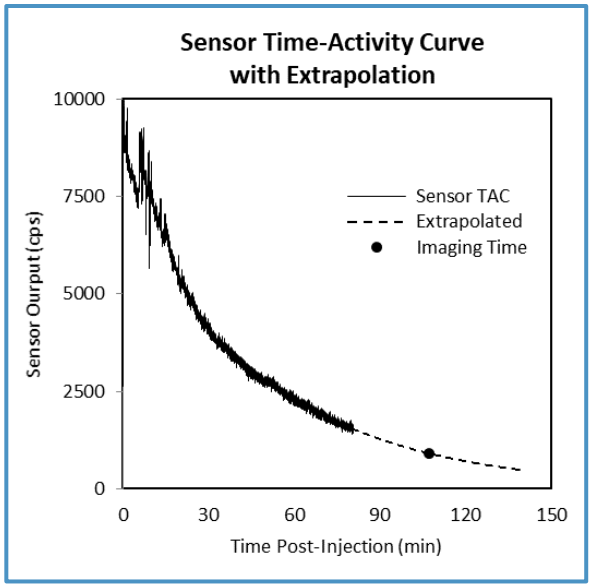

Figure 7. Sensor time-activity curve for Simulation B. with extrapolation after the sensors were removed.

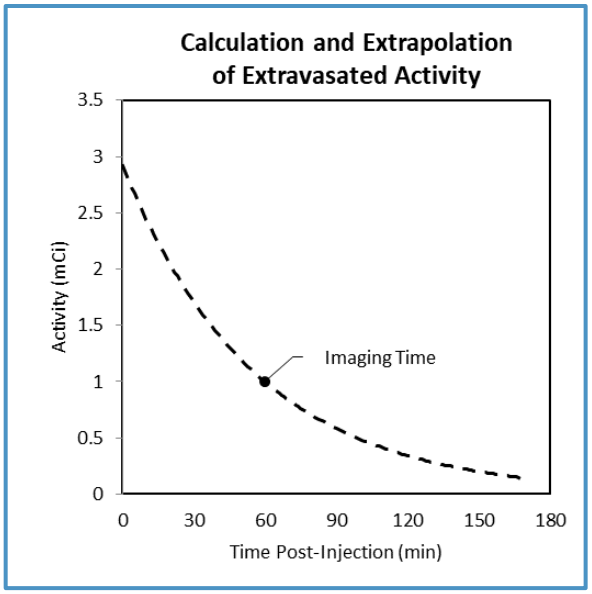

Figure 8. Graph showing calculation of extravasation activity for Simulation C using hypothetical imaging time activity and reabsorption rate.

Simulation C

Simulation C further demonstrates the general concepts with a hypothetical extravasation of ^{18}F-FDG resulting in 1 mCi remaining within a 5 cm^3 sphere at the imaging time of 60 minutes post-injection. This simulation used a reabsorption half-life of 60 minutes. Figure 8 shows the extravasation activity to the point where it is 5% of its initial value. In order to result in 1 mCi within the extravasation at the imaging time of 60 minutes, the initial activity was approximately 2.9 mCi.

Results

Analysis of the voxelized dose phantom models showed that although most of the body registered non-zero dose, none of the scenarios resulted in significant dose to organs or tissue other than the extravasation tissue. Thus, analysis will focus on radioactive dose to the tissues affected by the extravasation volumes only.

Simulation A

Figure 9 shows the simulation geometry with extravasation volume identified by the yellow arrow. Figure 10 shows equivalent dose over the entire extravasation time period. Using a reabsorption half-life of 60 minutes, the 12.6 mCi extravasation resulted in dose being deposited for 166 minutes resulting in a total equivalent dose of 11.5 Sv to the 5.5 cm^3 of infiltrated tissue.

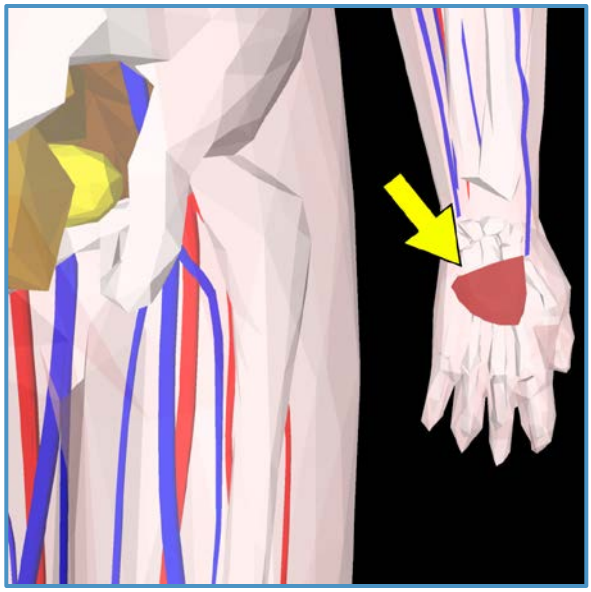

Figure 9. Geometry for Simulation A with extravasation volume identified.

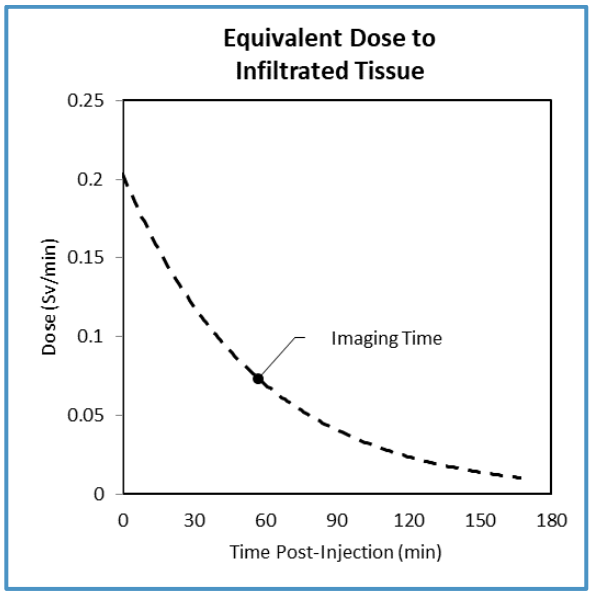

Figure 10. Dose to the infiltrated tissue in Simulation A over time. Total dose over 166 minutes was 11.5 Sv.

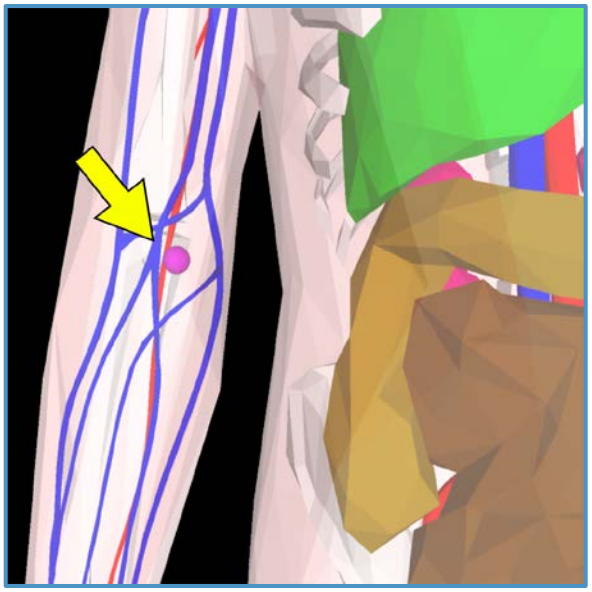

Figure 11. Geometry for Simulation B with extravasation volume identified.

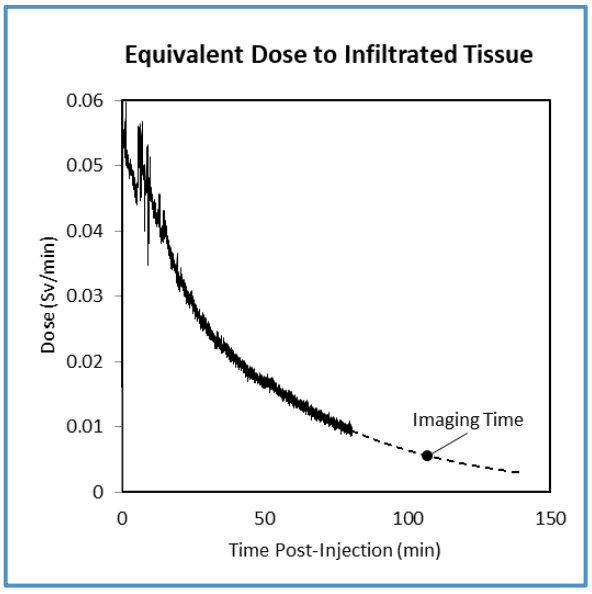

Figure 12. Dose to the infiltrated tissue in Simulation B over time. Total dose over 139 minutes was 2.26 Sv.

Simulation B

Figure 11 shows the simulation geometry with extravasation volume identified by the yellow arrow. Using an exponential fit (R^2=0.96) to extrapolate from the last 30 minutes of sensor TAC data, the 0.11 mCi extravasation resulted in dose being deposited for 139 minutes resulting in a total equivalent dose of 2.26 Sv to the 2 cm^3 of infiltrated tissue (Figure 12).

Simulation C

Figure 13 shows the simulation geometry with extravasation volume identified by the yellow arrow. Using a reabsorption half-life of 60 minutes, the 1 mCi extravasation resulted in dose being deposited for 166 minutes resulting in a total equivalent dose of 3.41 Sv to the 5 cm^3 of infiltrated tissue (Figure 14).

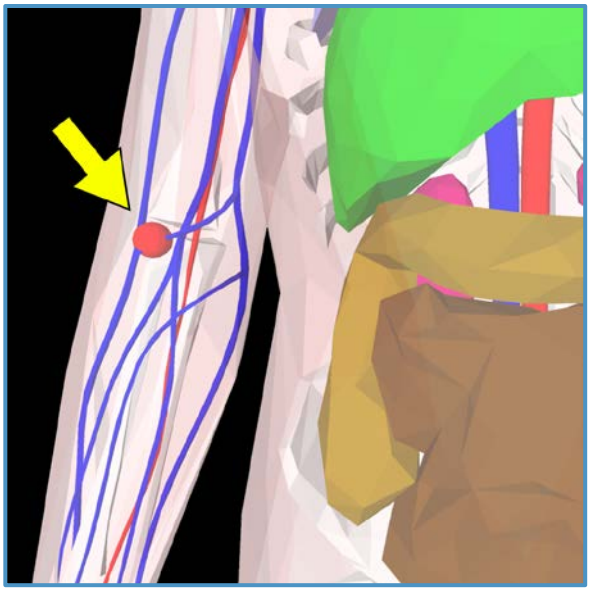

Figure 13. Simulation geometry for Simulation C with extravasation volume identified.

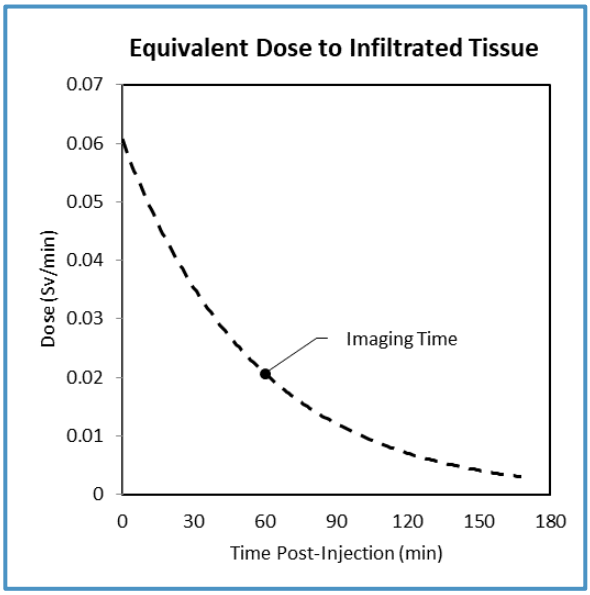

Figure 14. Dose to the extravasated tissue in Simulation C over time. Total dose over 166 minutes was 3.41 Sv.

Table 2 details the results of all three simulations in terms of total extravasation time and total equivalent dose to the tissue.

Discussion

In this work, we investigated three extravasation scenarios. Note that in these simulations, no activity was modeled in the rest of the body—only the activity within the extravasation. This means that all dose calculated is due to the extravasation itself.

In calculation of absorbed dose over time, it is important to understand the ways in which the extravasation changes. Shapiro, Pillay and Cox reported a method to estimate worst-case dose*(15)* by assuming no reabsorption. While this would produce an estimate, we feel it will be unrealistically high in most cases. For instance, if Simulation C were assumed to have no or very slow reabsorption, the resulting dose could be multiple times what it should be because all the radiotracer decays in situ. This impact is even more pronounced with longer-lived isotopes.

While we found no reports of measured reabsorption rate for extravasations of ^{18}F-FDG, there are mathematical bounds for specific situations. We tested our assumptions for Simulation A by calculating the extravasation magnitude required as a function of reabsorption rate. In order to result in a 50% change in SUV, the reabsorption half-life cannot be less than approximately 32 minutes as this would require an initial extravasation of greater than 100%. Likewise, as reabsorption rate increases, the extravasation magnitude required to result in an SUV reduction of 50% asymptotically approaches 50% (Figure 15).

Simulation Identifier	Imaging Time	Extravasation Activity at Imaging Time	Total Extravasation Time	Total Equivalent Dose
A	57 minutes	4.55 mCi	166 minutes	11.5 Sv
B	107 minutes	0.11 mCi	139 minutes	2.26 Sv
C	60 minutes	1.00 mCi	166 minutes	3.41 Sv

Table 2: Summary of simulation parameters and results.

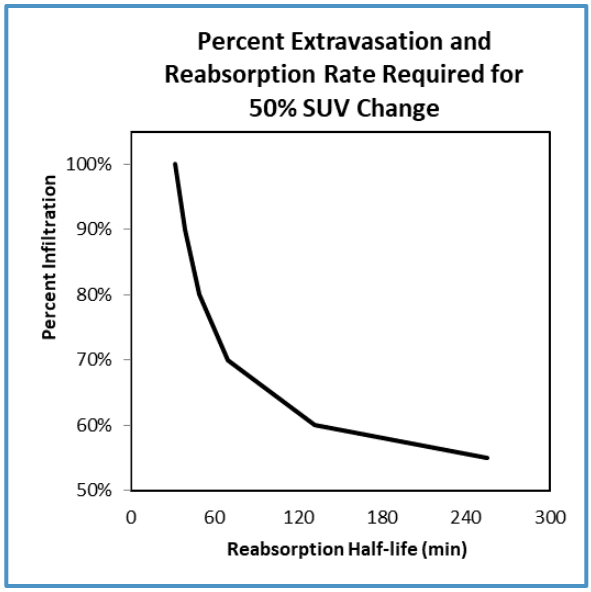

Figure 15. Relationship between percent extravasation and reabsorption rate that are required to result in a 50% change in SUV.

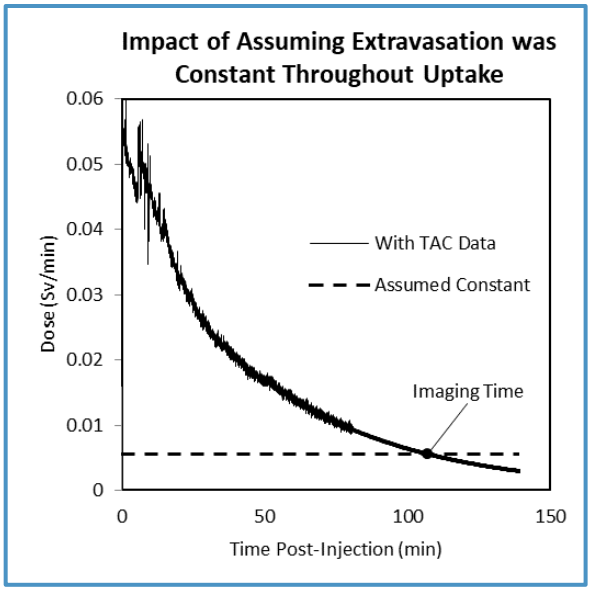

Figure 16. The difference between using sensor TAC data to estimate reabsorption vs assuming the extravasated activity was constant throughout.

For Simulation A, we used a nominal reabsorption rate in order to demonstrate the possible impact in terms of radiation dose. However, depending on reabsorption rate, results could be between 10 and 17 Sv.

Simulation B is interesting in that the extravasation was relatively small in both size and activity at the time of imaging. Simulation parameters were based on PET measurements, but imaging provided no information about the uptake period or reabsorption rate. We used sensor TAC data for a proxy of the reabsorption rate. Without access to the sensor TAC data, the reabsorption rate would have to be assumed.

We calculated the possible error due to assumption of reabsorption rate for Simulation B and found that rates between 20-70 minutes would be off by as much as a factor of 3 when compared to the sensor TAC results.

On the other hand, one might assume that the extravasated dose present at the time of imaging was constant throughout the uptake time. In the case of Simulation B, the dose estimate would be too low by a factor of 3 (Figure 16).

Assumption of the reabsorption rate is not enough to accurately quantify the dose. Repeated PET or SPECT imaging of the extravasation could be used*(7)*, but would increase imaging workload and cost.

We propose that injections be monitored using topical sensors and in the case of suspected extravasations, the injection site should be imaged. Together, image-based measurements of the extravasation activity along with time-activity curve data from topical sensors can be used to estimate radiotracer activity present over time and the deposited dose.

Conclusion

As demonstrated in this work, even extravasations that appear negligible on PET could be significantly worse throughout the uptake time. Imaging alone cannot be used for assessment of extravasated dose. Rather, it is important to know the time course over which the activity is reabsorbed during the uptake time—including after imaging time. We found no reports of soft-tissue injury due to diagnostic radiotracer extravasation, but as van der Pol et. al report*(16)*, cases could be underreported.

As discussed by Hoop*(17)*, the identification and mitigation of radiopharmaceutical extravasations must begin with monitoring the site immediately after injection. Prompt identification allows immediate implementation of harm mitigations*(16)*, but continued monitoring with topical sensors throughout the uptake period can be used to estimate the rate of reabsorption and equivalent dose.

In conclusion, diagnostic radiopharmaceutical extravasations can exceed 10 CFR Part 35 Subpart M Reporting and Notification criteria and have the potential to cause harm.

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Appendix B: Impact of Lutetium-177 Theranostic Infusion Extravasation—a Monte Carlo Investigation

Background

Paravenous extravasation of radio-pharmaceutical agents is not rare*(1-7)*. Hung et al.*(7)* report that:

> With infiltrated activity, the intended route of radiopharmaceutical administration usually is intravenous injection, and there is either a partial or complete extravasation of the intended dose. The possible consequences of an infiltrated radiopharmaceutical injection are not only misinterpretation (if the infiltration site is not identified) of the study or loss of diagnostic information or therapeutic value (if complete extravasation occurs), but also an unanticipated local absorbed radiation dose to the patient with other potential complications, such as local hematoma, phlebitis, phlebothrombosis, or sepsis.

While diagnostic radiopharmaceutical injections typically consist of 1 to 20 mCi*(7)*, *radiotherapeutic* administrations can be hundreds of mCi. Furthermore, radiotherapeutic agents typically emit beta radiation and have relatively long half-lives resulting in further increased risk of local radiation dose in the event of an extravasation.

In the case of suspected *radiotherapeutic* extravasation Van der Pol et al.*(8)* point out that several experts advocate mitigations such as elevation, hyperthermia, and massage. The goal of such actions would be timely dispersal the locally concentrated activity. However, mitigation requires knowledge or suspicion of an extravasation event. Several papers report cases of extravasation where the patient felt no pain and there was no immediate suspicion of extravasation*(9-11)*.

> At the conclusion of the injection, the patient volunteered that the injection had been the least painful i.v. entry he had experienced. Seven days later, imaging failed to detect any radioactivity in the field of view centered on the adrenal glands. Monitoring of the injection site demonstrated essentially complete retention of the radiopharmaceutical at the site*(11)*.

In the case of an unrecognized extravasation, the locally concentrated activity will disperse over time through lymphatic pathways. The rate of dispersal depends on the nature of the extravasation as well as the radiopharmaceutical itself. For instance, ^{131}I-Iodocholesterol is relatively insoluble in water*(11)* and will remain immobile in the interstitial space longer than 18F-FDG which is water soluble[†].

LUTATHERA [‡] (lutetium Lu-177 dotatate) is a prescription medicine using hormone receptor somatostatin to treat adults with a cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Infusions consist of 200 mCi with a volume of 20 mL administered intravenously over the course of 30 to 40 minutes diluted using a saline drip carrier. Prescribing information [§] describes administration instructions as:

> Insert a 2.5 cm, 20-gauge needle (short needle) into the LUTATHERA vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport LUTATHERA during the infusion). Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient. Do not allow sodium chloride solution to flow into the LUTATHERA vial prior to the initiation of the LUTATHERA infusion and

[†] Safety Data Sheet, Fluorodeoxyglucose-F18, Lantheus Medical, accessed Feb 5, 2019 http://www.lantheus.com/assets/fluorodeoxyglucose-f18_oct13-2015-2-1.pdf

[‡] LUTATHERA® is a registered trademark of Advanced Accelerator Applications SA

[§] LUTATHERA Prescribing Information, accessed Feb 5, 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf

> do not inject LUTATHERA directly into the sodium chloride solution.
>
> Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is prefilled with 0.9% sterile sodium chloride and that is used exclusively for the LUTATHERA infusion into the patient.
>
> Use a clamp or pump to regulate the flow of the sodium chloride solution via the short needle into the LUTATHERA vial at a rate of 50 mL/hour to 100 mL/hour for 5 to 10 minutes and then 200 mL/hour to 300 mL/hour for an additional 25 to 30 minutes (the sodium chloride solution entering the vial through the short needle will carry the LUTATHERA from the vial to the patient via the catheter connected to the long needle over a total duration of 30 to 40 minutes).

LUTATHERA emits both beta and gamma radiation. Extravasation during an infusion of LUTATHERA would not only prevent systemic administration of the agent but would expose the patient's arm tissue to potentially high levels of radiation. This exposure could cause radiation damage to the tissue which might take days*(11)*, months*(9)*, or even years*(7)* to become evident.

Pharmacokinetics are defined as the study of the time course of drug absorption, distribution, metabolism, and excretion*(12)*. According to the prescribing information for LUTATHERA, its pharmacokinetics are:

> Within 4 hours after administration, lutetium Lu-177 dotatate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid.
>
> The mean clearance is 4.5 L/h for lutetium Lu-177 dotatate. The mean effective blood elimination half-life is 3.5 hours and the mean terminal blood half-life is 71 hours.
>
> Lutetium Lu-177 dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA administration. Prolonged elimination of lutetium Lu-177 dotatate in the urine is expected; however, based on the half-life of lutetium-177 and terminal half-life of lutetium Lu-177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA.

No information was found in literature describing the pharmacokinetics or reabsorption of LUTATHERA with respect to tissue extravasation. However, based on the mean effective blood elimination half-life of 3.5 hours, we assume that the rate of reabsorption for extravasated tissue would be 1 to 8 hours.

The prescribing information also describes measures to be taken in the case of extravasation:

> The infusion of the medicinal product must be immediately ceased and the administration device (catheter, etc.) removed. The nuclear medicine physician and the radio-pharmacist should be informed. All the administration device materials should be kept in order to measure the residual radioactivity and the activity actually administered and eventually the absorbed dose should be determined. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated.
>
> To continue LUTATHERA® infusion, it is mandatory to use a new catheter possibly placing it in a contralateral venous access. No additional medicinal product can be administered to the same side where the extravasation occurred.
>
> In order to accelerate medicinal product dispersion and to prevent its stagnation in tissue, it is recommended to increase blood flow by elevating the affected arm. Depending on the case, aspiration of extravasation fluid, sodium chloride 9 mg/ mL (0.9%) solution for injection flush injection or applying warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

We are aware of LUTATHERA extravasation from FDA approval information, from one LUTATHERA center, and also from published literature. Tylski et al. report on an extravasation resulting in estimated dose to the arm of 2.8-7.8 Sieverts (Sv)*(13)*. In this case, warming and repeated massage of the injection site were used as mitigations.

The objective of our work reported here was to use Monte Carlo simulation to investigate the impact of a LUTATHERA extravasation in terms of localized radiation exposure, radiation exposure to the adjacent skin, and loss of systemic availability of the radiotherapeutic agent.

Methods

We developed an anthropomorphic model representing a 68 kg adult man. Tissue and organs were modelled accurately using geometry files from the BodyParts3D[**] database. Figure 1 shows the arm portion of the human model used for Monte Carlo analysis.

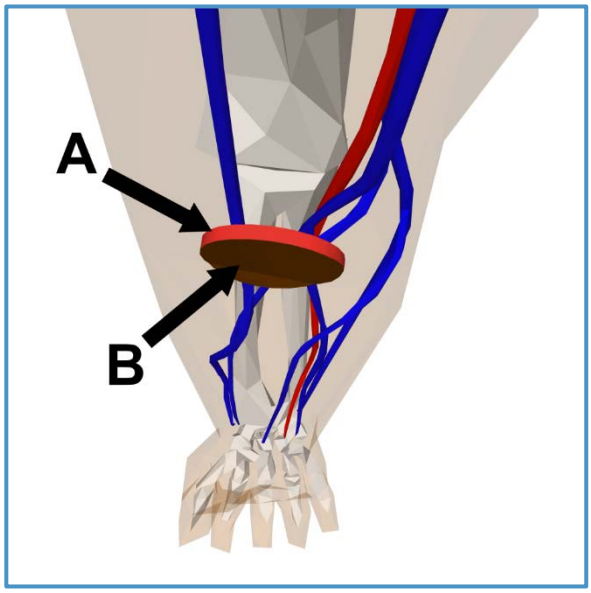

Figure 1. Anthropomorphic model used in simulations. The red disc (A) is the extravasation volume. The brown side (B) represents the skin volume.

For the extravasation volume, we modeled a cylinder within the antecubital fossa with thickness 3.93 mm and total volume of 5 cm^3. The skin was modeled as the circular area directly adjacent to the cylinder with thickness 0.07 mm[††]. Activity was added only to this extravasation volume and all dose calculated in this work is due to the hypothetical extravasation only.

Using administration guidelines provided for LUTATHERA, we calculated the total infusion volume to be 100 mL. In this case, a 5% extravasation would result in 5 mL containing 10 mCi within the arm tissue. The GATE [‡‡] Monte Carlo simulation framework was used to calculate equivalent radioactive dose to the antecubital fossa tissue. This result, in Sv/sec/mCi, was then used to calculate dose throughout the time of infusion.

We calculated the infusion activity over time by applying dilution formulae to the combination of saline and LUTATHERA throughout the infusion time. Figure 2 depicts the activity being infused during the procedure according to the administration guidelines for LUTATHERA. Radioactive decay (half-life = 6.647 days[§§]) is applied to all calculations. After 30 minutes, 2.9 mCi are left in the vial (1.5% of total) which would be infused through manual flushing.

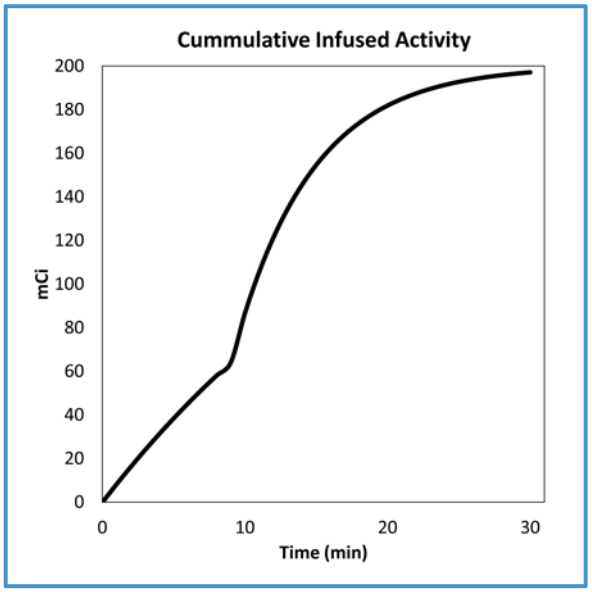

Figure 2. Graph of infused activity over time.

Re-absorption of the extravasation activity would cause the sequestered activity to enter systemic circulation over time. The exact rate of reabsorption is unknown but was modeled using a mono-exponential function with half-lives of 1, 2, 4, and 8 hours. The true reabsorption function likely depends on the nature of the extravasation as well as patient-specific factors.

Using the amount of LUTATHERA that decayed while sequestered within the arm tissue, we calculated the reduced therapeutic availability due to the extravasation.

Finally, dose to the skin was calculated using the modeled skin volume data.

[**] BodyParts 3D, Copyright 2008 Life Science Integrated Database Center licensed by CC Display - Inheritance 2.1 Japan

[††] United States Nuclear Regulatory Commission, Glossary, Shallow Dose Equivalent, https://www.nrc.gov/reading-rm/basic-ref/glossary/shallow-dose-equivalent-sde.html

[‡‡] Geant4 Application for Emission Tomography. www.opengatecollaboration.org

[§§] IAEA - Nuclear Data Section, accessed Feb 5, 2019, https://www-nds.iaea.org/

Results

Figure 3 shows the activity within the extravasation for each reabsorption half-life tested. Plotted data continues until the extravasation activity falls to 5% of its maximal value.

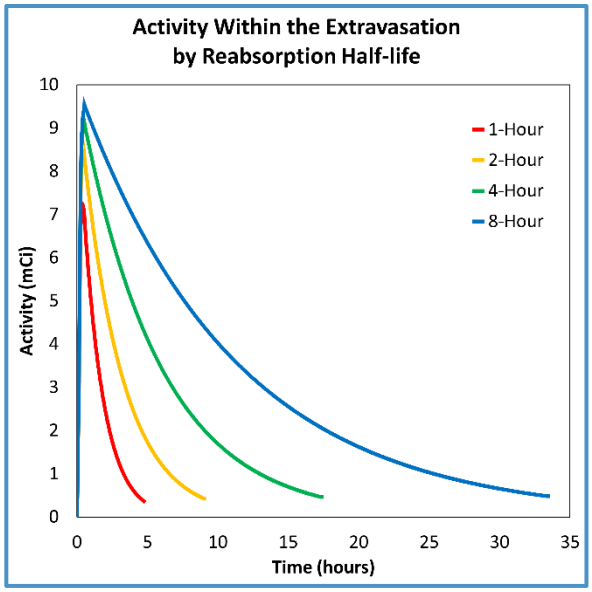

Figure 3. Graph of extravasation activity over time as a function of reabsorption half-life for a 5% extravasation.

Using this information along with the results of the Monte Carlo simulation for extravasation tissue dose (1.76E-04 Sv/sec/mCi), we calculated equivalent dose to the antecubital fossa tissue over time. Figure 4 shows this cumulative dose in Sv for each of the reabsorption half-lives.

Given the results of cumulative dose to the tissue, we can determine the amount of LUTATHERA that did not make it into systemic circulation as it should have. Based on the tissue doses calculated, the amount of LUTATHERA that decays in the arm and fails to fulfill its intended purpose is between 1.27% and 1.54% (Table 1).

Dose to the skin was calculated for each reabsorption half-life and was found to be between 2.6 and 22 Sv.

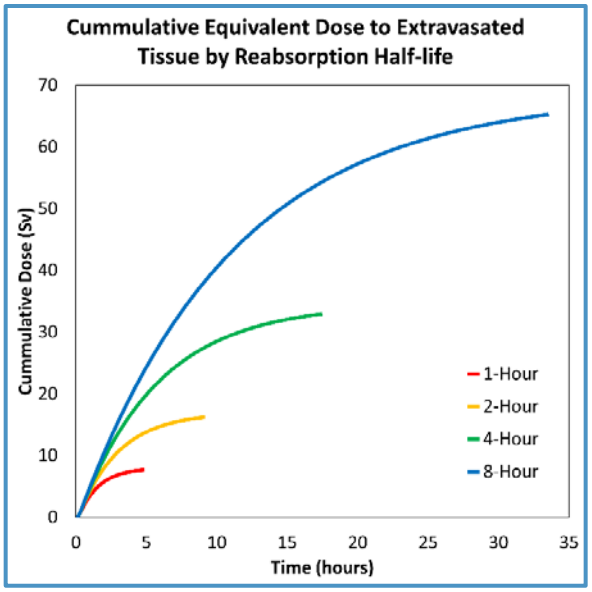

Figure 4. Graph of cumulative dose to the extravasated tissue as a function of reabsorption half-life.

Discussion

In this work, we first determined both the systemic and extravasated activity portions of an infusion of LUTATHERA with failed intravenous access. We assumed 5% of the infusion would be extravasated and then reabsorbed. Based on assumptions of the rate of this reabsorption, we calculated total equivalent dose to the extravasation site as well as the impact to the intended LUTATHERA therapeutic administration.

While we found that this 5% extravasation would only reduce the intended therapeutic LUTATHERA administration by 2-3%, the equivalent dose to arm tissue and skin could be severe (2-22 Sv Skin, 7-65 Sv Tissue) depending on reabsorption rate.

Tylski et al.*(13)* report a case of Lutetium-177 extravasation where they performed serial imaging of the injection site. In this example, they suspected extravasation and implemented warming and massage of the area as mitigation. With these mitigations, reabsorption half-life was estimated as

Reabsorption Half-life (hours)	Total Tissue Dose (Sv)	Total Skin Dose (Sv)	Reduced Therapeutic Availability (mCi)	Reduced Therapeutic Availability (%)
1	7.68	2.61	2.55	1.27%
2	16.19	5.50	2.82	1.41%
4	32.91	11.18	2.99	1.49%
8	65.21	22.15	3.08	1.54%

Table 1: Total extravasation dose, skin dose, and reduced therapeutic effectiveness as a function of reabsorption half-life.

3.5 hours. Although this was the only report of Lu-177 extravasation we found, it does grossly affirm our assumptions of reabsorption half-life. It is likely that the nature of an extravasation would impact its reabsorption rate along with patient-specific factors such as lymphatic health.

We made assumptions about the size and shape of the extravasation. Many factors could change the absorbed dose in specific cases. Because the mean penetration depth of beta radiation from Lu-177 is 0.67 mm*(14)*, skin dose is heavily dependent on where the extravasated activity resides. Likewise, the local concentration of the activity determines the dose to arm tissue.

Conclusion

In this work, we investigated a simulated LUTATHERA extravasation of 5%, which may go unnoticed during the infusion process. In this example, only 2-3% of the total radiopharmaceutical administration will decay while sequestered in the arm. The remaining activity is distributed systemically through reabsorption over time. Modeling the equivalent radiation dose for several reabsorption rates, we determined that significant dose could be absorbed by not only the skin, but the tissue itself.

For suspected radiopharmaceutical extravasations in general, several authors recommend implementation of mitigation measures*(9,10,15-20)* as well as repeated measurement of the injection site activity*(10,11)* to provide information on mitigation effectiveness and reabsorption rate. However, given the possible severity of radiotherapeutic extravasation and the difficulty in identification during the infusion, we suggest that a real-time feedback mechanism is needed. Feedback about the injection site activity during the infusion would allow cessation of a suspected extravasation and immediate implementation of mitigations according to the radiopharmaceutical prescribing information.

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Appendix C: Suggested Injection-Monitoring Procedure

To maximize patient safety, use the following method:

- Injections shall be monitored by localized gamma ray detectors during the uptake period for presence of extravasation.
- If extravasation is detected or suspected, the injection site shall be included in the imaging FOV during the imaging procedure.
- Images of the injection site shall be reviewed and quantitative measurements of the extravasation activity and volume shall be calculated.
- Estimates of effective dose equivalent to the tissue shall be calculated by assuming the activity was constant throughout the uptake time.
    - If the constant-activity dose estimate is greater than the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.
    - If the constant-activity dose estimate is less than the 0.5 Sv limit, the dynamic nature of the activity over the uptake time must also be considered. Estimate the dynamic-activity dose to the extravasated tissue by combining the measured extravasation activity and volume with the detector data. Detector data informs this estimate by representing the dynamic nature of the activity throughout the uptake time, and shall be used to extrapolate to a nominal level of exposure. If this dynamic-activity dose estimate exceeds the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.

Alternate method. If gamma ray detectors are not used, then injection sites should be routinely included in the imaging FOV in order to detect extravasation.

- If extravasation is detected on the scan images, injection site image data shall be reviewed and quantitative measurements of the extravasation activity and volume shall be calculated.
- Estimates of effective dose equivalent to the tissue shall be calculated by assuming the activity was constant throughout the uptake time.
    - If the constant-activity dose estimate is greater than the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.
    - If the constant-activity dose estimate is less than the 0.5 Sv limit, dynamic activity changes shall be estimated based on historical time-activity curve characterizations from literature. Estimate the dynamic-activity dose to the extravasated tissue by combining the measured extravasation activity and volume with the historical time-activity curve characterization. Historical data informs this estimate by approximating the dynamic nature of the activity throughout the uptake time, and shall be used to extrapolate to a nominal level of exposure. If this dynamic-activity dose estimate exceeds the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.

Monitoring injections for extravasation will result in a better understanding of the real rate of nuclear medicine extravasations and motivate improvement efforts that lead to better injection processes. These efforts will lead to fewer extravasations, less unintended radiation exposure to tissue, and higher-quality images used to help guide patient care.