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UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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VIDEO TELECONFERENCE

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THURSDAY,

SEPTEMBER 2, 2021

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The meeting was convened via Video Teleconference, at 1:00 p.m. EST, Darlene F. Metter, ACMUI Chairman, presiding.

MEMBERS PRESENT:

DARLENE F. METTER, M.D., Chairman

VASKEN DILSIZIAN, M.D., Vice Chairman

JOHN F. ANGLE, M.D., Member

RONALD D. ENNIS, M.D., Member

RICHARD L. GREEN, Member

HOSSEIN JADVAR, Member

JOSH MAILMAN, Member

MELISSA C. MARTIN, Member

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

ZOUBIR OUHIB, Member

MICHAEL SHEETZ, Member

MEGAN L. SHOBER, Member

HARVEY B. WOLKOV, M.D., Member

NRC STAFF PRESENT:

CHRISTIAN EINBERG, NMSS/MSST/MSEB, Designated Federal Official

MARYANN AYOADE, NMSS/MSST/MSEB

SAID DAIBES, Ph.D., NMSS/MSST/MSEB/MRST

DANIEL DIMARCO, NMSS/MSST/MSEB

LISA DIMMICK, NMSS/MSST/MSEB/MRST

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

IAN IRVIN, OGC/GCRPS/RMR

SARAH LOPAS, NMSS/MSST/MSEB

LYNN RONEWICZ, NMSS/REFS/MRPB

KATHERINE TAPP, Ph.D., NMSS/MSST/MSEB

ALSO PRESENT:

DANIEL FASS, M.D., Princeton Health Care Alliance

MIGUEL DE LA GUARDIA, Cook Children's Medical Center

RONALD LATTANZE, Lucerno Dynamics

RALPH LIETO, Michigan Radiological Society, American College of Radiology

JOSH KNOWLAND, Lucerno Dynamics

DAVID TOWNSEND, Ph.D., Lucerno Dynamics

MATT WAIT, Kaiser Permanente

PAUL WALLNER, D.O., American College of Radiation Oncology

DAVID WILLIAMS, M.D., Pediatrician

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

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

1:11 p.m.

CHAIRMAN METTER: Thank you, and welcome to the ACMUI public teleconference on the Extravasation Subcommittee's draft report on the NRC's Preliminary Draft Evaluation on Extravasation and Medical Event Reporting.

I'm Darlene Metter, the ACMUI Chair. And I would like to introduce Chris Einberg, the Designated Federal Officer, to begin the meeting.

Mr. Einberg?

MR. EINBERG: Thank you, Dr. Metter.

Good afternoon. I'm Chris Einberg, and I'm the Designated Federal Officer for this meeting. And I'm pleased to welcome you to this public teleconference of the Advisory Committee on the Medical Uses of Isotopes.

I am the Chief of the Medical Safety and Events Assessment Branch, and I've been designated as the Federal Officer for the Advisory Committee in accordance with 10 CFR Part 7.11.

Participating today we also have Lisa Dimmick, our Medical Radiation Safety Team Leader, as a Designated Federal Officer for the ACMUI.

This is an announced meeting of the ACMUI

that is being held in accordance with the rules and regulations of the Federal Advisory Committee Act for the Nuclear Regulatory Commission. This meeting is being transcribed by the NRC, and it may also be transcribed or recorded by others.

The meeting was announced in the July 12th, 2021, edition of the Federal Register, Volume 86, page 36588. The purpose of this teleconference meeting is to discuss the ACMUI Subcommittee on Extravasation's review and comment on the NRC staff's preliminary evaluation of radiopharmaceutical extravasation and medical event reporting.

The function of the ACMUI is to advise the staff on issues and questions that arise on the medical use of byproduct material. The Committee provides counsel to the staff but does not determine or direct 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 a 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. Darlene Metter, Chairman, diagnostic radiologist.

(Pause.)

MR. EINBERG: I think she's on mute, but she's participating today.

Dr. Vasken Dilsizian, Vice Chairman, nuclear cardiologist.

VICE CHAIRMAN DILSIZIAN: Present.

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

Dr. Ennis?

MEMBER ENNIS: Sorry. Present. Pressing the wrong button.

MR. EINBERG: No problem. Thank you.

Mr. Richard Green, nuclear pharmacist.

MEMBER GREEN: Present.

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

MEMBAR JADVAR: Present.

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

MEMBER MAILMAN: 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. He will be joining us late.

Mr. Michael Sheetz, Radiation Safety Officer.

MEMBER SHEETZ: Present.

MR. EINBERG: Ms. Megan Shober, state government representative.

MEMBER SHOBER: Present.

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

MEMBER WOLKOV: Present.

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

At this time, I'd also like to point out that we've selected Ms. Allen to serve as the Healthcare Administrator on the ACMUI. She is not participating in today's meeting, but in the future, while she's pending her security clearance to be processed, she may participate in future meetings.

I would also like to note that we have hired Dr. John Fritz Angle to serve as an interventional radiologist medical consultant to the ACMUI to provide expertise and support in the area of interventional radiology. Dr. Angle may participate in collective discussions but will not have voting rights. And Dr. Angle is with us here today as well.

All members of the ACMUI are subject to federal ethics laws and regulations and receive annual training on these requirements. If a member believes that he or she may have a conflict of interest as that term is broadly used within 5 CFR Part 2635 with regard to an agenda item to be addressed by the ACMUI, this member should divulge it to the Chair and the DFO as soon as possible before the ACMUI discusses it as an agenda item.

ACMUI members must recuse themselves from participating in any agenda item in which they may have conflict of interest unless they receive a waiver or prior authorization from the appropriate NRC official.

The NRC is continuing to operate in a maximum telework status where we are all working remotely and each individual calling in to this meeting. NRC staff members who are participating in

this meeting today are Ms. Lisa Dimmick, Ms. Sarah Lopas, Dr. Donna-Beth Howe, Dr. Katie Tapp, Dr. Said Daibes, Ms. Maryann Ayoade, and Mr. Daniel Dimarco and Ian Irvin also on the call.

Members of the public who've notified Ms. Jamerson that they would be participating in the teleconference will be captured as participants in the transcript. Those of you who did not provide prior notification, please contact Ms. Jamerson by email at kellee.jamerson@nrc.gov. That's K-E-L-L-E-E, dot, J-A-M-E-R-S-O-N, @nrc.gov.

We are utilizing a bridge line for this audio of today's meeting, and that phone number is 1-800-369-3360. The participant passcode is 5484914. Once again, that number is 1-800-369-3360. The participant passcode is 548914.

This meeting is also using the Webex application to view meeting material in real time. You can access this by going to usnrc.webex.com and searching for Event Number 1990854780. Once again, usnrc.webex.com, and the event number is 1990854780.

The meeting handout and the agenda for this meeting can also be accessed from the NRC's public meeting schedule. Dr. Metter, at her discretion, may entertain comments or questions from

members of the public who are participating today. Individuals who would like to ask a question or make a comment regarding a specific topic the Committee has discussed should dial star-1 to signal the operator that you wish to speak. Please clearly state your first and last name for the record.

Comments and questions are typically addressed by the Committee near the end of the presentation after the Committee has fully discussed the topic. We will notify the operator when we are ready for the public comment period of the meeting.

At this time, I'd ask that everyone on the call who is not speaking, please, to place your phone on mute. If you do not have the capability to mute your phone, please press star-6 to utilize the conference line mute and unmute functions.

I would also ask everyone to exercise extreme care to ensure that the background noise is kept at a minimum, as any stray background sounds can be very disruptive on a conference call this large.

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

Dr. Metter, you're on mute right now.

And we still can't hear you, Dr. Metter.

CHAIRMAN METTER: I don't --

MR. EINBERG: I think -- Dr. Metter?

CHAIRMAN METTER: Yes. I hear you.

MR. EINBERG: Okay. We can hear you now.

CHAIRMAN METTER: Can you hear me?

MR. EINBERG: Yes, we can hear you now.

CHAIRMAN METTER: Okay. Thank you.

I would like to introduce and thank the Extravasation Subcommittee for their review of this draft report on the NRC's Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting.

The Subcommittee members are Dr. Vasken Dilsizian, nuclear cardiologist and ACMUI Vice Chair; Richard Green, nuclear pharmacist; Melissa Martin, ACMUI Subcommittee Chair and nuclear medicine medical physicist; Mr. Michael Sheetz, Radiation Safety Officer; and Ms. Melissa Shober, agreement state representative. NRC staff resource is Lisa Dimmick.

At this time, Ms. Melissa Martin, the Extravasation Subcommittee Chair, will now present the Subcommittee's report.

Ms. Martin?

MEMBER MARTIN: Thank you very much. Am I operating slides or is someone else operating slides?

MS. RONEWICZ: Somebody -- Megan will be moving the slides for you, so just give her a prompt.

MEMBER MARTIN: Okay. Thank you very much.

So yes. This is the ACMUI Subcommittee's report on extravasation. This work -- we really appreciate the work done by the NRC on this topic. The Subcommittee considers the work done by the NRC in this preliminary report to be comprehensive, balanced, and accurate. It identifies the problems related with radiopharmaceutical extravasations, and the question is should they be included as medical events? And, if so, what are the criteria?

Next slide, please.

Again, our Subcommittee members were Dr. Dilsizian, Richard Green, myself, Michael Sheetz, and Megan Shober, with our staff resource as Lisa Dimmick.

Next slide.

Our Subcommittee charge was to review the U.S. NRC staff's memorandum entitled Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting -- this was dated April 1, 2021 -- and to provide feedback and recommendations to the full ACMUI and then to the NRC.

Next slide, please.

So what are the extravasation issues that we are dealing with? Since extravasation of radiopharmaceuticals is currently exempt from medical event reporting, events that result in patient harm and meet the abnormal occurrence, or AO, criteria do not need to be reported.

This leads to the question of, does extravasation merit regulation considering the objectives of the NRC's Medical Use Policy Statement? Is the radiation dose component from extravasation significant enough to merit reporting? And can extravasation be prevented with technology?

These are our four items that we considered and that we included in this report.

Next slide, please.

So let's look at the applicability of extravasation to medical event reporting. The purpose of medical event reporting is to capture errors or identify generic issues of interest to other licensees. We are well aware that extravasations are basically identified in each and every facility doing many procedures.

So the question is do we have a separate problem that causes these extravasations of

radiopharmaceuticals to be considered medical events? The current medical event criteria is really not applicable to extravasation. Extravasation is not an error or wrong site, which are two of the criteria for a medical event.

The tissue dose threshold, which is currently set at .5 sieverts, is not intended for very small volumes. Medical event reporting of extravasations will not contain root-cause analysis or provide causal information, which would be helpful to other licensees.

The desire to develop appropriate medical event criteria to capture serious injuries to patients is definitely recognized by both the Subcommittee and the NRC.

Next slide, please.

One item that we feel very strongly about is the discussion of, is extravasation a medical practice issue? Intravenous injection is a medical procedure. It is dependent on acquired technical skills and ability to navigate the patient's anatomy and physiological conditions. Every patient is unique.

Extravasation of diagnostic radiopharmaceuticals rarely affects the sensitivity

and quantification of the study. Neither does it compromise patient care and management decisions. Institutions should have a quality assurance program to monitor and improve the extravasation rate, but this should not be subject to regulation by the NRC. This is typically a hospital-wide policy to look at the rate of extravasations from all procedures done in a medical facility. It is not something regulated by the NRC.

Next slide, please.

So let's look at the frequency of extravasations. There was a study done of four sets of patients, nuclear medicine patients, that reported a frequency of radiopharmaceutical extravasations much greater than for similarly performed non-radiopharmaceutical injections.

So why was this? The reason for the higher rate is the criterion used to be counted as an extravasation of a radiopharmaceutical. An extravasation of a radiopharmaceutical was counted if there was any visualized increase uptake of the tracer at the injection site.

It takes very little activity to be visualized on a gamma camera at an injection site, whereas the criteria for a non-radiopharmaceutical

extravasation requires pain, swelling, or redness of the skin and tissue.

While visualized increase uptake of the radiotracer at the injection site may be frequent, it rarely results in enough activity to compromise the study or cause the patient harm.

Next slide, please.

So one of the challenges we face is determining the dose, the radiation dose, from extravasation. Accurate tissue and skin dose calculations require factors such as activity, volume, geometry, and clearance rate, all of which can vary with time.

The use of a simplistic model will result in gross overestimates of the actual radiation dose delivered to the patient. Factors difficult to determine for the tissue and skin dose are, one, the infiltrate and the surrounding tissue geometry or configuration; the second item is the infiltrate to the basal skin layer distance. How far away is it?

There are no standardized model or software program to perform dose calculations at this point. Using simplistic worst-case assumptions will result in doses readily exceeding the .5 sievert threshold.

Next slide.

We looked at the radiation-induced injury from extravasation. Extravasation of diagnostic radiopharmaceuticals rarely results in any patient harm. There are reports of severe tissue damage following extravasation, which are almost exclusively from therapeutic radiopharmaceuticals. The use of qualitative adverse event criteria to grade injuries from infusion-site extravasations for medical event reporting to the NRC -- next.

So this is the Subcommittee's comments on NRC's draft options. We were presented by the NRC six options to consider for actions on extravasations: one, no action, and options two through six would require certain extravasations to be reported as medical events.

The Subcommittee considerations were as follows. The medical event reporting is an effective tool to collect information on adverse consequences. Two, the data on frequency, severity, and causes of radiation injury are important. Three, complexities in radiation dosimetry to tissues from extravasation.

Number four, some radiopharmaceuticals cannot be easily imaged. And number five, consider consequences of extravasation with novel therapeutic

radiopharmaceuticals. There are several of these on the market today and many more to come in the near future.

The Subcommittee vote and our decision was to support Option 4. This would provide the Nuclear Regulatory Commission with information on the types and frequencies of radiation injuries caused by extravasation.

Next slide.

So let's look at the options that we chose not to support. Number 1, no action. If you choose Option 1, would maintain the status quo and extravasations would continue to be excluded from medical event reporting. The Subcommittee does not support Option 1 because we think extravasations of high consequence should be reported to regulatory authorities.

Next.

Option 2 deals with the 50 rem, or .5 sievert, dose threshold. Option 2 would require medical event reporting for extravasations that exceed a localized dose equivalent of .5 sievert or 50 rem. The Subcommittee does not support Option 2 because it would require a significant burden on licensees to monitor every administration to detect

or see if an extravasation occurred. This would result in over 200,000 potential medical events each year as being reported. Again, it takes very little activity remaining at the injection site to be seen on a gamma camera. And so that would have been classified as an extravasation, while it routinely happens in many, many injections.

Next.

Option 3, procedures requiring a written directive. Option 3 would require that for procedures requiring a written directive, extravasations resulting in a dose of 50 rem or greater and 50 percent or more than the expected dose to the administration site be reported as medical events. The Subcommittee does not support Option 3 because it excludes all diagnostic administrations, and the dosimetry methodology is not standardized at this time.

Option 4 -- next. Option 4, extravasations requiring medical attention. Option 4 would be a non-dose-based option for reporting extravasations that result in a radiation injury. If a patient requires medical attention due to skin damage near the administration site and the damage is determined to be caused by radiation, then this

extravasation would require medical event reporting. The Subcommittee supports Option 4. We think if these circumstances occur, we would support the idea that this be reported as a medical event.

Next.

Option 5, events that cause a significant dose. Option 5 would require medical event reporting for extravasations that meet the 10 gray or 1,000 rad dose threshold required for abnormal occurrences. Patients would self-report to their physicians. Dosimetry would need to be performed to determine if the extravasated dose was ten gray or higher.

Subcommittee does not support Option 5 because to be consistent with other types of medical events, the threshold for medical event reporting should be lower than the threshold for reporting an abnormal occurrence.

Next slide, please.

So then we're at Option 6, events that cause permanent functional damage. Option 6 would require extravasations that result in permanent functional damage to be reported as medical events. This would be similar to the current reporting requirements for events caused by patient intervention that result in unintended permanent

functional damage as determined by a physician.

Subcommittee does not support Option 6 because permanent functional damage is an extremely high threshold for reporting damage and may not provide the NRC with enough information on the types of radiation injuries patients may experience.

Next slide.

So what is our conclusion and recommendation? The Subcommittee supports Option 4. This would provide information on the types and frequency of radiation injuries caused by extravasations. It would also establish appropriate medical event criteria to capture those extravasation events that could result in patient harm and evaluated for meeting the abnormal occurrence criteria.

Monitoring for extravasations will not prevent them from occurring. There should be a quality assurance policy to monitor and improve extravasation rates, but it should not be subject to regulation by the NRC. Again, this is more of a quality assurance project for each and every medical facility.

Next.

Therefore, requiring extravasations that

result in localized tissue dose exceeding .5 sieverts to be reported as medical events would create significant licensee and regulatory burdens. There is sparse clinical evidence that patients are being harmed from radiopharmaceutical extravasation.

Next.

We want to make everyone aware that written comments have been received from the following organizations, and this is included in the material available online for participants.

Next.

These are the acronyms that we used. The ACMUI is the Advisory Committee on the Medical Use of Isotopes. AO is an abnormal occurrence. Gray is a unit of dose. ME is a medical event. NRC is the U.S. Nuclear Regulatory Commission. And sievert is, again, a unit of dose.

I think -- next -- that should be all the slides. Next. Yes. I will turn the meeting now back to Dr. Metter, and we will discuss it as a Committee.

CHAIRMAN METTER: Thank you, Ms. Martin, for your presentation and your Subcommittee report.

Do I have any questions from the Subcommittee members, any questions or comments?

VICE CHAIRMAN DILSIZIAN: Hi, Darlene. Vasken here. Can you hear me?

CHAIRMAN METTER: Yes.

VICE CHAIRMAN DILSIZIAN: First, I want to congratulate Subcommittee members for really spending a lot of time and being very thoughtful on various options that were provided to us by the NRC staff. And I want to thank NRC staff for actually being so detailed in giving us all these options.

One of the comments -- I read most of the written comments that were provided to us, and the one that caught my attention is from ASTRO, the American Society for Radiation Oncology.

And in their comment, they were concerned that in Option 4, when we say medical attention, that medical attention, the word itself, is quite ambiguous and that medical attention could trigger inappropriate medical event reporting if, for example, the extravasation was not really related to the radiation injury, but it could be, for example, a latex allergy or Band-Aid allergy. It could be some redness. That's medical attention, perhaps.

Perhaps the patient will seek the physician to look at the arm and determine whether that's something to be concerned about. And so the

-- ASTRO's proposal was that the fact that the patients seek medical attention -- it may fall under Option 4, and that would then trigger medical event reporting even if it's simply latex-related allergy or some irritation.

So their recommendation was to modify the medical attention term to say an event that requires intervention for suspected radiation injury. And I support that. Thank you.

CHAIRMAN METTER: Thank you, Vasken.

Are there any other comments or questions from the Subcommittee members?

MEMBAR JADVAR: This is Dr. Hossein Jadvar.

I just -- well, Vasken beat me to it, but I wanted to exactly say the same thing regarding that note from ASTRO. I agree with the ambiguity of the medical attention and all that Vasken has said regarding the actual comment, that it should be a little more clear of what we mean by medical attention and be specific to possible radiation injury. I just want to support that. Thank you.

CHAIRMAN METTER: Thank you, Dr. Jadvar.

Any other comments or questions from the Subcommittee members?

MEMBER MARTIN: This is Melissa Martin. I would just like to add a couple of comments.

I am in complete support of the comments about defining better what a medical injury is. The other comment I think that we have heard that deserves some type of support is that it should be a qualified physician, not just a general physician, making these decisions as to whether it's a radiation injury.

CHAIRMAN METTER: Thank you --

VICE CHAIRMAN DILSIZIAN: Melissa, Vasken Dilsizian here again. I just want to clarify, when you said other healthcare providers, are we saying that non-MDs, like PAs or nurse practitioners, should not be the ones to be reporting? Is that what you meant?

MEMBER MARTIN: That was my implication, but I'm also thinking I want the -- I would like the report of injury to be to the responsible -- or qualified physician to evaluate that injury for radiation damage. I'm not sure exactly how to restrict that, but that's --

(Simultaneous speaking.)

VICE CHAIRMAN DILSIZIAN: Yeah. Melissa, I have an idea. Vasken Dilsizian again. What about, since the authorized user is ultimately

responsible, why don't we specify that's the authorized user?

MEMBER MARTIN: That would be acceptable to me.

CHAIRMAN METTER: Okay. So what -- how would you like to rephrase that, then? Require intervention for suspected radiation injury due to extravasation as confirmed by the authorized user?

MEMBER MARTIN: Correct.

(Simultaneous speaking.)

CHAIRMAN METTER: Yes, go ahead.

MEMBER GREEN: Can we have that slide moved back to slide -- Option 4 so that we can see that text?

CHAIRMAN METTER: There. Yeah.

MEMBER GREEN: Thank you.

CHAIRMAN METTER: Did you have any comments, Mr. Green, on this?

MEMBER GREEN: Yes. I think I am also in favor of the two suggested changes to the text. One is the requiring the change from medical attention to medical intervention, and I think we should, again, point that back towards the authorized user/physician, and perhaps not other medical individuals or general practitioners. Thank you.

CHAIRMAN METTER: Thank you.

Any other comments from the Subcommittee members or the ACMUI?

(Simultaneous speaking.)

MEMBER MAILMAN: -- remember how to take myself off mute. This is Josh Mailman. I'm a patient advocate. I will say that this option, of course, does put burden on the patients who actually say they need medical attention and what type of medical attention they would need.

And so we're putting burden on the patients without necessarily educating them on when and how they should bring this up or what might cause these things to be reported. And it seems that -- you know, I want to make sure that we don't have any vague wording and that somehow we would be able to get this to, ultimately, the consumer so that they could know that they should report this if they felt that something was off.

We've got a lot going on, whether it's from latex or just having the tape ripped a little too fast. But, you know, we aren't often given instructions on what we should and how we should report things.

CHAIRMAN METTER: Thank you.

Any other comments?

MEMBER ENNIS: Yeah. This is Ron.

CHAIRMAN METTER: Yes. Go ahead, Dr. Ennis.

MEMBER ENNIS: So just a little nuance, but if something doesn't go smoothly, sometimes patients aren't enthusiastic or willing to go back to the practitioner. So we might want to change the language to an authorized user as opposed to the authorized user, to kind of get expertise but perhaps from another practitioner if the patient needed that and didn't want to go back to where the initial treatment had been.

CHAIRMAN METTER: So, Dr. Ennis, how would you want this? As confirmed by the authorized user or --

MEMBER ENNIS: As confirmed by an authorized user rather than the.

CHAIRMAN METTER: Oh, I'm sorry. I'm sorry. Thank you.

Any other comments or questions from the ACMUI Committee?

MEMBER MARTIN: This is Melissa. I would support that change.

CHAIRMAN METTER: Okay. Thank you.

So what I have here, just to clarify and just to sum up, is that within Option 4, we should also add requires intervention for suspected radiation injury due to extravasation as confirmed by an authorized user. Is that -- what I captured is appropriate for what was discussed?

MEMBER MARTIN: Yes.

CHAIRMAN METTER: Okay. Thank you.

Okay. Any other comments or questions?

Okay. I'd like to open up comments and questions for the NRC staff.

MR. EINBERG: Yeah, so this is Chris Einberg. Yeah, I wanted to also congratulate the Subcommittee on their extensive work and their recommendations, and the full Committee evaluating not only the NRC's proposed options but also evaluating the public comments that have been received. This is, again, very valuable as we move forward in our process for making any recommendations on medical event reporting.

I have no questions, per se, right now to the Committee. I'll open it up to Lisa Dimmick, who's the staff resource on this, and see if she has any comments or questions.

MS. DIMMICK: Sorry. I was on mute.

No, I don't have any comments or questions.

CHAIRMAN METTER: Okay. Thank you. And, again, I do also thank the Subcommittee members for their work and the NRC and Lisa Dimmick for her support of that Subcommittee.

Hearing no other questions or comments from the NRC staff, I'd like to open up to the public for comments and questions.

MS. LOPAS: All right. Thanks, Dr. Metter. So --

(Simultaneous speaking.)

MS. LOPAS: Oh, sorry. Sorry, Chris.

MR. EINBERG: Sorry. Yeah, go ahead, Sarah. Yeah, I was just going to say --

(Simultaneous speaking.)

MR. EINBERG: -- Ms. Sarah Lopas will be facilitating this public comment period.

CHAIRMAN METTER: I'm sorry. Did you say Sarah was going to -- thank you very much. Okay.

MS. LOPAS: Yep. That way, you guys can sit back and listen.

So my name is Sarah Lopas. I'm a Project Manager here in the NRC's Medical Radiation Safety Team. I'm also an NRC meetings facilitator, so I'll be facilitating the public comment portion of today's

meeting.

We will be taking comments over the phone here until about 2:45 or so Eastern Time. At that point, we do need to send it back to the ACMUI so they can deliberate a little bit more and finish out the business portion of today's meeting.

So I'm going to ask you right now, if you want to make a comment, go ahead right now and press star-1, and that's going to indicate to our operator, Holly, that you would like to make a comment. So press star-1 on your phone, and then there'll be some operator prompts and you just follow those prompts. So let me just finish this out, and then we'll get to Holly and the comments.

So this meeting is being transcribed, so please begin your comment by introducing yourself and stating your affiliation if you have one. And then please speak clearly so the court reporter can get an accurate transcript of your comment.

And your comments will, of course, be included in today's meeting transcript. And, as Ms. Martin noted in her presentation, all the written comments that we received -- thank you so much for those. Those are going to be appended to the end of the transcript, so they will be available for public

inspection as well.

Both the ACMUI and the NRC staff are going to be carefully listening to your comments today, but we're not going to be responding to comments or responding to questions at this time. And, I'm sure as many of you are very aware, the NRC staff with input from the ACMUI and the agreement states is reviewing a petition for rulemaking that requests medical event reporting of certain nuclear medicine extravasations. The staff is expecting to make a recommendation on the petition to the Commission in the spring of 2022, and the Commission will make the final decision on the petition.

So, with that bit of context, we can go ahead and get started with the public comments.

So, Holly, can we begin with our first caller?

OPERATOR: Yes. Our first caller is Dr. Daniel Fass with Princeton Healthcare Alliance.

You may go ahead.

DR. FASS: Good afternoon. I'm Dr. Fass. I'm a practicing radiation oncologist. I have 35 years' experience in the field. I personally administered innumerable radioisotopes for therapy, and I would say that the shortcomings of reporting

are obvious to those of us in clinical practice and that, unfortunately, the detriment to the patient is serious.

Side effects, acute and chronic sequelae, are unnoticed by my colleagues. I can tell you the way that patients are usually cared for is that the person administering the isotope may never see the patient again, and that the people caring for the patient may be completely unaware of the sequelae of an overdose, and that without robust reporting requirements, this will continue to be a major clinical problem.

And as radioisotopes become more and more commonly used in therapy for malignancies because of the advances in targeted radioisotopes, we're going to see more of these incidents. And without both quality assurance mechanism from the standpoint of preventing them and therefore the observer effect by requiring the reporting, this is going to become a more and more significant medical problem that if it were in the nuclear power industry, no way would this be acceptable.

And I think that as robust a reporting mechanism as required would behoove our patients and benefit oncology care and general care overall.

That's my comment.

MS. LOPAS: Okay. Thank you for that.

Holly, we'll go to the next caller.

OPERATOR: One moment while I grab the caller's name.

MS. LOPAS: And, everybody, just remember to press star-1 if you want to make a comment. Star-1.

OPERATOR: And our next caller is David Townsend.

You may go ahead.

DR. TOWNSEND: Hi. I hope you can hear me.

My name is David Townsend. I have been involved in the practice of nuclear medicine and PET for over 40 years before I retired from the Director of the Clinical Imaging Research Centre in Singapore.

It has always astonished me that all the steps in the nuclear medicine imaging procedure undergo very strict quality control measures, which includes the production of radiopharmaceutical, the functioning of the imaging device, the camera, and the image quality, the calibration of the system, and the image review.

But the injection of radiopharmaceutical

has never really undergone any sort of full quality control procedure such as monitoring for extravasations. And I think it's not correct to say that extravasations are really rare and that medical imaging reporting would represent a huge burden on the medical imaging centers.

So I would strongly urge the Committee to consider more Option 2, where there's really careful monitoring of extravasations and proper event recording. Thank you.

MS. LOPAS: Okay. Thank you.

So please press star-1 if you would like to make a comment to get it on the transcript. But, of course, we do also have -- we will append all the letters that we received to the transcript.

Okay, and make sure that you are unmuting your phone when you go to make a comment. So unmute your phone before you press star-1 because you're going to be prompted for your name when you press star-1, so you have to unmute your phone before you press star-1.

Sorry about that, Holly. Do we have anybody else on the line?

OPERATOR: Yes. Our next caller is Paul Wallner with the American College of Radiology.

You may go ahead.

DR. WALLNER: Yes. Thank you very much.

I'm board certified in radiation oncology, nuclear medicine, diagnostic radiology. I've been in practice for 50 years and was Chief of the Clinical Radiation Oncology Branch of the National Cancer Institute, where my primary area of research was in radiopharmaceuticals, targeted radiopharmaceuticals.

I disagree entirely with the previous two commenters. This is not a frequent problem. It is not a clinical problem. It is a medical issue that has been dealt with routinely by nuclear medicine physicians and radiation oncologists.

We believe that the reporting requirements would place an undue burden on medical practitioners and on patients, and we strongly supported Option 6 but could live with Option 4 with some of the amendments that have been suggested.

MS. LOPAS: Okay. Thank you, Dr. Wallner. Is that it?

DR. WALLNER: Yes.

MS. LOPAS: Okay. All right.

All right. And can we have -- so press star-1. Remember to unmute yourself and press star-

1, and we can take your comment. There is nobody in the queue right now, so if you press star-1, you'll be up next.

(Pause.)

MS. LOPAS: Okay. Holly, can we move on to the next commenter?

OPERATOR: Our next caller is Josh Knowland.

You may go ahead.

MR. KNOWLAND: Hi. Good afternoon. I would like to discuss comments made regarding dosimetry and its complexity for these cases.

I'd like to point out that there are recent publications demonstrating techniques that do not assume worst-case scenarios and that also do not rely on unrealistically small volumes of tissue. These techniques are based on reasonable assumptions using precalculated dose rates for standardized tissue volumes.

Based on these reasonable assumptions, the dosimetry calculation process can actually be done using just a spreadsheet, and it can be done in a matter of minutes. And it's also possible, using these published techniques, to include patient-specific details, such as the rate of biological

clearance.

I'd like to point out that information such as this would be impossible to include if dosimetry was not performed until possibly months later when a patient may report injury. So I'm not in favor of waiting until an injury is reported by the patient themselves. Thank you.

MS. LOPAS: Okay. Thank you, Josh.

A reminder to unmute yourself and press star-1 to make a comment.

Holly, can we go to the next commenter?

OPERATOR: Our next caller is Ronald Lattanze with Lucerno.

You may go ahead.

MR. LATTANZE: Hi. Can everybody hear me?

MS. LOPAS: We can.

MR. LATTANZE: Okay. Great. Thanks for giving me the opportunity to speak. I'd like to follow up on what patient advocate Josh Mailman was referring to just a few minutes ago. I didn't believe that his comments were recognized appropriately by the Subcommittee, and so I want to touch a little bit more on the patient aspect of this.

I have a lot of other questions that I'd

love to share with the Subcommittee, but I don't think we have enough time for that, so I'll focus on the patients.

I did read the meeting material ahead of time, and in the meeting material, the Subcommittee suggested that the NRC and the community considering that informing a patient of a significant extravasation would be considered a medical event may cause them psychological harm.

And, as we all know, if a radiopharmaceutical today is accidentally leaked onto a patient's skin and dosimetry is performed and the licensee realizes that the skin has been exposed to an absorbed dose of half a gray or a shallow dose equivalent of half a sievert, the licensee is required to inform the patient of the medical event, inform the patient's referring physician, and report the medical event to their state or the NRC within 24 hours.

So I just -- I want to be clear. I've got a couple questions about that. I know you can't answer them now, but I'd appreciate an answer. Are you suggesting that patients who experience a medical event like the one I just described no longer be told that this has happened, about -- no longer be told

about the exposure? Or are you suggesting that only patients who experience a leak into their tissue are the patients that may not be able to handle this information?

So that's one question I have. And for the extravasated patients, do you have a specific threshold of an absorbed dose to the patient's tissue or their skin as a result of an extravasation that the ACMUI believes that a patient or their referring physician should be informed about? And if so, what is that threshold, and how would a clinician know that the patient has experienced that threshold or exceeded it without dosimetry?

So Option 4 suggests no dosimetry for any extravasations until the patient comes back and reports an injury. So I think I'm missing something, and I would like clarification on that.

I also have a comment about Option 4, and this goes onto what Josh Mailman was saying about the expectations that you placed on a nuclear medicine patient. So, just a reminder, Option 4 states that if a patient requires medical attention -- and I know that's being adjusted as we talk today -- due to skin damage near the administration site that's determined to be from radiation, then this extravasation would

require medical event reporting. And dosimetry would only be performed on extravasations to determine whether it exceeds the abnormal occurrence threshold.

I'm suspecting that maybe the NRC had an oversight about not mentioning the underlying issue, so I'd like some clarification on that. But to summarize, what you're saying is you're recommending that only extravasations that are reported to regulators are those extravasations where patients report adverse skin and tissue reactions. So that puts the responsibility directly on the patient to identify that. And if that's the case -- and then this goes to Josh's question -- help me understand, how will patients -- what will they know to look for when it comes to tissue and skin damage associated with an extravasation?

Are you recommending that every patient who receives a radiopharmaceutical administration be informed that a possible side effect of the administration could be leakage into their tissue from that administration and that the symptoms could show up days to weeks to months to years later, and that if this leakage happens to cause skin and tissue damage, and if they experience any symptoms of that such as pain in the tissue surrounding the injection

site, tissue ulceration, tissue death, which will appear sort of as a blackened coal near the injection site, reddening of the skin, loss of hair on that part of the skin, moist desquamation, or blistering, that they should then contact the Nuclear Medicine Center or an authorized user and have a physician determine if these symptoms are caused by radiation?

Because if that's what you're suggesting, I think, back to Josh's point, that puts a big burden on the patient. And that approach does not seem consistent to me with the ALARA radiation principle. It would seem to me that you'd want to know immediately if this happens so that you can put mitigation in place right away to ensure that that patient experiences the lowest possible dose to their tissue.

I think if a patient receives a dose to their tissue or skin that is so severe that they're going to experience the tissue damage that will require reporting, isn't that the obligation of the licensee to minimize that dose as soon as possible? Why would you want to wait for that to happen when you can find out within seconds or minutes either using imaging or an ion chamber, or in our case our technology if you wanted, to know that that has

happened right away?

And we had a case like that -- one last example I want to talk about. I'm not a radiopharmacist. This would be a great question for Mr. Green. But I think, regarding the ALARA concept or the principle -- I think during radiotherapy, especially like Lutathera, you administer amino acids for a period of time after the administration of the radiopharmaceutical to help protect the kidneys. And I've seen in the meeting material that when you do a therapy delivery, if you extravasate that, it's been said that it gets -- reenters the venous system through the lymphatic system and eventually reaches the target tumor.

So, by missing the intended route of administration, the lymphatic clearance will eventually get the right dose to the target. But how long does that process take? So, if in the case of the Fox -- the recent Fox Chase Cancer Center Lutathera extravasation, where we believe about 86 millicuries of lutetium-177 was extravasated, that takes more than a couple hours to get back into the vascular system.

How are the kidneys going to be protected from that? Wouldn't you want to know immediately

that you have an extravasation and that you can take action right then to try to minimize the dose to the tissue and to other organs?

Those are some of my comments, and I'd love to engage with the Subcommittee one-on-one if I have that opportunity. Thanks.

MS. LOPAS: Okay. Thank you, Ron. We appreciate those comments.

Holly, can we go to our next commenter?

And just a reminder to press -- to unmute yourself first, and then press star-1.

OPERATOR: Our next caller is David Williams. He's a private pediatrician practice.

You may go ahead.

DR. WILLIAMS: Yes. I appreciate the chance to comment.

I've become familiar with this issue, and I would just like to point out to the NRC that the ACMUI has had a long time to study this issue. And it was not brought to the NRC's attention that this is a problem by the ACMUI. They were only brought to actually weigh in in a way other than ignoring the problem because of outside attention and the NRC having to go to them to say, hey, there's a problem here.

This recommendation by the ACMUI will not allow the NRC to understand the extent of the extravasation issue. There will be no lessons learned from this, which could happen if they were obligated to monitor their injections. You would find sites that do things very well, and you would find sites that don't do things very well.

And they say it's a medical practice issue, but they are putting radioactive materials into the wrong place. You can call it what you wish, but if it doesn't go in the vein cleanly, it's not being done as it was designed to do. And it's happening frequently, they now tell us, but they assure us in the vast majority of cases it's trivial.

You do not know that. The NRC does not know that to be true and, under the recommendation that they have made, will continue not to know if that's true. There will be no best practices learned because the only thing that's happening here is they do not want to have to improve the way they practice. It's an embarrassment. They are self-congratulatory, thanking themselves for the hours they've spent studying this.

I think, from listening in and reading the past transcripts of ACMUI meetings, they do not

want anybody telling them that they are anything but perfect; they are doing everything right. And it is just not true. I mean, it's obvious to me from reading these materials.

And the NRC is not going to learn anything if they allow this watered-down approach to getting to the bottom of this issue. And I hope they will act more forcefully than the ACMUI is recommending.

MS. LOPAS: All right. Thank you, Dr. Williams.

So unmute yourself and press star-1 if you would like to make a comment.

Holly, do we have another commenter?

OPERATOR: Yes, Paul Wallner, again with the American College of Radiology.

You may go ahead.

DR. WALLNER: Thank you very much. I must contain myself and my emotions because I find some of the previous comments rather insulting to clinicians who manage these patients on a daily basis.

As I said previously, I've been managing patients with radioactive materials for 50 years, and previous comments make it sound like any of those

interactions were cavalier, that we would treat patients with radioactive materials and simply, if you will, street them.

All of these patients are given tremendous levels of instructions. They're followed carefully. These interventions, these infusions, are not long-term infusions where patients are left in rooms. They're typically straight push with a few cc's of radioactive material. The provider sees immediately that there is a level of extravasation, a tiny level of extravasation. The infusion is discontinued immediately, and the patient is given instructions and informed exactly what's happened.

I find that these comments -- I also am rather distressed that previous commenters are not requested to inform us regarding their affiliations with the petitioner. I think that's very misleading and not informative to the ACMUI. Thank you.

MS. LOPAS: All right. Thank you, Dr. Wallner.

So a reminder to unmute and press star-1 to make a call.

And, Holly, can we go to the next commenter?

OPERATOR: Our next caller is Ralph

Lieto.

You may go ahead, sir.

MR. LIETO: Thank you.

My name's Ralph Lieto, and I want to echo Dr. Wallner's comments, which were just before me, in terms of complete, you know, revealing any conflicts of interest. I am currently the President of the Michigan Radiological Society of the American College of Radiology.

I would like to comment on one point that was made as a suggestion of change. I understand the intent was to improve, maybe, potential reporting. But I have real, serious concern that you would change this to any authorized user as being acceptable for a patient reporting this.

I think that it should be the licensee that does the evaluation and review. And if you wanted another authorized user of the licensee, I think that might be acceptable. But I think the important caveat should be that it's a physician with expertise because there are physicians who are not authorized users that may not -- or that could provide a very expert evaluation of skin injury, specifically dermatologists and radiation oncologists, who deal with skin injuries on a daily basis.

So I would have the ACMUI and NRC really clarify the other AU that you're going to find acceptable for evaluation of a potential medical injury to the skin, not just any, because you could have a patient doing a follow-up, seeing a cardiologist who may be an AU for cardiology, and you're saying that that type of person may be totally acceptable for doing this type of an evaluation.

I think it needs to be a physician with expertise. Thank you.

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

So unmute your phone and press star-1 to make a comment.

Holly, can we go to our next commenter?

OPERATOR: Yes. Our next caller is Miguel de la Guardia with Cook Children's Medical Center.

You may go ahead.

MR. DE LA GUARDIA: Good afternoon. Thank you for taking my call.

I'm the Radiation Safety Officer at Cook Children's Medical Center, and we treat children here with high-dose I-131 MIBG, anywhere from a couple hundred millicuries all the way up to 1,000

millicuries.

We also have a cardiac cath lab which we already have procedures whereby we inform patients when we suspect that -- when they go over a certain level of radiation during a procedure, we inform the parent or the patient what to look for. They get a sheet of paper explaining everything. They get phone numbers to call and exactly what to look for.

And if they report any of those symptoms, we have either the skin wound team or radiation oncologist evaluate the patient. And this is no more traumatic than the procedure that they just went through. So I disagree with the comment before that this is very traumatic to patients having to look for these things. If this is brought up ahead of time that this could be a consequence of the procedure and people know about it, there is no problem. So I think that that is just a fallacy.

The second thing is that with small doses of radioisotope, yes, it is easy to determine if an extravasation has occurred. However, when you're infusing anywhere between 40 mLs and sometimes up to 90 mLs of product, that becomes a lot more difficult to tell with radiation detectors and things like that. But we do monitor the patient and tell them

what to look for, if it's stinging and things like that, so that we become aware of what's going on.

We treat kids as young as two. Those obviously can't tell you, so we do check them often while the infusion is going on. It may take an hour and a half to two hours, so we go into the infusion room quite often to check on the status of the IV.

So this procedure can be done correctly, and I think Option 4 with the amendments that have been suggested could be the way to go as far as monitoring whether extravasations are occurring or not. I think imaging, especially with high dose -- if I'm telling you that once we put several hundred millicuries of iodine-131, it takes about three to five days before we can put a patient anywhere near a camera. And bringing a survey meter up to them, you'll read the same thing pretty much everywhere unless you extravasate the whole dose.

So I think we have to be careful what we're looking for because it will not work for everything. But instructing patients what to look for and having a procedure in place as to how to evaluate them, I think that's the way to go.

Thank you for taking my call.

MS. LOPAS: Thank you very much, Miguel.

So press star-1 to make a comment.

Holly, can we have the next commenter?

OPERATOR: Yes. Our next caller is Matt Wait with Kaiser Permanente.

You may go ahead.

MR. WAIT: Hi there. I'm a member of the AAPM's Government Relations and Regulatory Affairs Committee and a practicing diagnostic medical physicist at Kaiser Permanente in Southern California. But I want to clarify that I am not authorized to speak on behalf of either of those two entities, so I'm speaking purely from my position as a practicing medical physicist.

I support Option 4. I think that a good model to follow is the current process for reporting misadministrations. A patient can be injected with the wrong quantity of a radionuclide, but it is only considered a reportable event if it's more than 20 percent from the prescribed dose. So you're not reporting every single error that occurs in the practice of medicine.

My partner is an infection preventionist. It's the same with hospital-acquired infections. There is many different requirements for reporting, but it is not required that every single potential

event is reported federally. And my perspective on this issue is it feels very much like a solution in search of a problem, namely a private company trying to adjust regulations to create a demand for their product.

So that's my opinion. I support Option 4. Thank you.

MS. LOPAS: Thank you. We appreciate the comment.

Holly, can we go to the next commenter?

And just a reminder to press star-1. Unmute yourself and press star-1. We'll take the next commenter.

OPERATOR: The next caller is Ronald Lattanze with Lucerno. Go ahead.

MS. LOPAS: Yeah, Lattanze.

OPERATOR: Sorry.

And again, Ronald, your line is open. We're not able to hear you.

MR. LATTANZE: Sorry about that. This is Ron, and I am with Lucerno. And, to answer Dr. Wallner's question, I am the petitioner for the extravasation petition that is being considered right now.

And I did want to address a couple of his

comments regarding his concern about centers that do a great job in this area, and that's -- we certainly see many centers that do an excellent job, and I heard the Children's Center just a second ago being described. And that sounds like a really good process.

But we have also been in centers that extravasate all the way up to 50 percent of their patients, so every other patient. And so I think we just need to remember that not every center is as good as some other centers, which indicates that there are issues that can be learned from the centers that are doing things right that are not being learned today.

Dr. Wallner also mentioned the case about doing infusions and stopping administrations if you suspect something. In the vast majority of diagnostic procedures that are done, the injections happen within just a second or two followed by a quick flush, all very, very low volumes, all very -- many times, these are non-vesicant, so the patient doesn't know that they're burning.

I've stood near -- outside the uptake rooms near technologists who've come out and said, that was a perfect injection, and then they found

that they extravasated the patient when they put the injection arm in the imaging field of view.

And so I think there is a very great misunderstanding that is out there in the community about being able to detect an extravasation. And oftentimes, most of these images do not include the injection site. So I think that Dr. Williams made a point about -- that this is a problem that people truly don't understand because it's not being monitored today.

So those are my comments. Thank you very much.

MS. LOPAS: Okay. Thank you, Ron.

Okay. So please press star-1. Make sure you're unmuted, and then press star-1 on your phone. There's nobody in queue.

Okay. I just saw a commenter pop up, Dr. Wallner.

Holly, are we picking up on Dr. Wallner again?

OPERATOR: Yes.

Dr. Wallner, your line is open again.

DR. WALLNER: Thank you.

It's hard for me to keep still about this because, first of all, I am not related at all to the

petitioner. Petitioner is trying to sell equipment. I am in the process of practicing medicine.

Public policy should not be set by anecdotes, and all of us can relay anecdotes relating to anything in healthcare where there have been potential problems. I would refer the ACMUI to the Australian data, where everything is indeed reported. Everything is indeed monitored. And in greater than three million cases, you can count on the fingers of one hand the number of clinical problems that have arisen.

Practicing medicine setting policy by anecdote is inappropriate. Thank you.

MS. LOPAS: Okay. Thank you, Dr. Wallner.

Okay. Reminder to press star-1. Unmute yourself and press star-1 to make a comment.

All right. So nobody's in queue, so go ahead and press star-1, and you'll be first up to make a comment if you would like to make a comment on the transcript today. Unmute and press star-1.

(Pause.)

MS. LOPAS: Okay. We'll just give it one more minute. So we're not seeing anybody come up in the comment queue, so we'll just wait one more

minute. Please press star-1. Unmute yourself and press star-1 to make a comment.

If we don't hear from anybody soon, we will just send it back to the ACMUI to deliberate and vote and finish up with some other business portions of the meeting. So please press star-1 if you would like to make a comment before we do that.

(Pause.)

MS. LOPAS: Okay. Holly, I'm not seeing anybody else coming up. Are you seeing anybody else coming up to make a comment?

OPERATOR: I have no additional callers in queue at this time.

MS. LOPAS: Okay. All right. Great.

Okay. I think, with that, Dr. Metter and ACMUI, I think we're ready to hand it back to you all. Thank you.

CHAIRMAN METTER: Thank you very much, Sarah, for your help on facilitating the public comments and questions.

So, at this point, I believe we -- the ACMUI Committee needs to vote on the draft report by the Subcommittee on extravasation, with the option for a consideration that they support -- with the revision in the option as -- I'd like to require

intervention for suspected radiation injury due to extravasation as confirmed by the authorized user.

With the comments that were made from the public, I'd like to make an addendum that this is -- and for the ACMUI to review -- that it read as, requires intervention for suspected radiation injury due to extravasation as confirmed by a physician authorized user of the licensee with expertise in radiopharmaceutical administration, radiation safety, and biology.

May I have any comments or questions from the ACMUI regarding that revision?

MEMBER MARTIN: This is Melissa. Chairman, I would accept those revisions for discussion.

CHAIRMAN METTER: Thank you, Melissa.

Any other comments?

MEMBER GREEN: This is Richard Green. I'm in favor and support of Dr. Metter's suggestion. I think that adds clarity to the requirements, and I would be very supportive of that.

CHAIRMAN METTER: Thank you, Mr. Green.

VICE CHAIRMAN DILSIZIAN: Vasken Dilsizian here. I have one comment. I guess to see the medical event will ultimately be reported by the

AU, somehow the AU has to be involved in this. Say that the patient sees some other expert in radiation injury, but the AU was never notified. That would be problematic.

So, somehow, we should make sure that the AU is involved in this.

CHAIRMAN METTER: Okay. I believe, Vasken, it would be -- because required intervention by the physician AU, by the licensee, would be involved with that because they would be involved in the concern for radiation injury. Would that be appropriate?

VICE CHAIRMAN DILSIZIAN: Yes --

CHAIRMAN METTER: Because I believe --

(Simultaneous speaking.)

CHAIRMAN METTER: Any other questions or comments or concerns on this revision for Option 4 or a change of -- concern regarding the Subcommittee's recommendation?

MEMBAR JADVAR: Darlene, could you please read one more time the modified option for it? Just say it very slowly.

CHAIRMAN METTER: Okay. I will. So I'm not sure how to put it in the posted one, but I would like to have it -- and I believe the NRC staff can

appropriately include it in the Option 4. But it would require intervention for suspected radiation injury due to extravasation as confirmed by a physician authorized user of the licensee with expertise in radiopharmaceutical administration, radiation safety, and biology.

MEMBAR JADVAR: So those features of the knowledge of biology and radio -- is that referring back to the AU or somebody else other than AU?

CHAIRMAN METTER: That's referring to the physician -- I have it, as confirmed by the physician AU of the licensee who has expertise in these areas, which would be a nuclear medicine physician, nuclear radiologist, radiation oncologist, those individuals, because those are part of the requirements to become an AU for those areas.

VICE CHAIRMAN DILSIZIAN: So, Darlene, Vasken Dilsizian. I'd like to comment about the cardiologist that was brought up by one of the commentators.

Just remember that in order to be a cardiologist, you have to be fulfilling three years of internal medicine and then three years of cardiology. And most of the time, you would be dealing with, also, hematology, chemotherapy, as part

of your internal medicine training, very much a part of the Internal Medicine Board, and the -- becoming a Nuclear Cardiology Board certification requires understanding of radiation, the injuries and radiation tissue injury.

So I respectfully request that we don't necessarily specify all of those expertise you needed. I think that by being AU, we should expect the AU to have knowledge in all the things that you mentioned, radiation biology, radiation protection, radiation injury. By definition, being an AU requires those talents. And so I would not go further than that.

MEMBAR JADVAR: That's what I was trying to get at, and I agree with Vasken. I think AU -- that's embedded into the definition of AU. So I'm not sure why we kind of drag out biology, radiopharmaceutical therapy, and many, many other things and make it longer and more complicated. I think AU, a licensed AU, should have that knowledge. That should be embedded. It's already embedded in it. I agree with Vasken.

CHAIRMAN METTER: Thank you, Vasken and Hossein. I was just trying to incorporate one of the public comments, but I totally agree with you. We

can say that the required intervention for a suspected radiation injury due to extravasation as confirmed by a physician AU of the licensee.

MEMBER ENNIS: Ron. Darlene, two comments.

So, one, I don't really -- I'm okay with it; I don't feel strongly about it. I don't support the of licensee addendum because if you're in a smaller -- I mean, you know, you might not want to go back to that hospital. Say you had a bad event, and you want to go to the competing hospital.

I don't think requiring the person to go back and meet up with the -- I just don't think that that's necessary, and I don't see what it's really gained by doing that.

And, number two, it sounds like we've changed it slightly from medical attention to medical intervention. And, again, I don't feel strongly, but I'm feeling a little bit like that also is not something I support because to me, if it was enough for the patient to go to the doc because it was red or it was bothering them, that's, to me, already enough to qualify as an ME, not necessarily requiring an intervention, which could be interpreted as meaning a debridement or some actual procedure.

And if it didn't need any kind of procedure, then it would not qualify as an ME if we have that word, intervention. So those are my two thoughts.

CHAIRMAN METTER: So, Dr. Ennis, how would you want to change that? Require medical intervention or evaluation? Is that what you would prefer?

MEMBER ENNIS: Okay. That would work, or just say medical attention, as it is on the slide, to me works fine.

(Simultaneous speaking.)

CHAIRMAN METTER: -- incorporate both of those.

VICE CHAIRMAN DILSIZIAN: Vasken Dilsizian again here. I guess if I read the second sentence, it says, if a patient requires medical attention. And how the medical attention here is being defined, due to skin damage near the injection site and the damage is determined to be caused by radiation.

And the key word here is and. Then the extravasation would be a medical event. I think it's pretty clear.

MEMBER MARTIN: This is Melissa. I

would just like to add, too -- I'm not sure. Was it Dr. Ennis that made the earlier comment? Contrary to what you may be implying that the patient might be reticent to return to the initial facility where they had the procedure done, that is consistent with how we have all of -- at least as far as I'm aware, all of the requirements for damage from cardiology studies or high-dose fluoroscopy studies.

When skin damage might be suspected, it's always requested to return to the licensee or site of the injury so that you do know that there's damage.

MEMBER ENNIS: Okay. That's an important point, then. I wasn't aware of those. I don't do fluoroscopies. So maybe that means we should keep it consistent --

(Simultaneous speaking.)

MEMBER MARTIN: I would prefer -- as Radiation Safety Officer, I can tell you that's how we've got most of our -- every policy I've ever seen has them return to the site of the procedure.

MEMBER SHEETZ: This is Mike Sheetz. And it's the requirement of the licensee to report the medical event. So, if the patient is seen by another institution, that other institution could not report the medical event because they're not the

licensee who did the administration.

VICE CHAIRMAN DILSIZIAN: Yes.

MEMBER SHEETZ: So I agree with Melissa. And I think maybe we can just simplify this and say, you know, the damage as determined by the licensee, and not even say AU. And that way, it allows any physician or healthcare practitioner within the licensee who they want to involve to make the determination if the damage was radiation induced.

MEMBER ENNIS: Okay. I can go along with that, given all these comments and considerations.

CHAIRMAN METTER: So, Mr. Sheetz, you would say, looking at the PowerPoint as it's here, you would just add, attention due to skin damage as determined by the licensee? And then that would just be the insert there?

MEMBER MARTIN: That really -- I'm sorry. This is Melissa. That really takes it down to whether you could have a PA making these -- it requires no knowledge of radiation skin damage. I really object to that. I liked the earlier version that requires somebody to evaluate it that knows about skin damage.

VICE CHAIRMAN DILSIZIAN: Yeah. I support Melissa. Vasken Dilsizian here again. I

think that it should be the AU and not just some other person. If this is serious enough that they should know and should be aware, he or she should be the one that's been reporting it.

CHAIRMAN METTER: Okay. So, given everybody's comments, as we look at it here, then, we'll go back to the revision if that's okay. And it would say, if a patient requires medical attention due to -- requires medical attention, I'm going to say, for suspected radiation injury due to extravasation as confirmed by a physician AU of the licensee causing skin damage near the administration site, and the damage is determined to be caused by radiation, then this extravasation will require medical event reporting.

Is that kind of -- condenses what we just discussed?

MEMBER MARTIN: That's acceptable with me.

VICE CHAIRMAN DILSIZIAN: Yes. It just has to be a little bit shorter, but that's -- yeah. I agree with you, Darlene.

CHAIRMAN METTER: Okay. Well, would the NRC staff kind of take that and then make it a little more concise? But that would be the thought process

for Option 4.

Any other comments or concerns with the ACMUI Committee for this before we vote on it?

MEMBAR JADVAR: Just one more comment. This is Hossein Jadvar. Does it have to be a skin damage? Can it be tissue damage? Why skin damage?

CHAIRMAN METTER: We can revise that to be tissue damage. That's a very good point, Dr. Jadvar.

MEMBAR JADVAR: Thank you.

MR. EINBERG: So, Melissa, Chris Einberg again -- or Dr. Metter. Excuse me. If you could read that one more time so that when you do vote on this, then it's clear as to what you're voting on.

CHAIRMAN METTER: Okay. So I'm going to read the whole thing as what I believe is what we have revised it to.

Option 4 would be a non-dose-based option for reporting extravasations that result in a radiation injury. If a patient requires medical attention for a suspected radiation injury due to extravasation as confirmed by a physician of the authorized -- physician authorized user of the licensee due to tissue damage near the administration site and the damage is determined to be caused by

radiation, then this extravasation will require medical event reporting.

Is that the --

VICE CHAIRMAN DILSIZIAN: Yes. I like it.

CHAIRMAN METTER: Okay.

Any comments or concerns or questions regarding the revision?

Mr. Einberg, is that clear for the NRC staff?

MR. EINBERG: That's clear for the NRC staff. And to move it forward, I would ask that you have a motion to vote on it, and then if you have a second, then yeah, you can go through the process and vote on it.

But before doing that, I'll ask the Medical Team Leader, Lisa Dimmick, if she has any questions or concerns.

MS. DIMMICK: Thank you, Chris.

And so, no, no questions or concerns. It's clear with the description provided by the ACMUI under Option 4. So staff understands what the ACMUI is saying. So thank you.

CHAIRMAN METTER: Thank you, Lisa and Chris.

Okay. If there are no other comments or questions from the ACMUI, do I hear a motion to approve the Subcommittee report with Option 4 as revised?

MEMBER WOLKOV: This is Harvey Wolkov. Yes, I'd like to make a motion that we accept the Subcommittee's recommendation, Option 4. Included in the motion would be the amendments that have been recommended by the ACMUI Subcommittee and stated by Dr. Metter.

CHAIRMAN METTER: Thank you, Dr. Wolkov.

Do I have a second, please?

MEMBAR JADVAR: Second. Hossein Jadvar.

CHAIRMAN METTER: Thank you, Dr. Jadvar.

Any questions or comments?

All in favor, please say aye.

(Chorus of ayes.)

CHAIRMAN METTER: Any objections?

(No audible response.)

CHAIRMAN METTER: Any abstentions?

(No audible response.)

CHAIRMAN METTER: Mr. Einberg, the Subcommittee report is accepted by the ACMUI.

MR. EINBERG: Very good. Thank you, Dr. Metter.

And I would note that -- just for the public record -- that it was accepted unanimously by the ACMUI.

Is that correct, Dr. Metter?

CHAIRMAN METTER: Yes, Mr. Einberg, very correct.

MR. EINBERG: Thank you.

CHAIRMAN METTER: At this point, would you like -- Mr. Einberg, would you like to make a comment about the membership at this time, the current membership of the ACMUI?

MR. EINBERG: Yeah. So, as I pointed out earlier, Dr. Angle has joined the ACMUI as a medical consultant, interventional radiology consultant. And so we welcome Dr. Angle to provide the support to the ACMUI. This is a one-year term appointment as a pilot to see if the expertise of an interventional radiologist on the Committee is merited.

So he is available to serve on subcommittees as a consultant. He does not have voting rights, as I mentioned earlier. But we do welcome him and his service to the NRC and to the ACMUI. So thank you, Dr. Angle.

MEMBER ANGLE: Thank you. A pleasure to

be part of the team. Thank you.

MR. EINBERG: The other announcement, which I mentioned earlier, is that Dr. Rebecca Allen will be joining the ACMUI, also, as the Healthcare Administrator. And so she's going through the clearance and processing aspect of joining the NRC. So we look forward to her working with us, as well, in the future.

And with that, Dr. Metter, I believe we had a proposal for another subcommittee.

CHAIRMAN METTER: Yes, and thank you. I'm sorry. I think I lost the audio connection when you were doing that part of your introduction. I apologize. But welcome to our new members.

Yes, as a final agenda item, I would like to form a new Subcommittee on the Diffusing Alpha-emitter Radiation Therapy, or the DaRT manual brachytherapy source, DaRT, to be regulated under 10 CFR 35.1000.

The Subcommittee charge will be to review the staff's Alpha Tau Alpha DaRT manual brachytherapy licensing guidance and provide any guidance for change or acceptance of the guidance. The Subcommittee members will be Dr. Ronald Ennis, a radiation oncologist who will chair the Subcommittee;

Mr. Zoubir Ouhib, therapy medical physicist; Ms. Megan Shober, agreement state representative; Dr. Michael O-Hara, FDA representative; Dr. Hossein Jadvar, a nuclear medicine physician; and Rebecca Allen, our hospital administrator; and the staff resource will be Dr. Katie Tapp.

Any questions regarding this?

Okay. Any final, last comments from the ACMUI?

And any other comments from the staff before we adjourn?

MEMBER SHOBER: Dr. Metter, this is Megan Shober. Just the question on the timeline for the new Subcommittee, what did you have in mind?

(Simultaneous speaking.)

MEMBER SHOBER: -- obviously.

CHAIRMAN METTER: So, as far as starting this off, we can go ahead and -- I'm not sure as far as the final timeline, but as far as we'd like to have maybe a preliminary (inaudible) I think would be -- the spring would be better, do you think, Mr. Einberg, rather than -- it's kind of short for the October meeting.

MR. EINBERG: Yeah, I think the spring is appropriate. We can refine the timeline and get

back to you on that, but the October meeting is too short of a timeline for that.

CHAIRMAN METTER: Thank you.

MEMBER ENNIS: Is there a formal charge for the Subcommittee?

CHAIRMAN METTER: I'm sorry, Dr. Ennis?

MR. EINBERG: Is there a formal charge, like a request that's asked that we're supposed to do specifically?

CHAIRMAN METTER: Yes. The charge is to review the staff's Alpha Tau Alpha DaRT manual brachytherapy license guidance and provide any comments and recommendations to change or accept the guidance. And that will be provided by the staff, and you'll get the -- the formal charge will be in the request.

MEMBER ENNIS: Okay. Sounds good. Thank you.

MR. EINBERG: So, Dr. Metter, this is Chris Einberg. Before we adjourn, I'd like to thank the ACMUI members for their thoughtful deliberations today, all their hard work in evaluating the staff's proposed recommendations.

Also, I'd like to thank all of the members of the public who have formally submitted

your written comments to the ACMUI and to the NRC. We do carefully evaluate those comments and consider those and their recommendations moving forward; also, all the thoughtful comments that were expressed today in the public comment period, those are very valuable not only to the ACMUI members but to the NRC staff as we deliberate on medical event reporting here for extravasations; and lastly, to thank the NRC staff, who's put in a lot of time and effort in evaluating this process.

As Sarah mentioned earlier, the process is we will consider the ACMUI's recommendations, and we will make a recommendation to the Commission on medical event reporting for extravasations. If the Commission decides to move forward with a rulemaking in this effort, the public will have additional opportunities to make comments during the rulemaking process.

And as Sarah pointed out, we propose moving a paper forward to the Commission in the spring time frame. So that's the process, where we're at right now. And if there is a rulemaking in this area, the public will have additional opportunities to make public comments.

And with that, I thank everybody once

again, and I'll turn it back to Dr. Metter.

CHAIRMAN METTER: Thank you, Mr. Einberg, for those comments. And, yes, I thank the ACMUI Subcommittee, the ACMUI, NRC staff, and I really appreciate the public comments that were made, which will be considered.

I appreciate everybody's time today, and if there are no other problems or concerns, the meeting is adjourned. Thank you very much, everyone, for your participation.

(Whereupon, the above-entitled matter went off the record at 2:47 p.m.)

From: drwpeddoc@aol.com
To: Jamerson, Kellee
Subject: [External_Sender] Comments on the extravasation issue
Date: Tuesday, August 31, 2021 12:36:38 PM

I am a practicing physician with a deep understanding of the topic of extravasations. I have patients who have had nuclear medicine studies and have accompanied family members who required nuclear medicine diagnostic procedures. I appreciate that the NRC is studying this issue and for allowing me to comment. I believe the NRC has identified a serious problem and has the opportunity to limit unintended and unnecessary radiation exposure for millions of Americans. I doubt there is another situation where just requiring an industry to follow best practices could reap so many benefits.

It is undisputed that radiopharmaceuticals are being administered incorrectly in far too many cases. Call it what you will, when these radioactive materials do not go in the vein cleanly, it means something was not given as intended. Institutions that have tracked extravasations and focused on fixing the problem have improved their rates to levels much lower than what is occurring and accepted today. The assumption that the majority of these extravasations are trivial and do not cause harm is unproven and should not be accepted by the NRC.

The ACMUI's response is embarrassing, but not unexpected. As a physician who interacts with scores of patients face-to-face every day, I am offended by the ACMUI's attempts to evade telling patients that they have inadvertently received a high dose of radiation to their tissue as a result of an extravasation. Patients deserve and appreciate transparency in all their interactions with physicians. I have read their past statements on the issue and at least they are consistent. Their goal in this process has been to avoid regulation, not to improve safety. Concerning extravasations, they have misled the NRC in the past and are trying to do so again. Now that the NRC is aware of the extent of the problem, the ACMUI seeks to limit oversight rather than provide a plan that would improve the safe administration of radiopharmaceuticals.

The NRC has the responsibility of assuring the safe administration of these radioactive materials. The NRC is aware that these materials are being incorrectly administered on a frequent basis. After reviewing the NRC medical staff's preliminary findings, Option 2 is the option that patients and referring physicians need enacted now, not months from now.

The regulatory burden of addressing this issue is limited by the institutions themselves. As they lower their extravasation rates their burden decreases. The 40-year pass that has been given for not reporting extravasations has meant that these institutions have ignored the issue. The opportunity to lower the rate by improvement in training, use of technology and different materials has always been there, but has never been consistently implemented by most centers. That regulation is necessary to address the issue is a sad state of affairs, but is not a reason to avoid regulation.

The NRC is aware that institutions could dramatically improve their rate of misadministration if they focused energy into the effort. I encourage the NRC to expeditiously enact regulations that force them to do so. Failure to do this is a failure to protect patients.

Sincerely,
Rob Williams, MD

From: randrewgarner@bellsouth.net
To: Jamerson, Kellee
Cc: David.Crowley@dhhs.nc.gov
Subject: [External_Sender] Written statement for the July 15, NRC ACMUI meeting
Date: Sunday, July 11, 2021 2:39:26 PM

Good afternoon, Ms. Jamerson.

My name is Drew Garner. I am a recently retired executive with a finance background. I understand the importance of processes in getting repeatable results. I understand the need for quality control, checks, and balances, and for transparency. During my 40+ year career I was the Chief Financial Officer at several large organizations. While the financial processes were very similar from one business to the next, I had to quickly learn about the markets, customers, and product technical details for each new business I joined. As a result, I am no stranger to new concepts. When I became a nuclear medicine cardiology patient, I wanted to learn all about these processes, too. As a result, I became aware of the extravasation issues several years ago. As you may recall, I participated in, and provided a comment during, the December 8, 2020, public comment meeting. Thank you for providing the opportunity then and this opportunity now. I am also providing these comments to my representatives in Congress, as I have done in the past.

I was pleased to see that the last two ACMUI patient advocates who completed their terms, Dr. Darrell Fisher through public comment and Ms. Lara Weil through a dissenting opinion as a member of the Subcommittee on Extravasations, both support the reporting of significant extravasations.

However, as I mentioned during the December 8th meeting, it is concerning to me that the patient voice is typically not reflected in many of the conversations regarding extravasations. To help ensure the patient perspective is heard, I have continued to research the extravasation topic, including the associated physics, and I have several comments to provide the NRC and the ACMUI. I also have specific questions for the ACMUI members and would appreciate hearing their responses during the meeting.

In 2019, the ACMUI Subcommittee on Extravasations recommendations referenced the 2008/2009 ACMUI decision to retain the exemption. A review of the actual transcripts of these meetings (not just the final recommendation) showed that the previous ACMUI members discussed that diagnostic extravasations were common, that doses could easily exceed reporting limits, and that they could be avoided if licensees used the more careful therapy administration technique for diagnostics administrations. Comments regarding the causes of extravasations focused on the experience level and training of the technologists performing the administrations, as well as their techniques and injection tools that they used. Despite all the discussion of points that suggested the exemption should be removed, the transcripts provide insight into the reason the ACMUI supported the retention of the reporting exemption. ACMUI member Dr. Nag, discussing doses of 3-5 Sv that exceeded the reporting limit and would qualify as medical events without the exemption in place, said: “However the first thing before us is, should NRC consider it as a medical event. Now if we consider this as a medical event, if we go through all the procedures and identify whatever-3 or 4 or 5-- the patient will have to be informed; the physician have to be informed, blah blah blah, and the - you have to go into all the reporting mechanisms. And therefore, I am thoroughly against this being reported as a medical event.”

Did the subcommittee members or any of the ACMUI members read the actual transcripts of these meetings? If not, why not? If so, what has happened since 2009 that has resulted in “passive patient intervention” to be the cause of extravasations rather than the causes your predecessors outlined several years ago? If so, why did they ignore the evidence that the exemption should be removed? And how could they endorse this previous recommendation that traded patient safety for keeping clinician reporting to a minimum?

It is my understanding that the reason that the NRC initially exempted extravasations from being reported in 1980 is because the NRC was told that extravasations were nearly impossible to avoid. Since one of the reasons for misadministration or medical event reporting is to share learnings from these events to prevent them from occurring again, I am assuming the NRC concluded that if these events are impossible to avoid then they should not be reported. I read the Association for Vascular Access position statement. I also attended a recent webinar to hear what vascular access experts

had to say about radiopharmaceutical administration techniques. All of these vascular access experts clearly state extravasations can be avoided. They also claim it is NOT the patient's fault. I also have read many examples in the literature that show definitive, immediate reduction in extravasation rates from hospitals that actively monitor their administrations. I also saw an interesting letter submitted on March 16, 2021, by Dr. Daniel Fass. Dr Fass and several other experts highlighted a statement by an SNMMI leader. This leader submitted a comment to NRC that "monitoring is not expected to improve administration techniques." However, this same leader co-authored a poster presented at an SNMMI meeting. In the poster, he clearly stated that active monitoring did in fact improve administrations and ongoing monitoring was important to ensure technologists did not return to their previous ineffective techniques.

What specific evidence did the Subcommittee on Extravasation members find that would support the 1979-1980 comment that extravasations are nearly impossible to avoid? Have the members talked to vascular access experts about "passive patient intervention," and if so, what did the experts say?

The subcommittee members also concluded that no diagnostic radiopharmaceutical extravasation could in fact, exceed the reporting limit of 0.5 Sieverts. I understand that diagnostic isotopes produce gamma rays that will not deposit significant energy in patient tissue, but in that same webinar, I heard Dr. Fisher explain that these isotopes also have other energy emissions. I also read Dr. Sheetz' comments in the March 16, 2021, transcripts regarding the "cystic" model of radioactivity in the tissue.

Mr. Sheetz is a radiation safety officer. Can he explain his cystic comment that he made to Dr. van der Pol? Does he think that the extravasated radioactivity is somehow not irradiating tissue in the area near the injection site? Can he describe what happens when 10 mCi of 18F is extravasated during an FDG injection like the recent case from North Dakota that the NRC asked the center to retract? Isn't a positron essentially a positively charged electron? If the fluorine atoms can be imaged in an area of arm tissue near the injection site, wouldn't all of the positron energy be deposited within in just a few millimeters of the fluorine atoms? If you know that you injected the entire dose into the tissue and you determine the amount of extravasated activity at time of imaging, Dr. Fisher says you can estimate biological clearance; in this case, would not the absorbed dose to 5-10 cm^3 of arm tissue be far greater than 0.5 Gy?

In the recent NRC staff report on medical events, a patient received a dose of 7 sieverts when a Lu-177 therapeutic radiopharmaceutical leaked on their skin during a procedure. The patient confirmed that her tissue did experience radiation injury. My understanding is that the unit of measure, sieverts, takes into consideration the type of energy emission.

So, isn't the 7 sieverts irradiation from F-18 the same as 7 sieverts from Lu-177 in the medical event accepted by the NRC? If so, other than the 1980 policy, does it make any sense that the North Dakota case is not a medical event? Shouldn't we follow this patient to see if tissue damage happens later?

As I noted earlier, I attended a webinar in May where experts discussed radiopharmaceutical extravasations. Two vascular access experts showed an image of patient that had gone through the same cardiology study that I went through. Unfortunately, it appeared that much of the Tc99M radioactivity from both injections was extravasated. Dr. Fisher described that Tc99M is more than a gamma emitter. That ~12% of the energy emitted are conversion electrons, Auger electrons, and low energy gamma rays, while I am not sure what all this energy actually is, by the end of the week, the patient began experiencing very disturbing tissue reactions. This leads me to two questions.

Didn't this diagnostic radiopharmaceutical extravasation obviously exceed the reporting limit? Since radiation injury can take weeks, months, or more likely years to show, how does a licensee, how do the societies, how does the ACMUI actually know that tissue doses are not exceeding either the reporting or adverse tissue reaction thresholds if hospitals do not perform dosimetry on these extravasations?

I would like to make one final observation; this is directed for the NRC staff. There seems to be a belief that there is a conflict of interest regarding the petition. As a patient, here is what I have seen and heard. There have been comments that the company Lucerno Dynamics has a product to sell that can help solve this problem. If so, what is the problem? In the NRC request for public comments

the NRC stated that they encourage authorized users to use the latest technology to help them deliver radioactive material safely. It seems to me that this company has developed technology that cannot only help clinicians know when they have an extravasation, but also help technologists improve their technique and to determine the biological clearance of a radiopharmaceutical. I think the device can provide the technologist insight right away if there may be a problem. From the patient perspective, I would be asking the NRC and providers why aren't you REQUIRING this process be monitored with that device? Again, from the patient perspective, if this company discovered that the 1980 exemption is incorrect, why do I care if they sell their products to hospitals to help them fix this issue. To me the really important question that has come from my researching this issue is the fact that the ACMUI has the true conflict of interest. Dr. Nag's specific comment is very disturbing. The ongoing ACMUI focus on blaming patients for extravasations makes me question the ACMUI's motives. And then I read the transcripts of the meeting between the subcommittee members and the NRC Commissioners. The changing stories, the evasion, and the misinformation shared with the Commissioners is not what I expect as a taxpayer paying these members to advise the NRC. My concerns were certainly reinforced by Dr. Schleipman's comments in the December 8 meeting. He mentioned his role in the ACMUI and then went on to describe a very large study. He implied to the NRC and to all who were listening that if extravasations were an issue, they would have been described in this million-patient study on adverse events. His comments made me take pause before I decided to speak at that meeting and certainly tempered the public statements I did eventually make at the end of that same meeting. Then, months later, I read the comment from Dr. Daniel Fass that pointed out that Dr. Schleipman had failed to mention that extravasations and any issues from extravasations had been specifically excluded from the million-patient study. I thought that was completely unacceptable and it frankly makes me question the credibility of the ACMUI. I would encourage the NRC and Congress to reevaluate the role that the ACMUI specifically plays and should play when it comes to discussing the merits of regulations intended to protect patients from inadvertent radiation doses.

Thank you again for providing me an opportunity to offer my opinions as a nuclear medicine patient.

Sincerely,

Drew Garner

August 27, 2021

Attn: Kellee Jamerson
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Subject: (ML21223A085) NRC Staff Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting; Comments of the American College of Radiology

The American College of Radiology (ACR)—a professional association representing over 40,000 diagnostic radiologists, interventional radiologists, nuclear medicine physicians, radiation oncologists, and medical physicists—appreciates the opportunity to provide feedback to the Nuclear Regulatory Commission (NRC) and the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI) regarding extravasation and medical event (ME) reporting. The following comments address the NRC staff's preliminary evaluation report and corresponding ACMUI Subcommittee on Extravasation recommendations packaged in ML21223A085. As of this writing, the publicly accessible documentation does not include the NRC staff recommendations.

In general, the ACR appreciates the NRC's consideration of qualitative options to focus ME reporting on rare, clinically significant extravasations of byproduct material resulting in deterministic radiation harms. The NRC should not require licensees to purchase novel monitoring products or use nonstandard dosimetry based on assumptions that are essentially universally contested by national medical physics and health physics organizations. Arbitrary quantification in the manner described in PRM-35-22 would not demonstrate that any radiation harms or preventable errors occurred, nor would using exotic monitoring products prevent small volume extravasations from occurring. A quantitative ME reporting mandate would, however, result in clinical, professional, financial, and medicolegal impositions on health care providers with negative impacts on patient access, cost, comfort, and safety. These impacts were discussed in the ACR's comments on PRM-35-22.

The ACR continues to recommend "Option 6." Option 6 would require ME reporting of extravasations determined by a physician to meet the significant harm standard of §35.3045(b). The ACMUI Subcommittee on Extravasation is currently recommending "Option 4." Option 4 would require reporting if "*a patient requires medical attention due to skin damage near the administration site, and the damage is determined to be caused by radiation.*" Option 4 is preferable to the identified quantitative reporting options; however, the ACR has the following concerns regarding this option:

1. **"Medical attention" is ambiguous.** Taken to an unintended extreme, "medical attention" could be interpreted by NRC or Agreement State agencies as including basic care for transient erythema, mild discomfort, or swelling at the injection site. The ACMUI must clearly define the manner and intensity of the "medical attention" that should or should not trigger ME reporting requirements.

2. **Injury assessments and attribution to radiation should be done by physicians with expertise.** Option 6 would require a physician-level determination that the harm standard of §35.3045(b) has been met. Conversely, the descriptions of Option 4 in the documentation did not specify the qualifications of individuals making harm determinations and attributing cause. Ideally, an Authorized User (AU) or AU-eligible physician is best capable to differentiate "radiation-caused damage" from transient reactions to the pharmaceutical component of the radiopharmaceutical or other reactions to any nonradioactive drugs/materials administered during treatment.

3. **Option 4 would require rulemaking to create a new Medical Event type.** Depending on the position of NRC's Office of General Counsel, the essential approach of Option 6 could possibly be implementable via subregulatory policy without modifying the CFR by following ACMUI's previous recommendations on extravasation and patient intervention.

Moving forward, the ACR recommends that ACMUI reaffirm its previous position (Option 6), which is less susceptible to downstream misinterpretation than the current iteration of Option 4. Should the ACMUI wish to endorse Option 4, committee members must amend the subcommittee report to resolve concerns #1 and 2 prior to approval.

The ACR appreciates the NRC and ACMUI's consideration of this statement. Please contact Gloria R. Romanelli, JD, ACR Senior Director of Legislative and Regulatory Relations, at gromanelli@acr.org, and Michael Peters, ACR Government Affairs Director, at mpeters@acr.org or (202) 223-1670 with questions or concerns.

Sincerely,

Howard B. Fleishon, MD, MMM, FACR
Chair, Board of Chancellors
American College of Radiology

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July 9, 2021

U.S. Nuclear Regulatory Commission
Advisory Committee on Medical Uses of Isotopes
Attention: Ms. Kellee Jamerson
Email: *Kellee.Jamerson@nrc.gov*

Re: ACMUI Subcommittee on Extravasations and Medical Event Reporting Draft Report

Dear Chair Darlene F. Metter, M.D. & Advisory Committee Members,

I am the CEO of AltusLearn, an online education platform for healthcare professionals. One of our key areas of educational focus is "Imaging". For this area of focus, our motto is: "Stay Current, Stay Safe." Because of our imaging focus, our emphasis on safety, and through our connections in radiology and nuclear medicine, we became aware of and very interested in the radiopharmaceutical extravasation issue before the NRC at this time.

In May 2021, we hosted a CE-accredited webinar on radiopharmaceutical extravasations with six experts in the fields of physics, nuclear medicine, radiation protection radiation biology, and vascular access. Three of the nuclear medicine experts are long-term members of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), frequent lecturers, and authors of countless papers. One of the three is also a member of the Health Physics Society as well as a member of the Medical Imaging Radiation Dose committee. One is a co- author on the second most cited technical paper published in the Journal of Nuclear Medicine and Molecular Imaging. The radiation biology expert who is not a member of SNMMI was asked by the SNMMI to present on the topic of radiation toxicity to healthy tissue in a radiotherapeutic seminar with the NIH and FDA. In June, we conducted individual webinars with follow-on questions for each presenter. These interviews will be combined into one webinar, which will also receive one CE credit.

One of our presenters was Dr. David Townsend, an IEEE Life Fellow, the co-inventor of the PET/CT scanner, and a pioneer of three-dimensional PET and its required reconstruction algorithms. Dr. Townsend and I are providing this written statement for the July 15, 2021, Nuclear Regulatory Commission (NRC) and Advisory Committee on the Medical Uses of Isotopes (ACMUI) meeting.

Between the two of us, we have followed the NRC and ACMUI discussion of extravasations since the April 2, 2019, ACMUI Spring meeting. We have also read some public comments that are inaccurate and not supported by science, indicating lots of misunderstandings regarding radiopharmaceutical extravasations. We want to make sure that there are no misunderstandings of the following points regarding significant extravasations, all of which can be supported by an extensive collection of peer-reviewed articles.

1. They negatively affect the reconstructed image quality and compromise quantification.
2. They negatively affect the interpretation of images used to guide patient care, and more disturbingly, can often go undetected.

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3. The non-penetrating, short-range ionizing emissions (positrons, electrons, internal conversion electrons, and Auger electrons) and low-energy photons and x-rays associated with diagnostic radiopharmaceuticals as well as the emissions from therapeutic radiopharmaceuticals, can result in absorbed doses well beyond NRC medical event reporting limits.
4. Ionizing radiation will result in latent effects that will NOT be readily visible to anyone in the nuclear medicine community immediately. Instead, symptoms of adverse tissue effects can take many days – years to manifest. Additionally, higher absorbed doses lead to increased stochastic effect risks.
5. Vascular experts, who routinely assist providers in gaining venous access for the most difficult patient cases, expect first time vascular access success (98%). This high-level of success rate, combined with the official statement of the Association for Vascular Access, clearly indicates that extravasations are not "nearly impossible to avoid."

We encourage the NRC staff and the ACMUI members, who have any misgivings about the previous five statements to watch the webinar (https://altuslearn.com/radiopharmaceutical-extravasations-hazards-mitigation-and-prevention/) or to reach out to the webinar presenters directly with questions. An open dialogue rather than dueling statements would be welcomed.

Because of these points and our awareness (based on data we have collected and from our review of the literature) that radiopharmaceutical extravasations occur frequently, we believe it is essential that extravasations be identified as early as possible during the administration of radiopharmaceuticals. This will allow for immediate mitigation steps to reduce absorbed dose. We also see no reason why extravasations should be treated any differently than any other medical event. If the absorbed dose is >0.5 Gy (dose equivalent >0.5 Sv) the NRC should receive a report.

While we can understand the medical communities' reluctance to increase reporting, that does not change the facts. Injecting radioactivity into patient tissue, rather than into the vascular system as intended, can result in a high absorbed radiation dose. The facts are clear on this point. The resulting transparency of reporting will lead to the necessary quality improvement efforts in centers that warrant improvement. This effort will lead to safer and more precise nuclear medicine procedures – good for patients, nuclear medicine, and regulators.

Should you have any questions or require clarification Dr. Townsend and myself are available to answer questions.

Sincerely,

DocuSigned by:
Daniel G. Guerra Jr.
0E86F3D0476A466...

Daniel G. Guerra Jr, CEO
AltusLearn

DocuSigned by:
David W. Townsend
D5EA983B41B146D...

Dr. David Townsend

To Whom It May Concern:

I am writing in response to the Subcommittee Review and Comments on the "NRC Staff Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting" Draft Report, dated July 30, 2021.

For the record, I believe the NRC should adopt the recommendations included in the petition in Docket: NRC-2020-0141 - specifically, that patients, their physicians, and the NRC should all be notified when a radiopharmaceutical extravasation occurs.

I was particularly troubled to note one section of the draft report that warrants further examination:

Furthermore, with the Medical Event regulatory reporting and patient notification requirements, there must be consideration of the psychological harm to the patient if his/her administration procedure results in an extravasation and is labeled as a Medical Event. Even though "Medical Event" does not necessarily imply clinically significant problems with the procedure, public perception is it constitutes a medical error.

This, I fear, is at the misguided heart of the extravasation reporting debate: the worry about optics and public relations above all else. The concern expressed here – that "public perception" will attach itself in a negative way to reporting of a significant extravasation – completely and shockingly discounts the one stakeholder that matters above all others: the affected patient.

In addition, the notion that "psychological harm" will come to a patient notified of a significant extravasation is an insulting dismissal – even infantilization - of the patients we serve, who are relying on the medical community to help them through a devastating, life-threatening condition.

When extravasation occurs, the patient absolutely has a right to know. The suggestion that psychological harm may result is an arguable point at best, and pales in comparison to the very real, downstream effects of a significant extravasation: the patient may come to severe physical harm around the injection site, and the images may well be compromised, which can then result in misdiagnosis and a course of treatment that is not optimally effective.

I respectfully urge the NRC to reframe this discussion in a way that gives patients agency, arming them with all information about their condition. That obviously includes reporting incidents of signification extravasation, which can negatively impact the patient's health and course of treatment.

By shining a light on significant extravasations now, you are helping to ensure that patients are treated with the respect and honesty they deserve. Again, I respectfully ask that you adopt the recommendations included in the petition in Docket: NRC-2020-0141. Thank you for your consideration and attention to this matter.

Kind Regards,

Amanda R. Ferraro
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DEBORAH K. ROSS
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Congress of the United States
House of Representatives
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July 12, 2021

Dr. Darlene Metter
Chair
Advisory Committee on the Medical Uses of Isotopes
U.S. Nuclear Regulatory Commission
11555 Rockville Pike
Rockville, MD 20852

Kellee Jamerson
U.S. Nuclear Regulatory Commission
11555 Rockville Pike
Rockville, MD 20852

Dear Dr. Metter and Ms. Jamerson:

I have followed with interest the U.S. Nuclear Regulatory Commission's (NRC) evaluation of its policy on medical event reporting on extravasations. As you are aware, this 41 year-old policy exempts from medical event reporting requirements incidents in which patients are irradiated unintentionally during nuclear medicine procedures due to an injection extravasation, regardless of the severity of the irradiation.

I am concerned by scientific literature demonstrating the frequency with which extravasations occur, the high levels of radiation to which patients can be unintentionally exposed, and the potential consequences. Literature also shows that these events are largely preventable. There are compelling reasons for patients to know if they have been irradiated at high levels as a result of an extravasation during a diagnostic or therapeutic nuclear medicine procedure. NRC should take interest in these incidents in order to determine if a particular facility is having trouble safely handling radioactive materials.

As you are aware, a bipartisan group of Members of the U.S. House of Representatives and the U.S. Senate has urged NRC to update its outdated policy through public comment to petition for rulemaking PRM-35-22. Patients, patient advocacy groups, the Commission's own regulatory partner — the Organization of Agreement States (OAS), and scientific and clinical experts have also supported the petition.

I urge NRC to take this opportunity to protect patients, improve health care quality, and increase transparency. Again, extravasations can be prevented, and changing NRC's current policy would likely be beneficial for patients undergoing diagnostic and therapeutic nuclear medicine procedures.

Very truly yours,

Deborah K. Ross
Member of Congress

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August 31, 2021

Dr. Darlene Metter
Chair, Advisory Committee on the Medical Use of Isotopes
US Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Dr. Metter,

The American Society for Radiation Oncology[1] (ASTRO) commends the Nuclear Regulatory Commission's (NRC) Advisory Committee on the Medical Use of Isotopes' (ACMUI) Subcommittee on Extravasation on their thorough review of the NRC staff's preliminary evaluation of radiopharmaceutical extravasation and medical event reporting.

In its evaluation, the NRC staff outlined six potential options for radiopharmaceutical extravasation and medical event reporting:

1. **"No Action"** would maintain the status quo, and extravasations would continue to be excluded from medical event reporting.
2. **"50-rem dose threshold"** would require medical event reporting for extravasations that exceed a localized dose equivalent of 50 rem.
3. **"Administration site dose for procedures requiring a written directive"** would require that for procedures requiring a written directive, extravasations resulting in a dose 50 rem greater and 50 percent or more than the expected dose to the administration site be reported as medical events.
4. **"Extravasation events that require medical attention"** would be a non-dose based option for reporting extravasations that result in a radiation injury.
5. "**Extravasation events that cause a significant dose"** would require medical event reporting for extravasations that meet the 10 Gy (1,000 rad) dose threshold requirement for Abnormal Occurrences (AO).
6. **"Extravasation events that cause permanent functional damage"** would require extravasations that result in permanent functional damage to be reported as medical events.

The ACMUI subcommittee reviewed the staff's options and is supporting Option 4 ("Extravasation events that require medical attention"). In its report, the subcommittee stated that Option 4 would "provide NRC with information on the types of radiation injuries caused by

[1] ASTRO is the largest radiation oncology society in the world, with more than 10,000 members who specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, biology and physics, the Society is dedicated to improving patient care through education, clinical practice, advancement of science and advocacy. ASTRO's highest priority has always been ensuring patients receive the safest, most effective treatments.

extravasation, and the frequency of such injuries." ASTRO believes that adding NRC oversight of extravasation will unnecessarily increase regulatory burden for licensees without a radiological or patient safety benefit, and therefore prefers Option 1 ("No action"). Monitoring extravasations is a medical issue that is overseen by the licensee's quality management program.

ASTRO opposes any option that would require additional dosimetry, a dose threshold, or the purchase of proprietary equipment to measure dose to determine whether an extravasation must be reported as a medical event. Therefore, we oppose Option 2 ("50-rem dose threshold"), Option 3 ("Administration site dose for procedures requiring a written directive"), and Option 5 ("Extravasation events that cause a significant dose").

If, however, the NRC is determined to require reporting on extravasations, and given the options presented, ASTRO is generally supportive of Option 4 ("Extravasation events that require medical attention") or Option 6 ("Extravasation events that cause permanent functional damage").

We do have concerns that under Option 4, the term "medical attention" is ambiguous and raises more questions than it answers. For example, what is the definition of "medical attention"? What intensity of medical attention triggers the reporting mandate? Under this option, a patient noticing a red mark or swelling and merely going to talk to their physician—regardless of whether radiation was the cause—would trigger a medical event report. Or is it something more complicated and serious, like a non-healing skin ulcer or skin and soft tissue necrosis that requires medical intervention?

A patient may not seek medical attention until well after the administration of a radiopharmaceutical, and in the rare case that an expert determines the cause of the red mark or swelling is from radiation and requires medical intervention—such as applying hyperthermia—then a medical event report is reasonable. Therefore, ASTRO recommends the ACMUI change "Extravasation events that require medical attention" to "Extravasation events that require medical *intervention for a suspected radiation injury*".

We appreciate the opportunity to provide comments on this important issue. Should you have any questions, please contact Cindy Tomlinson, Senior Patient Safety and Regulatory Affairs Manager at cindy.tomlinson@astro.org or 703.839.7366.

Sincerely,

Laura Thevenot

Laura I. Thevenot
Chief Executive Officer

PATIENTS
FOR SAFER NUCLEAR MEDICINE

August 31, 2021

To Whom It May Concern:

We contact you on behalf of nuclear medicine patients across the United States to respectfully ask the Nuclear Regulatory Commission to adopt the recommendations made in the petition in Docket: NRC-2020-0141. We believe that patients, their physicians, and the NRC should all be made aware of radiopharmaceutical extravasations that exceed the medical event reporting limit.

The Patients for Safer Nuclear Medicine Coalition is comprised of numerous advocacy organizations, across several therapeutic areas, representing thousands of patients across the US. We are dedicated to ensuring the safety of nuclear medicine procedures, which are commonly used to support cardiology, neurology, cancer, and many other types of patients.

Radiopharmaceutical extravasations can inadvertently irradiate patient tissues with doses that far exceed the reporting limit (0.5 Sv) and the threshold that the nuclear medicine community says will lead to adverse tissue reactions (1.0 Sv). We also know that these significant extravasations that exceed the reporting limit happen far more often than they should, even though they are preventable.

In addition to contributing to injury, significant extravasations can also lead to misdiagnosis and incorrect course of treatment for patients. When it comes to cancer, for example, a significant extravasation can compromise diagnostic images, leading to a misdiagnosis that can take a patient down the wrong treatment path. Similarly, when it comes to cardiology and neurology patients, a significant extravasation can lead to doctors making decisions for treatment based on inaccurate images. The idea that information regarding a significant extravasation should continue to be kept from the patient and their physician is simply unacceptable.

We further believe the NRC should be aware of significant extravasations. The agency is responsible for protecting patients during procedures involving the use of isotopes. Unfortunately, the current problem is compounded by a lack of reporting. There is no way to address this serious issue when information is incomplete or unavailable in the first place. Patients have the right to know which nuclear medicine centers have issues in the proper administration of medical isotopes.

By adopting the recommendations included in the petition in Docket: NRC-2020-0141, we can begin to tackle this serious problem while continuing to make strides forward in the diagnosis and treatment of patients. On behalf nuclear medicine patients, we thank you for considering our request.

Sincerely,

The Patients for Safer Nuclear Medicine Coalition

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ican international cancer advocacy network
the virtual lifeline for proactive cancer patients

August 30, 2021

U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: NRC-2020-0141

Dear Sir/Madam,

I write this letter to formally ask the NRC to adopt the recommendations included in the petition in Docket: NRC-2020-0141, requiring that patients, their physicians, and the NRC should all be notified when a significant radiopharmaceutical extravasation occurs.

I also read the Subcommittee Review and Comments on the "NRC Staff Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting" Draft Report, dated July 30, 2021. Certain key assertions were made in that document that I respectfully disagree with. However, I wish to highlight one passage that, inadvertently, makes a virtually unassailable case in favor of significant extravasation notification:

"In addition, extravasation of diagnostic radiopharmaceuticals rarely affects the sensitivity and quantification of the study, or compromises patient care and management decisions because of the generally small amount of extravasate, and that it is reabsorbed via the lymphatic channels. If the amount of extravasation results in poor quality images, making it technically unreliable for clinical interpretation, the study is usually repeated on another day. This is no different than repeated procedures due to wrong imaging protocol or improper positioning.

All nuclear medicine facilities <u>should</u> have comprehensive quality control measures in place to monitor and track extravasations to improve the quality and safety of patients undergoing medical procedures involving the use of radiopharmaceuticals."

The most obvious counterargument is that significant extravasations currently are not reported. Therefore, how can anyone claim with any degree of certainty that extravasation "rarely affects the sensitivity and quantification of the study, or compromises patient care and management decisions?" That is

simply unknowable under the current structure.

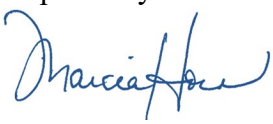
Furthermore, we know from speaking with significantly extravasated patients who were not notified – and suffered visible, obvious healthcare complications as a result – that their imaging procedures were not repeated. Those patients can tell their story better than I can, and I am certain that some have already reached out to you. Again, there are currently no standards in place that require a repeated imaging study in the event of a significant extravasation.

As to the point that "[a]ll nuclear medicine facilities should have comprehensive quality control measures in place," I agree that there ***should*** be such measures, but we know for a fact that this is not the case. A survey of eight leading U.S. cancer centers, conducted by Vascular Wellness, found that not a single center had protocols in place for significant extravasations.

It is troubling that the best argument against significant extravasation reporting is based on a perceived honor system that all available evidence shows is not being honored. Therefore, I respectfully urge the NRC to do the right thing on behalf of cancer patients and adopt the recommendations included in the petition in Docket: NRC-2020-0141.

Thank you for considering this request.

Respectfully submitted,



Marcia K. Horn, JD
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ICAN is a 501(c)(3) tax-exempt charitable organization (EIN 86-0818253) serving Stage IV metastatic cancer patients across the United States and in 54 countries since 1996. ICAN is one of the few national cancer organizations that is both Platinum-rated (the highest rating) on GuideStar, and five-star rated (also the highest) on Great Nonprofits.

ICAN, operating with the highest standards of board governance, has received the "Top-Rated Health Care Nonprofit" award from Great Nonprofits every year since 2010.

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August 31, 2021

Kevin Williams
Director, Division of Materials Safety, Security, State, and Tribal Programs
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Delivered via email

Dear Mr. Williams:

This statement is submitted for the September 2, 2021, NRC/ACMUI extravasation public meeting.

Executive Summary

The NRC medical staff researched the topic of radiopharmaceutical extravasations for 14 months (January 2020 - April 2021). On April 1, 2021, the staff delivered their findings to the ACMUI subcommittee and provided the subcommittee over four months to deliberate on these findings and respond. Despite receiving and responding to three written requests in July for public access to the April 1, 2021, findings, the medical staff withheld them from the public until August 11, 2021. On that same date, they also released the subcommittee recommendations. This allowed the public 20 days to review the NRC findings, the ACMUI recommendations, and then to submit comments.

A comparison of the findings and recommendations to previously stated positions suggests that the NRC and ACMUI have increased their understanding of the topic of radiopharmaceutical extravasations. Examples of this increased understanding include:

- the 1980 extravasation reporting exemption prevents the NRC from accurately fulfilling their obligation to Congress to report on Abnormal Occurrences,
- extravasations of high consequence should be reported,
- both diagnostic and radiopharmaceutical extravasations can exceed current reporting limits,
- the catastrophic classification of “permanent functional damage” should no longer be considered as the only reason to report an extravasation, and
- acute cellular effects caused by ionizing radiation will not immediately be evident to patients or the nuclear medicine community.

While some progress has been made, substantial issues still exist. A large number of NRC findings and ACMUI recommendations are not scientifically sound and inexplicably remain inconsistent with existing NRC positions (including some positions reflected in the NRC’s denial of three petitions on August 17, 2021). Some examples of where the NRC medical staff needs to accelerate their understanding include:

- extravasations are preventable,
- current reporting thresholds are appropriate for extravasation reporting,
- patient harm and frequency of occurrence are not reporting criteria,
- patient harm can result from therapeutic **and** diagnostic radiopharmaceutical extravasations,
- appropriate dosimetry is not a burden,

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- patients have a right to know when they have been significantly extravasated but should not assume the licensee's responsibility for medical event reporting,
- the NRC's regulatory partner, the Organization of Agreement States, supports the petition, and
- options other than Option 2 fail to adequately protect patients.

The NRC has received an abundance of detailed evidence regarding extravasations over the past 32 months. The shortcomings listed above, the comments that follow, and the more detailed analyses in the attached appendices suggest the NRC is not following evidence-based policy making, is demonstrating a lack of urgency to improve the care of hundreds of patients who are harmed every day by these extravasations and is not meeting their goal to protect the public from radiological hazards associated with NRC-licensed materials.

The NRC should expeditiously correct the 1980 policy that exempts extravasations from medical event reporting by implementing NRC preliminary finding Option 2. This option, combined with appropriate rulemaking, will result in the dramatic reduction of radiopharmaceutical extravasations, improved patient care and safety, and result in minimal burden on licensees and regulators.

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Background

In December 2018, the NRC medical staff became aware of evidence that radiopharmaceutical extravasations could be prevented. This evidence demonstrated that the premise of the NRC policy that exempted extravasations from being reported as medical events was incorrect. At the request of the NRC, these findings were presented to the ACMUI in April of 2019. At the end of that presentation, the Chairman of the ACMUI created a subcommittee on extravasations to assess if extravasations that exceed medical event reporting limits should continue to be exempted. In the Fall of 2019, the subcommittee presented their findings. They concluded that the exemption should remain. The patient advocate on the subcommittee provided a written dissenting opinion. The ACMUI justification for their conclusion lacked scientific rigor and was factually incorrect, as outlined in a communication to the NRC in October 2019.

In January 2020, the NRC announced they had not accepted the ACMUI recommendations and were conducting an independent evaluation. From January 2020 through today, the NRC medical staff has received an abundance of scientific evidence on the extravasation topic. On April 1, 2021, the medical staff provided the ACMUI subcommittee with their independent evaluation preliminary findings and six potential options to consider. The subcommittee, comprised of members of the regulated community and medical societies that have vigorously opposed the petition, had more than four months to review these findings and make a recommendation.
In mid-July, the NRC medical staff received and responded to three emails over eight days that requested access to the April 1, 2021, findings as soon as possible. On July 16, 2021, the medical staff stated that the findings would be withheld until the week of August 9 in order “to allow for subcommittee deliberations,” even though publicly releasing these findings would in no way hinder subcommittee deliberations.

On August 11, the NRC medical staff posted the findings and the subcommittee recommendations. This timing allowed the public 20 days to deliberate and make public comments. This process has been less than transparent and inadequate to allow for proper public analysis. Furthermore, the process favors the community that the NRC regulates.

Some progress

The NRC medical staff’s preliminary findings include the following:

1. Extravasations that meet the public health and safety significance criteria for abnormal occurrence (AO) are not currently being reported.
2. Medical events may not necessarily cause patient harm, but the NRC requires their reporting because they have the potential to cause harm and they may indicate a potential problem with how a medical facility administers radioactive materials or radiation from radioactive materials.
3. It is assumed that the likelihood of developing cancer increases linearly with dose without a threshold.
4. Acute cellular effects from ionizing radiation will not be immediately observed and may take several days to months to manifest.

Furthermore, the ACMUI Subcommittee on Extravasations reached the following conclusions:

1. Extravasations that meet the public health and safety significance criteria for abnormal occurrence (AO) are not currently being reported.
2. Extravasations of high consequence should be reported.
3. Diagnostic and therapeutic extravasations can exceed reporting threshold of 0.5 Sv.

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4. The catastrophic classification of “permanent functional damage” is no longer being considered as the only reason to report an extravasation.
5. NRC preliminary findings Option 1 of “no action” is not supported.
6. NRC preliminary findings Option 3 is not supported since it would exclude diagnostic extravasations.

These conclusions represent advancements in awareness regarding radiopharmaceutical extravasations. And although the subcommittee continued to intimate that patient anatomy is a major reason for extravasations, they did not repeat their previous recommendation that extravasations were the result of “passive patient intervention.”

Misrepresentations, misunderstandings, and inconsistent application of NRC policies

While the ACMUI members and the NRC medical staff have increased their awareness of certain aspects of the extravasation issue, substantial and important issues in understanding, unfortunately, still exist. A large number of NRC findings and ACMUI recommendations are not based on clinical evidence, and many are not scientifically sound. Additionally, several of the findings and recommendations remain inconsistent with existing NRC positions (including some positions reflected in the NRC’s denial of three petitions on August 17, 2021).
Several important examples of where the NRC medical staff needs to accelerate their understanding can be found below and additional details are included in the following appendices.

Appendix A – Analysis of the NRC findings and options and the ACMUI recommendations
Appendix B – Extravasation case studies
Appendix C – Analysis of the ACMUI “pocket” extravasation dosimetry analysis

Extravasations are preventable.

The high absorbed radiation doses that are accidently delivered to patient tissue as a result of significant extravasations are avoidable and are a perfect example of the type of misadministration that the NRC was charged by Congress to address in the late 1970s. The NRC needs to remove the 1980 reporting exemption to be consistent with their Medical Policy Statement and their stated position regarding regulation of the delivery of radioactive material.

> “The Commission has a role in assuring accurate delivery of radiation doses and dosages to patients and has rejected the notion that NRC should not regulate patient radiation safety (44 FR:8243, February 9, 1979). NRC will continue to regulate the radiation safety of patients when justified by the risk to patients, primarily to ensure that the authorized user physician’s directions are followed. The Commission recognizes that physicians have the primary responsibility for the protection of their patients. However, the NRC’s role is also necessary to ensure radiation safety of patients.”

In the denial of the three petitions (PRM-20-28, PRM-20-29, and PRM-20-30) and in support of existing NRC policies, the NRC repeatedly stressed the importance of national and international authoritative scientific bodies with expertise in the science of radiation protection, such as the ICRP and IAEA. The NRC stated that the IAEA is an “international authoritative scientific advisory body” and that it “has been the longstanding practice of the NRC to generally place significant weight on the recommendations” of such a body. Last month, the IAEA published **QUANUM 3.0:**

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An Updated Tool for Nuclear Medicine Audits. Here is what IAEA said about radiopharmaceutical extravasations in their QUANUM 3.0:

1. Extravasations are preventable
2. Extravasations should be documented
3. Extravasations require root cause analysis
4. Extravasations should be prevented
5. Extravasations are errors in the administration and are not caused by patients

Over the past 32 months, the following evidence that extravasations are preventable has been shared with the NRC.

1. Evidence from IAEA conferences and ICRP guidance on radiopharmaceutical extravasations—the international authoritative bodies are clear that these are preventable misadministrations.
2. Evidence from multi-center studies, involving millions of CT and chemotherapy patients at multiple centers over three decades, clearly demonstrates that extravasations are preventable.
3. Evidence from the largest ever quality improvement (QI) project—peer-reviewed and published in the JNMT, **an SNMMI journal**—clearly showed extravasations are preventable.
    a. An author of the paper also submitted a comment in opposition to the petition stating that diagnostic extravasations do "not require medical attention and should not be considered a medical event." This comment does not conflict with the findings of the paper in any way. The paper "demonstrated that nuclear medicine infiltration rates can be reduced and sustained through QI. Ongoing monitoring of nuclear medicine injection processes will help ensure that injection processes remain in control or continue to improve, just as contrast CT and chemotherapy injection process have continued to improve."
4. Single center data that show extravasations are preventable (more to follow in the Recommendations section below).
5. Public comments from experts in vascular access that clearly indicated that extravasations are preventable.

As the NRC staff explained in their preliminary findings,

> "The purpose of medical event reporting is to identify the causes of events in order to correct them, prevent their recurrence, and allow the NRC to notify other licensees of the events so they too can avoid them. Through medical event reporting, the NRC can track and trend medical events and subsequently share operational experience, and the ACMUI has recommended that the NRC communicate information about medical events to licensees to raise awareness about emerging trends."

A significant extravasation can irradiate patient tissue with a very high absorbed dose. As a result, the current exemption is inconsistent with the NRC obligation to protect patients. With the reporting exemption in place, the NRC is unaware of significant extravasations and unable to share root causes with other licensees.

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Despite all of the presented evidence to the contrary, the ACMUI subcommittee members still conclude that, “Monitoring for extravasations will not prevent them from occurring.” The NRC medical staff stated, “The medical community firmly views extravasation as a ‘practice of medicine’ issue, i.e., an unavoidable, non-radiation related aspect of an IV administration, that should not be regulated by the NRC.” **Reinforcing the misperception that extravasations can’t be prevented, through ACMUI comments or by the NRC ignoring the evidence, needs to stop immediately.** This misperception is parroted by societies and licensees, irresponsible, and jeopardizes patient care and safety. Consistent with the NRC policies regarding “reasonable measures” and “adequate protection” outlined in the recent denial of three petitions (PRM-20-28, PRM-20-29, and PRM-20-30), extravasations are preventable if reasonable measures are taken by licensees. With proper training, techniques, and tools, extravasations of radiopharmaceuticals can be virtually eliminated overnight. A licensee that does not take steps to provide adequate protection from significant extravasations to patients is not meeting their obligation.

Current reporting thresholds are appropriate for extravasation reporting.

Existing reporting thresholds are consistent with the Linear No Threshold (LNT) model, As Low As is Reasonably Achievable (ALARA) guiding principles, and risk-informed regulatory reporting. If these reporting thresholds are exceeded, this is indicative that a licensee may have had a potential issue in the handling of radioactive material.

When properly administered, most diagnostic and therapeutic radiopharmaceuticals will result in an absorbed dose to arm tissue of approximately 1 mGy. A reportable event indicates that tissue or skin has experienced an absorbed dose approximately 500 times what was intended. There is no need to modify medical event reporting criterion of 0.5 Sv for extravasations. In the denial of the three petitions (PRM-20-28, PRM-20-29, and PRM-20-30) and in support of existing NRC policies, the NRC reiterated their acceptance of this threshold. Furthermore, creating different limits for medical event reporting would create irrational reporting inconsistencies. There can be no rational explanation of how two different reporting thresholds—0.5 Sv and 1.0 Sv (for example), could be consistent with existing NRC policies. There is no rational explanation why a leak of a radiopharmaceutical ***onto*** a patient’s skin that results in a skin and tissue absorbed dose of 0.5 Gy is reported as a medical event, but an extravasation that leaks ***into*** a patient and results in the same or higher dose (0.5-0.99 Gy) is not reported.

Patient harm and frequency of occurrence are not reporting criteria.

Both the NRC medical staff and the ACMUI subcommittee members discuss patient harm and the frequency of occurrence of extravasations as though these characteristics are medical event reporting criteria.

Patient harm and frequency of occurrence are irrelevant to medical event reporting. The NRC has been consistently clear for nearly 20 years that a medical event does not necessarily indicate patient harm. If a licensee accidently administered a low dose diagnostic radiopharmaceutical to 15 out of every 100 patients who were not supposed to receive a radiopharmaceutical, the NRC and patients would want to know—even if all 15 patients experienced no harm from the properly administered diagnostic radiopharmaceutical. The NRC should also want to know if a licensee is routinely injecting radiopharmaceuticals into patients’ tissue rather than the vein as intended. This practice indicates that there may be a potential issue with the handling of radioactive material.

And while it is understandable that the frequency of potentially reportable events may be a consideration during rulemaking, the NRC staff’s findings and ACMUI’s recommendations

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suggest that frequency should be a consideration for determining medical event reporting. It should not. Whether the frequency is so high that it would be a burden or so low that it is no different from other non-radioactive pharmaceuticals is irrelevant to medical event reporting. Lessons learned from thousands of significant extravasations or only a handful can prevent these events from affecting other patients and are worth reporting.

Comments from both the NRC and the ACMUI regarding truly significant diagnostic extravasations that would affect imaging suggest that these extravasations very rarely occur. These comments are completely contradicted by evidence and are not supported by the reference they cited which sought to quantify the amount of activity in an extravasation *at the time of imaging*. A static image is not an accurate indicator of the effects of the extravasation on the quality of the image since it ignores biological clearance prior to imaging. Comments regarding significant extravasations and their effect on images and patient care reveal a lack of understanding of image reconstruction, quantification, the frequency of injection sites outside the imaging field of view, the rate of repeated imaging studies and demonstrate a gross misunderstanding of these aspects of extravasations. In our experience monitoring over 23,000 radiopharmaceutical administrations, between 25-50% of significant extravasations negatively affect an image to such an extent that they could compromise patient care. Examples of these effects are available in the literature and have been provided to the NRC already.

Patient harm can result from therapeutic AND diagnostic radiopharmaceutical extravasations.

While patient harm is not a criterion for medical event reporting, the ACMUI recommendations and the NRC staff's preliminary findings repeatedly state that diagnostic radiopharmaceuticals do not, or rarely, cause harm. These "no patient harm" comments are inaccurate and need to be addressed. The NRC's goal is to protect patients.

ACMUI incorrectly states,

> "There is no clinical evidence that patients are being harmed, either from excess radiation dose or compromised diagnostic studies because of radiopharmaceutical extravasation."

The NRC incorrectly states,

> "the dose threshold criteria for medical event reporting precludes most diagnostic administrations from being reported as medical events"
>
> "However, a high radiation dose does not equate to radiation injury. While radiation injury after parenteral administrations of radiopharmaceuticals is probably unlikely, extravasation incidents have been described in published case studies with patients receiving skin doses in the range of deterministic effects following extravasation of, for example, I-131 metaiodobenzylguanidine, Lu-177 dotatate, and Ra-223 dichloride."

These comments are inconsistent with the position taken by the NRC in the recent denial of three petitions (PRM-20-28, PRM-20-29, and PRM-20-30). These include:

- exposure to ionizing radiation is a known cancer risk factor for humans,

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- the potential health risk from ionizing radiation is proportional to the dose received and there is an incremental health risk associated with even very small doses, and
- the probability of stochastic effects occurring increase linearly with the function of the dose.

In addition to being inconsistent with current NRC positions, the NRC medical staff and AMCUI positions and statements also reflect a lack of understanding of the references they cite and the specific energy emissions of diagnostic radiopharmaceuticals. Comments to the effect that “the community does not see harm” suggests that members and staff also don’t understand the latent effects of ionizing radiation to healthy tissue and how damage done to subdermal tissue may not cause visual evidence initially to the overlying skin. Additionally, the ACMUI members and NRC staff must believe that patients who are not aware that they have been extravasated will somehow associate latent injuries with a previous nuclear medicine procedure. The members and staff do not seem aware of the NRC position “in general, the inability to observe an effect does not mean that the effect has not occurred” outlined in the recent denial of the three petitions (PRM-20-28, PRM-20-29, and PRM-20-30).

The ACMUI members, and to some extent the NRC medical staff, continue to express an unacceptably cavalier attitude towards patient harm caused by significant extravasations of diagnostic radiopharmaceuticals. This attitude is completely inappropriate. Recently, a patient experienced a 99mTc-MDP extravasation. It occurred at a premier medical institution during a bone scan to assess if her metastatic breast cancer tumors have increased in number. No mitigation or dosimetry was performed by the staff even though the patient likely experienced a significant extravasation that should have been reported to the NRC. Much of the emission energy from the extravasation is unlikely to reach the skin’s basal cell layer. However, damage to her subdermal tissue caused pain days after the extravasation and routinely woke her up at night. This patient is fighting metastatic breast cancer and is undergoing treatment with severe toxic side effects that cause extreme fatigue. Now, she is dealing with extravasated tissue in her injection arm. Based on published extravasation rates, cases like this one are happening hundreds of times a day in the United States.

If members of the ACMUI or NRC staff are so sure that diagnostic radiopharmaceutical extravasations won’t cause patient harm, then consider a human challenge study to assess patient harm for diagnostic radiopharmaceutical extravasations and to expedite knowledge about this subject. Members would choose either 10 mCi 18F FDG followed by a flush of 10 cc of saline or 20 mCi 99mTc MDP to be injected directly into their arm tissue. The MDP injection will not be followed by a saline flush since straight sticks (not a best practice in venous access) are still commonly used for bone scan injections in the United States. The injection site would be imaged periodically after the injection to assist in accurate dosimetry. Members would be clinically followed to assess their injection site for the next six months and to look for adverse tissue reactions. While this would provide members with a new perspective on extravasations, unfortunately, it would be difficult to conduct this human challenge study since the question of patient harm is already known. The Institutional Review Board (IRB) would never approve a protocol that indicated subjects would receive 4 to 5 Gy to their arm tissue. Knowing that these doses would lead to tissue and skin harm and increase the likelihood of stochastic events, the IRB would find the study unethical. Yet, the ACMUI members think the hundreds of patients who experience significant extravasations every day in the United States are not being harmed. Has anyone at the NRC or ACMUI done these basic math calculations? If not, why not? Has the NRC or ACMUI consulted with a radiation biologist to determine what would happen if 5-10 cc of healthy

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tissue was irradiated with approximately one quadrillion decays of either positrons or internal conversion electrons?

F-18	
Initial Activity:	10 mCi
	370,000,000 Bq
Half-life:	109.77 min
Clearance Half-time:	45 min
Effective Half-life:	31.9 min
Total Number of Decays:	1,022,202,429,436
Average positron energy per decay:	250 keV
Positron Fraction:	97%
Total Absorbed Energy:	247,884,089,138,126 keV
	0.039 Joules
Tissue Volume:	10 cm^3
Tissue Mass:	0.01 kg
Total Dose:	4 Gy

Tc-99m	
Initial Activity:	20 mCi
	740,000,000 Bq
Half-life:	6 hours
Clearance Half-time:	4 hours
Effective Half-life:	2.4 hours
Total Number of Decays:	9,224,015,013,428
Average absorbed energy per decay:	17 keV
Total Absorbed Energy:	156,808,255,228,270 keV
	0.025 Joules
Tissue Volume:	5 cm^3
Tissue Mass:	0.005 kg
Total Dose:	5 Gy

To provide further insight into tissue damage caused by a significant diagnostic extravasation, attached is a case study of a significant 99m-Tc extravasation during a cardiology procedure (Appendix B) that resulted in serious damage to the patient's tissue and surely resulted in an invalid imaging procedure. The appendix also includes a radiotherapy extravasation case. Neither of these cases was reported to their states' radiation protection branch nor to the NRC. Neither case was evaluated as a potential Abnormal Occurrence. Neither patient was informed at the time of administration that they were extravasated. The diagnostic patient did not have a repeat imaging procedure. Over the past several years, the NRC has received several dozen cases of diagnostic radiopharmaceutical extravasations with doses that easily exceeded NRC medical event reporting limits. Several would likely qualify for Abnormal Occurrence reporting, as well.

When the radiopharmaceutical is administered properly into the vasculature, diagnostic radiopharmaceutical administrations result in a very low radiation dose to patients. The benefits of the procedure far outweigh the radiation risk. However, that is clearly not the case when radiopharmaceuticals are extravasated. **The NRC is reinforcing the misperception that diagnostic radiopharmaceuticals are low risk even when extravasated. The misperception ignores basic physics, math, the effects of ionizing radiation on healthy tissue and reflects poorly on the scientific expertise of the NRC and the ACMUI. This needs to stop immediately.** Incorrect statements made by the NRC and ACMUI are often repeated by licensees—jeopardizing patient care and safety.

Appropriate dosimetry is not a burden and self-forming "pocket" extravasations don't really exist.

The ACMUI frequently claims that dosimetry is complex, time consuming, and costly and that licensees are ill-equipped to characterize extravasations. They also state that the "0.5 Sv dose threshold was not intended to be applied to very small volumes of tissue, such as that surrounding an extravasation, which do not result in patient harm." This statement creates confusion and prevents proper regulation.

Extravasation dosimetry is not a burden. A new, more accurate dosimetry method for extravasations was accepted without revision and published in *Health Physics* in January 2021. This method uses **free software** and takes **only 3-5 minutes of incremental work** beyond what the medical guidance already suggests should be done when an extravasation is suspected. The

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authors of the dosimetry publication would welcome the opportunity to demonstrate to the NRC and ACMUI how the method uses patient-specific biological clearance, one quantitative assessment, and realistic and appropriately sized references tissue volumes (larger than skin volumes currently mandated today in regulations) to help characterize the absorbed dose to tissue. Unlike the ACMUI's "pocket" extravasation concept, this method does not attempt to minimize the patient dose by assuming extravasated radiopharmaceutical re-forms into a sphere between layers of tissue. Nor does it overestimate the dose by assuming the worst-case scenarios when there is clear patient-specific evidence that the worst-case scenarios did not occur. Appendix C provides a detailed analysis of the ACMUI's "pocket" extravasation concept and shows that even if such an unlikely event happened, the absorbed dose to the tissue bordering the sphere could still easily exceed reporting limits.

Patients have a right to know when they have been significantly extravasated but should not assume the licensee's responsibility for medical event reporting.

The ACMUI continues to intimate that patients should not be told when they have been significantly extravasated. In the recommendations, they state:

> "Furthermore, with the Medical Event regulatory reporting and patient notification requirements, there must be consideration of the psychological harm to the patient if his/her administration procedure results in an extravasation and is labeled as a Medical Event. Even though 'Medical Event' does not necessarily imply clinically significant problems with the procedure, public perception is it constitutes a medical error."

This paternalistic approach is embarrassingly unacceptable and is yet another attempt by the ACMUI to keep important healthcare information from patients. This approach is inconsistent with current medical practice. A patient that is accidently irradiated with an absorbed dose that exceed reporting limits has experienced a significant enough extravasation that the diagnostic study may be compromised. The patient may also have been irradiated with a dose that will lead to deterministic effects and may experience an increased likelihood of stochastic effects later in life. It is inconceivable that an organization advising the NRC in their goal to protect patients would take this position and suggests that the NRC should revisit the role and qualifications of the members of the ACMUI.

While the ACMUI does not think that patients can handle being told they were significantly extravasated, they expect them to be responsible for notifying a nuclear medicine center when the patient's extravasation turns into a reportable event, even, as stated before, when the patient has no idea that they have been extravasated. It is completely irresponsible for the ACMUI to think that a patient who is receiving a nuclear medicine procedure should take on the licensee's responsibility to identify a medical event. When a patient has been significantly extravasated, the licensee, not the patient, should characterize the dose, share it with the patient and the referring the physician, and clinically follow the patient for an extended period of time.

Organization of Agreement States (OAS) position has been misrepresented.

Contrary to the NRC's characterization of the July 2020, government-to-government meeting, more recent interaction with the OAS indicates that many Agreement States are in favor of the petition. The OAS Annual Meeting was held in Philadelphia, PA from August 16-19, 2021. We spoke to nearly all Agreement State representatives present and most indicated that they now expect extravasation reporting or support the petition so that it's required nationally. The findings

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were consistent with OAS Board comment on the petition which shared that 24 of 30 states that responded to a poll expected to be informed of extravasations. Additionally, the OAS Board public comment is very clear in their support of the removing the exemption and moving to rule making immediately.

The NRC findings also mentioned the North Carolina Radiation Protection Commission and their unanimous opposition to the petition. The public comment included the following:

- Patients have difficult anatomy.
- Individual centers should address their own extravasations and reporting when patients are significantly extravasated will have no positive impact on patient care.
- Dosimetry for extravasations has not been standardized and is difficult and would require additional time, effort, and cost.
- Nuclear medicine is not a lucrative business.
- Monitoring for extravasations would require time, effort, and cost.
- Significant extravasation reporting would not be in keeping with a “risk-smart” regulatory focus.
- The petitioner would make money if the extravasation issue was regulated.
- Licensees, on their own, could improve their safety culture, develop a quality management program to assess extravasation rates and establish thresholds that lead to corrective action, increase training, determine best practices, improve technologist certification and training, and use different access tools, and purchase/use measuring equipment.

The North Carolina Radiation Protection Commission argues that regulation will result in licensees having to spend incremental time, money, and effort to address extravasations. In the recent denial of the three petitions, the NRC stated that “the Commission may not consider the economic costs of safety measures. The Commission must determine and impose on licensees, regardless of costs, the precautionary measures necessary to provide adequate protection to the public.”

Ironically, the North Carolina Radiation Protection Commission stated the petition was disingenuous and then proceeds to argue that individual licensees will, without any regulation, improve their safety culture, develop a quality management system to address extravasations and also invest time, energy, and money to purchase tools, increase training, and determine best practices. Basically, the North Carolina Radiation Protection Commission argued that nuclear medicine departments barely getting by financially and that could not afford the monitoring burden of regulation would incur the same financial, effort, and time burden on their own without regulation. They also implied that the reporting of significant extravasations is already covered by existing regulations. The NRC should reach out to the North Carolina Radiation Protection Branch to see how many extravasations have been reported in the past 12 months and the past five years. It is important to note that one of the two extravasations highlighted in Appendix B was a North Carolina patient. That case was not reported.

The OAS member states are becoming aware that the exemption policy is based on an incorrect premise and that extravasations are preventable. As the states learn how the ACMUI has been actively working to maintain the exemption, their skepticism is transferred from the petition to the ACMUI.

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Options other than Option 2 fail to adequately protect patients.
The NRC provided several options for the ACMUI to consider.

The NRC has been presented with evidence again that extravasations are preventable and can exceed medical event reporting limits. Therefore, choosing Option 1, 3, 4, 5, or 6 would be irresponsible and inconsistent with the NRC goals, medical use policy, previous statements regarding accurate administration of radiopharmaceuticals, and would prevent the NRC from fulfilling its obligation to Congress to report Abnormal Occurrences. Furthermore, these options preclude immediate mitigation on significant extravasations to reduce the absorbed dose. Additionally, many of the options shift the burden of identifying medical events to patients from the licensees.

The shortcomings from the NRC staff preliminary findings, five of the six provided options, and the ACMUI subcommittee recommendations described above, are only a sample of the issues in the meeting material. A thorough review of the attached appendices will reveal that the findings and recommendations prevent licensees from complying with ALARA requirements. In the recent denial of the three petitions, the NRC was clear in their support for ALARA.

> "In general, the NRC determines compliance with the ALARA requirement based on whether licensee has incorporated measures to track and, if necessary, to reduce exposures; not whether exposures represent an absolute minimum or whether the licensee has used all possible methods to reduce exposures."

Recommendation

Option 2 ensures that extravasations that exceed the existing reporting threshold are characterized and reported to the patient and regulatory bodies. This option is consistent with the NRC position that the 0.5 Sv threshold is appropriate for radiation protection purposes. This option also eliminates the irrational reporting requirements today that prevent extravasations from being reported. Option 2 will drive licensees to reduce the frequency of their extravasations, necessary because there is a long-standing and clear reluctance by the community to address this issue voluntarily. Most importantly, it will protect patients. Patients who experience significant extravasations will know that this has occurred, can evaluate how this event affects their care, and will be followed by their providers. Providers that follow NRC guidance and that choose existing or new technology to monitor for extravasations will also have information about an extravasation sooner under Option 2 than in any of the other options. Immediate mitigation of a significant extravasation is consistent with ALARA principles and is in the best interest of patients and their care.

Option 2 is also consistent with licensees' current and appropriate emphasis on and substantial investment in quality control and assurance for other aspects of their nuclear medicine procedures. Additionally, Option 2 is consistent with current medical guidelines and international radiation protection guidelines that suggest providers monitor administrations and that state extravasations are preventable, should be characterized, should be mitigated, should be analyzed for root cause, and should be reported to regulators, patients, and their referring physicians.

The ACMUI and the NRC medical staff have suggested similar cons for Option 2, but these can be assuaged. Dosimetry is no longer a burden. It is now possible to provide appropriate, patient-specific extravasation dosimetry at no cost and with only 3-5 minutes of incremental work beyond what the medical guidelines suggest providers should already do when they suspect an

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extravasation. Concerns about over-reporting due to use of very small tissue volumes resulting in high doses are also addressed in the recently published method. This method suggests using a minimum reference volume of 5 cc of tissue, a volume that is ~70 times larger than the volume of 10 cm^2 of skin currently recognized for regulatory reporting. This is a very reasonable tissue volume for appropriate extravasation dosimetry.

Arguments that the economic burden to address extravasations is too great ignore the economic and patient burden outside of nuclear medicine. Incorrect images that lead to wrong treatments, repeated studies, additional procedures, and patient tissue damage all come with a cost that the nuclear medicine community does not bear, but that the healthcare system and patients do bear. Investing up front to ensure licensees administer radiopharmaceuticals correctly the first time will drive overall healthcare costs down; this is no different than what happens in other healthcare settings when doing procedures correctly the first time. Furthermore, any financial, effort, training, tool, and time investment will be the exact same if licensees address this issue without regulation—an aspect of correcting a problem that the community conveniently ignores when arguing that regulation will drive up cost.

The reporting burden that both the NRC medical staff and ACMUI recommendations suggest will come with Option 2 ignores the role that rulemaking can play in this option. Implementing and promoting a 12-month grace-period provides more than enough time for licensees to address their extravasation issues and should make the reporting burden an inconsequential issue for the vast majority of licensees and regulators. An example from the multi-center quality improvement project illustrates how minimal the burden can be.

Prior to monitoring, and as part of the largest quality improvement project ever conducted on radiopharmaceutical extravasations, Licensee A, a PET Center of Excellence, extravasated 13.3% of their administrations. Severe extravasations represented 2.2% of their overall administrations. Monitoring led to statistically significant improvement in their extravasation rate. Over the past 18 months, Licensee A monitored 2,477 administrations—97.1% were ideal administrations, 73 (2.94%) were not ideal. **Only 3 were severe and required dosimetry** (0.12%). Of the three, only two exceeded the 0.5 Sv reporting threshold (0.08%). Both patients were entered into a registry for periodic phone follow-up. Had Licensee A not embarked on this quality improvement effort, they estimate they would have had to follow an additional 34 patients who had extravasations exceeding 0.5 Sv during the past 18 months. The vast majority of Licensee A's improvement occurred within six months from the commencement of the quality improvement effort.

If all licensees used the grace period to actively monitor their administrations and improve the quality of administrations similar to that of Licensee A, it is likely that only 36,000 cases out of 30 million administrations would be so severe that they would require dosimetry. Of those, perhaps only 24,000 would need to be tracked. Only the most severe of these would likely exceed the 10 Gy AO reporting criteria.

At this performance level, the daily burden is quite modest for monitoring and dosimetry. 36,000 annual cases (143 per day) of dosimetry using the January 2020 Health Physics dosimetry method and free software would require ~12 hours of incremental work across 7,500 licensees per day in the United States. That is, on average, less than six seconds per day per licensee. The monitoring of 119,000 cases per day (30,000,000 annually) averaged over 7,500 licensees is less than 16 minutes per licensee per day. Therefore, monitoring all administrations and performing

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dosimetry for significant extravasations would add approximately 16 minutes on average to each licensee's daily workload. A small investment to reduce radiopharmaceutical extravasations.

Reporting time requirements should be considered during rulemaking to minimize reporting burden. If reporting time requirements are based on dose, only the most serious extravasations would be reported within 24 hours. Extravasations at lower doses, but above the reporting limit, could be reported on different deadlines or tracked by the licensee's radiopharmaceutical administration monitoring program and audited periodically. Licensees who are actively monitoring administrations for extravasations, performing dosimetry on significant extravasations, notifying patients and following them for tissue damage, and demonstrating ongoing control of their administration process with very low extravasation rates are meeting ALARA principles. Centers that are not monitoring their administrations or that significantly extravasate their patients routinely and are not performing dosimetry, following patients, or taking actions to reduce the high frequency of inadvertent irradiations should be addressed. These centers would experience increased reporting burden, but that is appropriate given their performance.

Concerns about volume of medical event reports and difficulty with dosimetry are without merit and should not be taken seriously. Centers that routinely exceed 0.5 Sv or don't even know how many of their patients are being significantly extravasated should be more concerned about the unacceptable frequency of poor patient care than medical event reports. And patients should know which centers should be avoided.

To expeditiously resolve any questions about the information provided, a working meeting with the medical staff would be welcomed. The meeting can include experts who have no fiduciary interest in the matter and the petitioner so references can be provided that will allow the NRC to follow evidence-based policy making. It is imperative that the NRC act more quickly on this matter than they have demonstrated so far, since significant extravasations continue to negatively affect hundreds of patients every day.

Thank you for your consideration of these comments.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ronald Lattanze
Chief Executive Officer

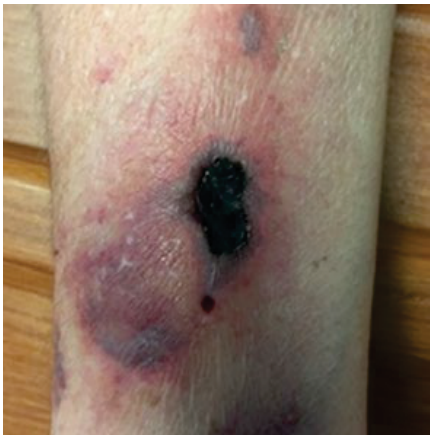
Appendix A – Analysis of the NRC findings and options and the ACMUI recommendations
Appendix B – Extravasation case studies
Appendix C – Analysis of the ACMUI "pocket" extravasation dosimetry analysis

Cc: NRC: Chairman Hanson, Commissioners Wright and Baran
NRC: Chris Einberg, Lisa Dimmick
OAS: Augustinus Ong, David Crowley
FDA: Kish Chakrabarti PhD, Shane Masters MD, PharmD, PhD

Appendix B: Extravasation Case Studies

Extravasations of **therapeutic** and **diagnostic** radiopharmaceuticals can harm patients. When some or all of the prescribed dose fails to enter circulation, target lesions absorb less radiopharmaceutical than was intended. This may result in under-delivery of therapy or a misdiagnosis of the patient's diagnostic image. In addition, concentrated radiopharmaceutical at the site of an extravasation may irradiate tissue with a high absorbed dose of radiation. Symptoms resulting from the absorbed dose may take weeks, months, or even years to develop.

Therapeutic Radiopharmaceutical Case - A 29-year-old male was treated for non-Hodgkin's Lymphoma with ZEVALIN® (Yttrium-90 ibritumomab tiuxetan). He arrived in nuclear medicine with a pre-existing 24-gauge IV catheter in his forearm. A nuclear medicine technologist administered the ZEVALIN® via the existing catheter, and the patient was discharged 2 days after treatment.



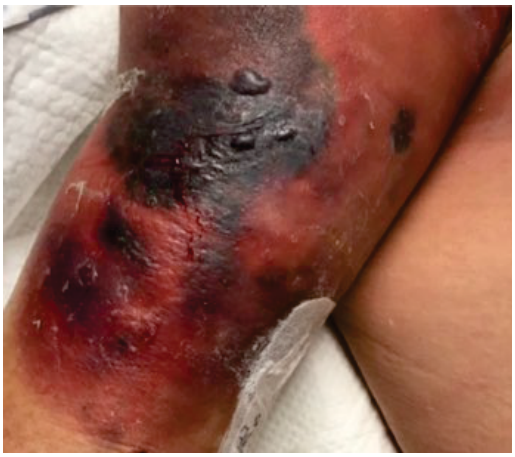
Yttrium-90 (^{90}Y) produces beta particles (average energy of 933 keV). When used as a therapy, its purpose is to kill cells. When extravasated, these beta particles travel 5-10mm while depositing their energy into the surrounding healthy tissue. The physical half-life of ^{90}Y is 64 hours—99% of the administered activity has decayed after 3 weeks.

Twenty-five days later, the patient returned to his oncologist complaining of blackened skin "where the IV was" and was referred to the Emergency Department. The Emergency physician contacted nuclear medicine and was told to apply ice and to elevate the arm (likely ineffective instructions for this situation). A review of the medical records found that the technologist had used the existing IV catheter and had not ensured the catheter was functioning correctly.

An 80 kg patient will be administered 32 mCi of ZEVALIN®. If just 10 mCi had been extravasated into 5 cc of tissue (an estimate of the size of the black area in the image above), the tissue would have received an extraordinary, absorbed dose of ~3,000 Gy.

Diagnostic Radiopharmaceutical Case - A 44-year-old male with end-stage cardiac failure underwent a Myocardial Perfusion Scintigraphy procedure using a ^{99m}Tc radiopharmaceutical. The patient presented with a functioning 18-gauge midline catheter in the basilic vein. Because midlines are routinely contraindicated for radiopharmaceutical use, the nuclear medicine team placed an 18-gauge IV in the patient's cephalic vein. Two doses (10 mCi and 32 mCi) of radiopharmaceutical were administered through the 18-guage IV during the procedure.

The most commonly used medical radioisotope, ^{99m}Tc, emits 140 keV gamma rays that leave the body with minimal energy deposition in the tissue. However, 11% of ^{99m}Tc decays emit internal conversion electrons with an average energy of 119 keV. When extravasated, the internal conversion electrons travel ~5 mm while depositing their energy in healthy tissue. The physical half-life of ^{99m}Tc is 6 hours—99% of the administered activity has decayed after 36 hours.



Several days later the patient developed skin discoloration in the upper arm that was treated with ice (likely ineffective treatment for this situation). Seven days after the procedure, vascular access experts used venous doppler ultrasound to confirm that the midline catheter was operating properly and that the tissue and skin damage was along the patient's cephalic vein as a result of the ^{99m}Tc extravasation from the 18-gauge IV.

To increase blood flow to the region, the vascular access experts removed the midline from the basilic vein. Nonetheless, the patient's skin sloughed away over the next several days. Five weeks later the patient expired from other causes.

In this case, assuming that 75% of the dose was extravasated into 15 cc of tissue (the black and blistered area in the image above), the tissue received an absorbed dose of approximately 9 Gy.

Appendix A: Analysis of the NRC findings and ACMUI recommendations

NRC STAFF PRELIMINARY EVALUATION OF RADIOPHARMACEUTICAL EXTRAVASATION AND MEDICAL EVENT REPORTING

Original Text	*Analysis*
April 1, 2021 MEMORANDUM TO: Subcommittee on Extravasation Advisory Committee on Medical Uses of Isotopes FROM: Christian Einberg, Chief (LDimmick for) Medical Safety and Events Assessment Branch Division of Materials Safety, Security, State, and Tribal Programs Office of Nuclear Material Safety and Safeguards SUBJECT: U.S. NUCLEAR REGULATORY COMMISSION STAFF PRELIMINARY EVALUATION OF RADIOPHARMACEUTICAL EXTRAVASATION AND MEDICAL EVENT REPORTING	
INTRODUCTION: The purpose of this memorandum is to summarize the U.S. Nuclear Regulatory Commission (NRC) staff's preliminary evaluation of whether and how radiopharmaceutical extravasations should be reported as medical events, and to request feedback and recommendations from the Advisory Committee on the Medical Uses of Isotopes (ACMUI) on this preliminary evaluation. Extravasation is the unintentional leakage of an intravenously (IV) administered drug around the infusion or injection site into the surrounding tissue. Currently, the NRC excludes extravasation of radiopharmaceuticals from its medical event reporting regulations. As a result, extravasations that cause patient harm, and even those that meet the public health and safety significance criteria for an abnormal occurrence (AO), are not required to be reported. Considering recent and anticipated advancements in nuclear medicine, the NRC staff is reevaluating whether certain extravasations should be reported as medical events. The NRC staff's evaluation seeks to determine whether extravasations should be reported as medical events and, if so, what is the appropriate reporting criteria for these events. The staff's evaluation is based on whether: (1) extravasation merits regulation considering the objectives of the NRC's medical use policy statement;1 (2) the dose consequence from extravasation is significant enough to merit reporting; and (3)	In addition to the issues identified by the NRC, the current exemption allows for **extravasations that exceed current medical event tissue and skin dose reporting limits** to remain unreported. The basis for the staff's evaluation should be whether: (1) the reporting of extravasations is consistent with the NRC's medical use policy statement; (2) the reporting is consistent with the intent of the purpose of medical event reporting; and (3) extravasations can be prevented. The NRC has already determined dose limits to skin and tissue for medical event (ME) reporting. These limits have been reaffirmed over the past 20 years, most

extravasation can be prevented with technology. In its evaluation, the NRC staff: (1) reviewed input from the ACMUI, medical community stakeholders, the public, and Agreement States; (2) reviewed published literature, including extravasation experiences in other areas of medicine, plus data submitted as part of petition for rulemaking (PRM) PRM-35-22;2 and (3) conducted a retrospective assessment of the NRC's medical use policy statement and medical event regulations.	recently when denying three petitions this summer. Considering whether the dose consequence is significant enough to merit reporting is inconsistent with NRC policy. Furthermore, considering whether extravasation can be prevented *with technology* is not necessary. The NRC should simply consider whether extravasations can be prevented, however it is done—tools, training or technique.
BACKGROUND: *Regulatory History of Medical Event Reporting Requirements* In 1980, the NRC updated Title 10 of the Code of Federal Regulations (10 CFR) Part 35, "Medical Use of Byproduct Material," establishing the reporting of medical misadministrations.3 The purpose of the misadministration reporting requirements was to allow the NRC to investigate the misadministration,4 determine if there was a violation of NRC regulations, evaluate the licensee's corrective action to minimize recurrence, inform other licensees of the potential problem, and take generic corrective action if there was a possibility of other licensees making the same error.5 In the final misadministration rule, the Commission recognized that extravasation frequently occurs in otherwise normal intravenous or intraarterial injections and they are virtually impossible to avoid, and, therefore, the Commission did not consider extravasation to be a misadministration nor require them to be reported.6 Furthermore, in the "Summary and Analysis of Comments" for the final rule,7 the staff agreed with commenters who objected to classifying extravasation as the wrong route of administration, and the staff's comment response went on to state that the rule was not intended to include extravasation. In 1991, the NRC amended 10 CFR Part 35 to add dose criteria to the misadministration reporting requirements (0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue).8 The dose criteria are based on dose levels described by the National Council on Radiation Protection and Measurements9 as having a total detriment from stochastic effects of less than one percent.10 The dose criteria were added to better clarify the definition of a misadministration and to screen out diagnostic radiopharmaceutical administrations, which are considered low risk. The Commission noted that these dose criteria also corresponded to the annual dose limits for occupational workers, which	The results from chemotherapy infusion and contrast-enhanced CT (contrast CT) show that extravasations can be virtually eliminated from practice. The foundational assumption of the 1980 exemption is no longer true. An extravasation should logically be characterized as the wrong route of administration. The radiopharmaceutical was intended for venous circulation, not subcutaneous injection into tissue. Bolus injection is critical to many nuclear medicine procedures. An injection into the tissue prevents the proper distribution and can result in a dangerous irradiation to the tissue and lymphatic system. The NRC should reconsider this decision. Diagnostic radiopharmaceuticals, when administered without extravasation, are indeed low risk. However, it is inappropriate to classify a procedure as low risk based solely on its intended use without considering the risks from extravasations or other foreseeable events. Lucerno has

are thresholds for reporting overexposures to the NRC; therefore, it was reasonable to apply them to patient exposures from misadministrations. The 1991 rule did not revisit the 1980 decision to exclude extravasation from medical event reporting.11	provided clinical evidence that diagnostic extravasations can result in very high dose to tissue and skin as well as other patient harm. For ME reporting, if an administration results in dose that surpasses the threshold, it should be considered a reportable event no matter what the intention was. **The NRC is reinforcing the misperception that diagnostic *extravasations* are low risk—there is abundant evidence that diagnostic extravasations can and do cause harm.**
The next major update of 10 CFR Part 35 was in 2002.12 While the term, "misadministration" was replaced with "medical event," the existing dose reporting criteria for patient exposures from medical events was retained and a dose threshold of 0.5 Sv (50 rem) shallow dose equivalent to the skin was added. The regulations for a quality management program were removed, but the requirement to provide high confidence that byproduct material will be administered as directed by the authorized user physician through written procedures for medical administrations requiring a written directive were retained. Again, the 2002 rule did not revisit reporting extravasations as medical events, however, during an ACMUI meeting that discussed the draft final rule, the ACMUI confirmed the staff's 1980 determination that subcutaneous infiltration is not the wrong route of administration.13 Aside from new medical event reporting requirements for permanent implant brachytherapy in 2018,14 medical event reporting has not significantly changed since the 2002 rulemaking.	
<u>DISCUSSION:</u> *Medical Event Reporting* Licensees are required to report medical events that meet the criteria defined in 10 CFR 35.3045, "Report and Notification of a Medical Event." The purpose of medical event reporting is to identify the causes of events in order to correct them, prevent their recurrence, and allow the NRC to notify other licensees of the events so they too can avoid them. Through medical event reporting, the NRC can track and trend medical events and subsequently share operational experience, and the ACMUI has recommended that the NRC communicate information about medical events to licensees to raise awareness about emerging trends. The NRC's medical event reporting dose threshold criteria are conservative dose levels that would not be expected to cause patient harm.15 This conservatism is a notable contrast to other organizations,	We agree, ME reporting tracks the performance of the licensee, not the radiopharmaceutical, as input to the quality improvement process—and other licensees can learn from the information.

such as the U.S. Food and Drug Administration (FDA)16 and the U.S. Centers for Medicare and Medicaid Services (CMS),17 whose patient safety reporting thresholds are based on adverse effects. Medical events may not necessarily cause patient harm, but the NRC requires their reporting because they have the potential to cause harm and they may indicate a potential problem with how a medical facility administers radioactive materials or radiation from radioactive materials.	NRC is monitoring the performance of the licensee. FDA is monitoring the performance of the drug/device. With different objectives, different approaches are used. We completely agree with the highlighted sentence to the left. All radiopharmaceuticals, when extravasated, have the potential to cause harm and can exceed ME reporting threshold. If they happen frequently at a license, the NRC should be concerned about how the facility administers materials.
Under the NRC's current medical event regulations for all modalities, the number of reported medical events is extremely low—on average fifty events per year—considering the estimated 20 million18 nuclear medicine and radiotherapy procedures performed per year. Generally, about 50 percent of reported medical events involve Y-90 microspheres; 20 percent involve high dose rate afterloaders; 20 percent involve manual brachytherapy; and the remaining 10 percent is comprised of diagnostic nuclear medicine, radionuclide therapy, and gamma stereotactic radiosurgery events.19 As the statistics indicate, the majority of medical events involve therapy procedures; the dose threshold criteria for medical event reporting precludes most diagnostic administrations from being reported as medical events. However, if extravasation was included in the current medical event reporting regulations, and given the published rates of radiopharmaceutical extravasation ranging from 3 to 23 percent,20 anywhere from 600,000 to 4.6 million extravasation events could potentially be subject to reporting each year, many of which would be at or near the 50-rem dose threshold.	We agree that most diagnostics administrations will not be extravasated. Of the extravasated ones, most will result in a dose that is below the reporting threshold. But it is wrong to exclude those extravasations that do exceed the ME reporting threshold. Since all extravasations are excluded from reporting as ME, it is unclear how the conclusion "dose threshold criteria for medical event reporting precludes most diagnostic administrations from being reported as medical events" can be drawn. The necessary data to draw that conclusion remains uncollected due to the exemption. While large numbers of ME reports would be difficult for any organization to handle, consider that every one of those reports is a patient that should not have had an extravasation. By announcing a reporting requirement with a grace period before reporting begins, the NRC can reduce the influx of reports. A grace period announcement will cause licenses to address what has been ignored for 40 years. The tools, techniques, and training to virtually eliminate extravasations are known—it has been done in chemotherapy and contrast CT, and in several licensees interested in reducing their extravasation rates. Transitioning this know-how to nuclear medicine will take some time and some effort, but the result will be far fewer extravasations for patients, and accordingly fewer ME reports than if no improvement is accomplished. The goal is not reporting—the goal is better patient safety.

Medical event reporting is mandatory and dictates a sense of urgency—it requires notification to the NRC Operations Center by the next calendar day and submission of a written report within 15 days after discovery of the medical event. In addition to timely notification to the regulator, the licensee must notify the referring physician and the individual who is the subject of the medical event no later than 24 hours after its discovery, unless based on medical judgment, informing the individual would be harmful. If the referring physician or the affected individual cannot be reached within 24 hours, the licensee shall notify the individual as soon as possible thereafter. In considering options for whether extravasations should be reported as medical events, the NRC staff is considering comments from the medical community concerning the possible negative impacts of medical event reporting of extravasations—including the regulatory and financial burden that would be placed on licensees—especially if most extravasations do not impact image quality or cause patient harm.	It is logical that most extravasations are minor, and therefore unlikely to negatively affect image quality or cause patient harm. It follows that these minor extravasations are unlikely to meet the ME reporting threshold. It is also logical that extravasations that do meet the ME reporting threshold may well negatively affect image quality and cause patient harm. Ignoring all extravasations because only some will make a difference is irresponsible. The only way to know is to monitor and measure. Lucerno estimates that 500,000 significant extravasations per year occur in the US. Why? Because the NRC has allowed them to occur with the 1980 exemption. If nuclear medicine deployed the tools, techniques, and training currently used for the administration of chemotherapy, this number could be cut dramatically. ALARA principles alone would demand that this happen. The NRC considers the regulatory and financial burden on licenses, but the recent petition denial statement maintains that cost is not a consideration for implementing ALARA principles.
Abnormal Occurrence Reporting The NRC is required by law to report AOs to Congress and make certain information concerning AOs publicly available. An AO is defined as an "unscheduled incident or event which the Commission determines is significant from the standpoint of public health or safety."21 Currently, the AO criteria for events involving medical uses are: (1) it must be a medical event as defined in 10 CFR 35.3045, and (2) it must exceed by 10 Gray (Gy) (1,000 rad) the expected dose to any other organ or tissue from the administration defined in the written directive. Because extravasations are excluded from medical event reporting, they would not meet the AO criteria even if they had significant effects to a patient.	By exempting all extravasations from ME reporting, NRC is failing to collect AO due to extravasation, and thereby failing to fulfill its AO obligation to Congress.
The Medical Policy Statement In 1979, the NRC published its first medical use policy statement informing NRC licensees, other Federal and State agencies, and the public of the Commission's general intent on regulating medical uses of radioisotopes.22 The NRC updated the medical use policy statement in 2000 to guide the NRC's future regulation of the medical use of byproduct material, specifically: 1. "NRC will continue to regulate the uses of radionuclides in medicine as necessary to provide for the radiation safety of workers and the general public.	

2. NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public. 3. NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions. 4. NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety."	As there is no medical benefit to an extravasation, an extravasation cannot be considered medical judgment. No physician would prescribe an extravasation. Published nuclear medicine extravasation rates are 10 to 100 times higher than the extravasation rate in chemotherapy and contrast CT. How can this be tolerated this as professionally acceptable? International bodies like IAEA have specifically stated that extravasations are preventable.
In the response to comments on the medical use policy statement, the Commission explained a key assumption in its medical use policy: The purpose of NRC regulation of the medical use of byproduct material is to reduce unnecessary radiation exposure to patients, workers, and the public. Protection of patient radiation safety is an overall goal in regulating the medical use of byproduct material. The focus of NRC regulation to protect the patient's health and safety is primarily to ensure that the authorized user physician's directions are followed as they pertain to the administration of the radiation or radionuclide, rather than to other, non-radiation related aspects of the administration. The medical community firmly views extravasation as a "practice of medicine" issue, i.e., an unavoidable, non-radiation related aspect of an IV administration, that should not be regulated by the NRC. However, stakeholders that support regulating extravasation argue that the purpose of the NRC's medical use regulations is to reduce unnecessary radiation exposure to patients and that regulating extravasations could help reduce their occurrence, thereby reducing unnecessary radiation exposure to the tissue around the administration site or through repeat diagnostic procedures. The staff is considering these opposing views on regulating extravasation and the objectives of the medical use policy statement in its evaluation.	Again, as there is no medical benefit to an extravasation, an extravasation cannot be considered practice of medicine issue. Extravasation rates can and should be reduced. Perfection (extravasation rate of 0%) may not be achievable, but a rate in nuclear medicine of <<1% certainly is. This level of performance has already been demonstrated in chemotherapy with a similar patient set. The proper administration of a radiopharmaceutical is a certainly a procedure performed by clinicians. But when this procedure results in the inadvertent irradiation of tissue and skin with doses that far exceed medical event reporting limits, it becomes a patient safety concern and therefore a reportable event. The NRC has clearly stated that it is responsible for the accurate administration of radioactive material. "The Commission has a role in assuring accurate delivery of radiation doses and dosages to patients and has rejected the notion that NRC should not regulate patient radiation safety (44 FR:8243, February 9, 1979). NRC will continue to regulate the radiation safety of patients when justified by the risk to patients, primarily to ensure that the authorized uses physician's directions are followed. The Commission recognizes that physicians have the primary responsibility for the protection of their patients. However, the NRC's role is also necessary to ensure radiation safety of patients."
Injection Technique and Medical Imaging Quality Extravasation can occur when a medical professional is following physicians' directions, and its occurrence does not necessarily indicate	

there is a problem with a facility's use of byproduct material. Performing an IV administration requires technical skill to locate the vein and position the needle in the vein to administer the radiopharmaceutical without any leakage. Even with correct insertion of the needle into the vein and flushing after radiopharmaceutical administration, there may still be a small amount of leakage at the venous puncture site when the needle is removed. Patient anatomy, age, body habitus, hydration, and prior medical treatment are all factors that may impact a successful IV administration. The factors for extravasation remain unchanged from 1980 and are why the medical community strongly argues that oversight of extravasation and injection quality are best managed on an institutional level and at the discretion of the authorized user, and should not be subject to NRC regulation.	Agree that any given instance of an extravasation does not necessarily indicate a problem with the licensee's use of byproduct material. But a pattern of extravasations that exceed the ME threshold certainly does indicate a problem. Agree that the small amount of leakage described here is of little concern and accordingly would not be enough to trigger mitigation or ME reporting. All those patient factors (patient anatomy, age, body habitus, hydration, and prior medical treatment) are also true for chemotherapy, yet chemotherapy has achieved far lower extravasation rates. The factors for extravasation have remained unchanged since 1980, but there are improved tools, techniques, and training today which allow for far less frequent extravasations. Lucerno has shared with the NRC clinical evidence that extravasations can result in high dose, improper care and patient harm. The NRC should determine what acceptable levels of performance are, and no longer leave this up to the authorized user.
Nuclear medicine image quality is an aspect of medical use that the NRC does not regulate. If an extravasation occurs, there will be a variable delay in the radiopharmaceutical biodistribution after the administration, but the patient may still be imaged. The extravasation may affect the positron emission tomography (PET) standard uptake value, for example, but physicians do not rely solely on the standard uptake value to interpret a PET scan. Physicians are trained to interpret diagnostic scans—they can recognize subpar scans and know when a scan needs to be repeated in order to make an accurate diagnosis or determine disease progression. If an extravasation occurs to the extent that the image quality is compromised, the procedure may need to be repeated at the discretion of the physician. Therefore, it's in the physician's best interest to ensure supervised staff are trained to use best practice IV administration techniques. In a published study that staff reviewed for this evaluation, the rates of extravasation for radiopharmaceutical injections ranged from 3 to 23	The same pressures that the nuclear medicine community claim prevent them from monitoring (time, money, schedule) also prevent them from repeating images. In Lucerno's experience, imaging is rarely repeated, and the report to the referring physician rarely indicates the extravasation. SUV is increasingly used as a required biomarker. To be clear, the SUV from an extravasated image will be incorrect. A significant extravasation will result in a significant underestimation of the SUV and other important quantitative values used to guide patient care. Lucerno's observation is that best practices are generally not employed in nuclear medicine. The NRC exemption removes the impetus for the licensee to reduce extravasations, like their chemotherapy and contrast CT colleagues have done.

percent.23 The author noted that any visualized increased uptake of the radiopharmaceutical at the injection site was considered to be an extravasation, which could explain the higher end of this range. Another study sought to quantify the amount of the dosage in the extravasation and found that in 98 percent of the studied extravasations, less than 1 percent of the injected dosage was extravasated.24 So, while the visualized increased uptake of the radiopharmaceutical at the injection site may occur in up to 23 percent of radiopharmaceutical injections, the quantity extravasated will rarely be enough radioactivity to interfere with the nuclear medicine images or cause patient harm.	This paper fails to account for the biological clearance that occurs between time of extravasation and time of imaging. Therefore, the activity visible on imaging is not necessarily representative of the amount of extravasate present during the uptake period. Our published research, previously shared with the NRC, shows that this difference can be substantial, both from a dose to tissue and impact on image quality. The conclusion drawn—the quantity extravasated will rarely be enough radioactivity to interfere with the nuclear medicine images or cause patient harm—is simply untrue. The only way to know this is monitor administrations for extravasation and characterize them when they occur.
Effects of Ionizing Radiation Ionizing radiation is used daily in hospitals and clinics to perform diagnostic imaging procedures and radiopharmaceutical therapy, for which the medical benefits outweigh the risk of radiation exposure. For the purpose of radiological protection, it is assumed that the likelihood of developing a health effect, like cancer, increases linearly with dose without a threshold (i.e., the risk of developing a health effect increases as one's radiation dose increases). The occupational dose limits in 10 CFR Part 20, "Standards for Protection Against Radiation," and corresponding dose thresholds for medical event reporting, were established to minimize the risk for these random (i.e., stochastic) health effects. On the other hand, acute cellular effects that result in skin reddening or other skin injuries (i.e., deterministic effects) occur only above a certain dose threshold. The effects resulting from cell death will not be immediately observed and may take several days to months to manifest. The threshold dose for erythema is 6 to 10 Gy,25 and the skin reddening may not be observed for a few weeks.	The skin is not the only area of concern from an extravasation. The NRC should broaden its attention to the symptoms of radiation exposure to underlying tissue. As noted in the petition, *The Guide to Diagnostic Nuclear Medicine* determined that a dose of 1.0 Sv is the threshold that will likely lead to deterministic events.
Nuclear medicine is a specialty that uses radiopharmaceuticals to diagnose and treat certain diseases. Physicians and technologists performing these procedures are trained to use the minimum amount of radiation necessary for the procedure. For the past fifty years, there have been very few cases reported (e.g., to the FDA or described in publications) of adverse tissue reactions occurring from extravasations involving diagnostic or therapeutic radiopharmaceuticals.26 For diagnostic radiopharmaceuticals, this is because extravasation of the low administered dosages is highly unlikely to cause deterministic effects,	A lack of published examples of skin reaction following extravasation is not due to the "low administered dosages." The absorbed dose potential from

like erythema. Therapeutic dosages of radiopharmaceuticals are prescribed to kill cancer cells. Therefore, it is possible for extravasation of a therapeutic radiopharmaceutical to cause a localized deterministic effect.	significant extravasations of diagnostic radiopharmaceuticals with 18F or 99mTc as isotopes is more than enough to cause erythema (and underlying tissue damage). The reasons for a lack of published examples are because: • most of the radiation dose from 99mTc extravasation is absorbed by underlying tissue, not skin, • patients are not followed for presentation of any radiation-induced symptoms, • diagnostic radiopharmaceutical administrations are not monitored, and • no reporting is required for any radiopharmaceutical extravasations. Furthermore, the reasons a radiopharmaceutical is prescribed has no bearing on its ability to cause deterministic effects. Therapeutic administrations are assumed to be capable of injury due to their beta or alpha emissions. However, ionizing radiation from PET tracers and from Tc99m affect tissue just like ionizing radiation from beta emitters. The deciding factors for deterministic effects are the amount of radiopharmaceutical extravasated, the volume of tissue affected, and the rate of biological clearance—not the radiopharmaceutical's prescribed function.
Input from the Advisory Committee on the Medical Uses of Isotopes, the Public, and Agreement States There have been a number of opportunities for the public, ACMUI, and Agreement States to provide input to the NRC on whether radiopharmaceutical extravasations should be reported as medical events. This input is briefly summarized below.	
Past Input from the Advisory Committee on the Medical Uses of Isotopes In 2008 and 2009, the ACMUI reviewed whether extravasations should be reported as medical events in response to an extravasation of fluorine-18 fluorodeoxyglucose that possibly exceeded 50 rem to the surrounding tissue. The ACMUI discussed the clinical aspects of extravasation, including extravasation of therapeutic radiopharmaceuticals, and ultimately recommended that extravasation continue to be excluded from the NRC's medical event reporting requirements.27 In response to increasing numbers of emerging therapeutic radiopharmaceuticals, the ACMUI established the Extravasations	The transcripts from the 2008 and 2009 ACMUI meetings clearly show that the ACMUI members knew that: • extravasations, including diagnostic extravasations, could lead to very high doses, • extravasations happened frequently, and • the know-how existed to virtually eliminate extravasations, but the effort was not expended to accomplish this every time. The transcript is clear that the real reason that the ACMUI wanted to retain the exemption was so they could avoid telling referring physicians and patients, and having to fill out the ME reporting paperwork. Based on

Subcommittee in 2019 to reevaluate and provide recommendations on the Commission's 1980 decision to exclude extravasations from medical event reporting. In its final report, the ACMUI determined there was no evidence at the time to recommend a reclassification of radiopharmaceutical extravasations as medical events. However, the ACMUI recommended that extravasations be considered a form of "passive patient intervention" and those that lead to unintended permanent functional damage be reportable as a medical event under 10 CFR 35.3045(b).28	these transcripts, the NRC should have rejected the ACMUI recommendation and immediately considered eliminating the exemption. In 2019, the ACMUI chose to ignore the ample evidence available. The invention of "passive patient intervention" is perhaps the most cynical output from the ACMUI to date. Extravasations are not the responsibility of the patient, and they can be virtually eliminated with proper tools, training and technique, as demonstrated by chemotherapy and contrast CT. Nuclear medicine extravasation rates could be one to two orders of magnitude less frequent if the licensees were held accountable for their performance. Blaming the patient is unprofessional.
December 2020 Public Comment Meeting on Extravasation The NRC staff held a public meeting on December 8, 2020, to obtain medical community and other stakeholder feedback on whether extravasations should be reported as medical events.29 Most meeting participants were medical professionals (i.e., physicians, nuclear medicine technicians, medical physicists, radiation safety officers, etc.) who strongly opposed regulating extravasations. A smaller number of commenters supporting the reporting extravasations as medical events participated in the public meeting, including individuals associated with the petitioner for PRM-35-22 and a nuclear medicine patient. Broadly summarized, commenters opposed to reporting extravasations as medical events stated that significant injury from extravasation was extremely rare, monitoring for extravasation would not prevent extravasations from occurring, and requiring extravasations to be reported as medical events would create significant regulatory burden on medical licensees with no additional benefit to patient safety. Commenters stated that there was no technology that could prevent extravasation and that, while monitoring for extravasations could allow clinicians to begin mitigation measures sooner, monitoring would not prevent extravasations. Commenters stressed that extravasation is a "practice of medicine" issue that should not be regulated and is best left to individual institutions to handle, and that injection quality monitoring and improvement initiatives are already being done at many institutions. Commenters pointed out that extravasation is a clinical issue not limited to radiopharmaceuticals, and, for example, extravasation in	The summary succinctly captures the arguments of those opposed to the petition. On the whole, these objections are without merit. • <u>Extravasation injury is rare</u>: this objection is without any factual basis. There is currently no monitoring or measuring for extravasations, and even when observed, patients are not followed, and their physician is likely not told. Furthermore, it has been shown that extravasations can regularly cause significant absorbed doses to patient tissue, in excess of the levels of that cause deterministic effects. As the NRC has noted in their recent denial of three petitions, "the inability to observe an effect does not mean that the effect has not occurred." Finally, patient injury is not a criterion for ME reporting. • <u>Monitoring will not prevent extravasations</u>: this objection is absurd. No vigilance step prevents, by itself, the event it is intended to detect. ME reporting will not, by itself, prevent any misuse of byproduct material—but it is a vital vigilance and accountability function that is used to drive performance improvement. Monitoring for extravasations is the same. The purpose of monitoring is to identify when extravasations occur so that mitigation steps for the patient can be taken, dosimetry performed, and data fed into improvement efforts. Furthermore, the act of monitoring, the "observer effect," is a well-known deterrent. • <u>ME reporting of extravasations is a burden</u>: for centers that extravasate frequently beyond the ME threshold, it will be a burden—as well it should. At the very least, patients will no longer be kept in

chemotherapy is not regulated but has been improved over time through injection quality improvement efforts. In their opposition to the NRC regulating extravasation, another commenter noted that there exist multiple mechanisms to evaluate and promote the safe medical use of byproduct materials, including regulation and monitoring by the FDA, CMS, and the Joint Commission on Accreditation of Healthcare Organizations. Commenters stated that reporting extravasations as medical events would not improve patient safety and, that in fact, unnecessary regulation could divert resources away from more important safety issues. Commenters also stressed that dosimetry for extravasation is complex and involves many uncertain factors and also stressed that many medical licensees (especially those in a smaller, community hospital-type setting) would not have access to staff and technical resources needed for "these types of very lengthy and involved calculations."30	the dark. Hopefully, the burden of ME reporting will motivate the center to improve their performance, so that they provide better care and have fewer ME reports to complete. If significant extravasations are as rare as the community claims, this should be a non-issue for the vast majority of centers. • Practice of medicine issue: Prescribing nuclear imaging and determining the dose of radiopharmaceutical required are examples of practice of medicine issues. There is no medical or clinical benefit to an extravasation, so they should be avoided. Chemotherapy practitioners have shown that extravasations can be virtually eliminated, occurring <<1% of the time yet the national benchmarking studies report that oncologists are still satisfied. The continual efforts for over 30 years to drive these chemotherapy extravasation rates towards zero is noteworthy. The rate of nuclear medicine extravasations is 1 or 2 orders of magnitude higher, as referenced in the petition. The difference between these two practices is the chemotherapy practitioners application of quality improvement processes to optimize tools, techniques, and training. Routine inadvertent irradiation of patient tissue with doses greater than 0.5 Sv is a regulatory issue because it shows the center may have a problem properly handling radioactive material. This kind of issue is precisely what ME reporting was designed to uncover. • Other organizations regulate the safe medical use of byproduct material: aside from the obvious point that the safe use of medical byproduct material is not the role of those other organizations but is specifically the role of the NRC, the other organizations mentioned provide little oversight of nuclear medicine. The FDA has limited oversight duties for prescribers of a drug. CMS has no quality measures for nuclear medicine. Lucerno has not found a single accreditation body that asks for information on nuclear medicine extravasations. Hospital chief medical officers have told Lucerno that, while they are notified of contrast CT extravasations, their hospitals do not track or report radiopharmaceutical extravasations. The high rate of extravasations in nuclear medicine compared to chemotherapy is evidence that no other organization is doing the NRC's job. • Reporting extravasations would not improve patient safety: similar to the objection above, this is also absurd. The only way this would be

	true is if a center that frequently extravasated beyond the ME threshold fails to take any steps to improve their performance. We trust that the NRC would find this lack of improvement unacceptable. • Dosimetry is complex: nuclear medicine is itself complex, yet the field has developed standards and practices which allow it to be practiced with consistency. The goal of dosimetry following extravasation is to make a reasonable estimate without undue complexity. Throughout medicine, standard practices incorporate simplifications and approximations which make them easier to follow. Peer reviewed publications already offer such solutions for extravasation dosimetry. It need not be lengthy and involved. Note that current medical guidelines direct that dosimetry should be performed on significant extravasations. Practitioners unable to do dosimetry today are thereby not following medical guidelines. There are some other observations from the public comment period that should be noted: • Conflict of interest: several accused Lucerno of a conflict of interest (COI) related to the petition. It is true that we have a product that can be of assistance to a center for monitoring, dosimetry, and improvement—but our product is **not** required to solve extravasations at a center. Chemotherapy and contrast CT have dramatically improved their extravasation performance having never heard of Lucerno or our product. We are interested in seeing this problem solved for both personal and professional reasons. The nuclear medicine community must also acknowledge they have their own COI in this matter—they do not want to do the work to solve the extravasation problem. This is clearly evidenced in the 2009 ACMUI meeting transcript. • Misrepresenting clinical data: as previously communicated to the NRC, an ACMUI member grossly misrepresented a clinical publication to try and convince the public there was no issue with extravasations. • The patient: there was an astounding absence of any mention of patients—other than patients should be not be told they have been extravasated. One must conclude that the nuclear medicine community does not understand the patient impact from

	extravasations. This alone should compel the NRC to act so that nuclear medicine patients are better protected.
Commenters who support monitoring and reporting requirements for extravasations stated that injection quality monitoring plus improvement processes would improve injection administration techniques, thus improving patient safety. The commenters stated that because the medical community does not monitor for nor evaluate the effects of extravasations, we cannot know whether extravasations are causing harm or not. These commenters stated that extravasation of even diagnostic radiopharmaceuticals can result in doses higher than the existing 50-rem threshold reporting criteria and these events should not be given "a pass" from medical event reporting. In response to comments objecting to the financial and regulatory burden of reporting extravasations, one commenter suggested that the notification requirements for medical events could be delayed in order to minimize regulatory burden. Another commenter who identified as a nuclear medicine patient strongly supported reporting extravasations to improve patient safety.	
Comments on Petition for Rulemaking PRM-35-22 The NRC received 484 comment submissions during the 90-day public comment period on PRM-35-22, all comments are available on regulations.gov (NRC-2020-0141). About 80 percent of the comments were from medical professionals who opposed the petitioner's request to report extravasations exceeding 50 rem as medical events.31 Many commenters objecting to the petition were associated with the Society of Nuclear Medicine and Molecular Imaging (SNMMI), which believes that extravasation is best managed on an institutional level and at the discretion of the authorized user, and it does not require additional NRC regulation.32 SNMMI stated that there is no clinical data supporting the petitioner's claim that extravasation of diagnostic radiopharmaceuticals is a patient safety issue, and that similar to extravasation of chemotherapeutic agents, there are well-established procedures in place to manage extravasation of therapeutic radiopharmaceuticals. SNMMI also commented that it recognizes the potential effect extravasation may have on the quality of diagnostic images, particularly on quantitative studies, therefore the SNMMI Technologist Section is actively addressing extravasation as a quality-control issue, rather than a	NRC received 67 unique comments opposed to the petition and 320 form letter comments, many of which were signed as: **Your Name** and **Your Organization**. NRC guidance suggests that the Commission makes "determinations for a proposed action based on sound reasoning and scientific evidence rather than a majority of votes. A single, well-supported comment may carry more weight than a thousand form letters." Twelve of the 67 unique comments were from medical societies or leaders of the SNMMI. These comments were systematically reviewed by experts in the fields of nuclear medicine, physics, vascular access, radiology, and radiation biology. Dr. Dan Fass submitted this systematic review which was recorded as comment number 485. This expert review was excluded from the staff evaluation summary. The extravasation issue is not being managed well at the institution level. Recently, a patient being treated at a premier medical institution was extravasated. The technologist did not know what to do. No mitigation was performed. No dosimetry was performed. SNMMI is incorrect

patient safety issue. Other comments opposing the petition were similar to those received during the Medical Radiation Safety Team's December 8 public meeting (summarized above), generally expressing that extravasation does not merit regulatory reporting because there is no evidence that it produces any health consequences for patients.	regarding their assertion that well-established procedures are in place and extravasations should be left to individual institutions. NRC regulation is obviously required to protect patients. The SNMMI has done very little to establish standards that institutions can follow. Some of what they have done is not helpful—an SNMMI brochure suggests mitigation by icing the injection site, exactly the wrong thing to do immediately post-extravasation. Comments that suggest there is no evidence of health consequences not only demonstrate that the commenters do not understand medical event reporting requirements, but also show that they have ignored the presented evidence.
Of the roughly 20 percent of comments that supported the petition, more than half of those comments were from non-medical professionals, including one U.S. Senator and a number of U.S. House representatives. The U.S. lawmakers' comments supported the petition, citing concerns about patient safety and stating that monitoring for and reporting extravasations would improve diagnostic imagery and patient health. Another commenter submitted highlights from their peer-review article that was pending publication in the Health Physics Journal, providing a step-by-step worksheet to estimate radiation dose from extravasation. The commenter used three example dose calculations to demonstrate that diagnostic radiopharmaceuticals can result in doses that meet the current dose thresholds used for medical event reporting criteria. Other commenters supporting the petition reiterated the point that even diagnostic extravasations could exceed 50 rem at the injection site, extravasations are avoidable with improvements in injection technique, and that monitoring for and tracking extravasation events would improve patient safety and health outcomes.	Please note that the pending publication referenced was published in Health Physics in January 2021.
Input from Agreement States The NRC held a government-to-government meeting with the Agreement States on July 23, 2020. About 100 Agreement State representatives, including Organization of Agreement State (OAS) Executive Board members, attended the meeting, in which staff presented background information on extravasations and the current medical event reporting criteria, the NRC's 1980 decision to exclude	

extravasations from medical event reporting, recommendations from the Advisory Committee on the Medical Uses of Isotopes, and PRM-35-22. Agreement State representatives asked clarifying questions on the published studies regarding prevalence and outcomes of extravasations, expressed doubt that licensees would have the dosimetry capabilities to determine whether extravasations met a certain dose criterion for reporting, and questioned the burden reporting extravasations would place on licensees. The overall sentiment from Agreement States was skepticism at reporting extravasations as medical events but that a less formal and non-punitive mechanism to track extravasations would be useful. The OAS Board and two Agreement States submitted comments on PRM-35-22.33 OAS urged the NRC to accept the petition for rulemaking, stating that the rationale for excluding extravasation from medical event reporting in 1980 was no longer appropriate given advancements in nuclear medicine. The North Carolina radiation protection program strongly supports the petition, and the Arkansas program stated that rulemaking was not necessary but that extravasations exceeding the current dose criteria in 10 CFR 35.3045 should be reported as medical events. The North Carolina Radiation Protection Commission, a Governor appointed 21-member commission that advises the North Carolina Department of Health and Human Services, voted unanimously to oppose the petition, but noted that extravasation is already addressed in the existing medical event reporting requirements (North Carolina does not exclude extravasation from the requirements).	The North Carolina Radiation Protection Commission did oppose the petition; however, their positions clearly indicate their misunderstanding and misrepresentations of the evidence regarding extravasations. Despite the Radiation Protection Commission's belief that extravasations are already addressed, no extravasations are being reported in North Carolina.
<u>OPTIONS:</u> The staff evaluated the "no action" and several rulemaking options. All rulemaking options would require that certain extravasations be reported as medical events, which would close the regulatory gap for reporting extravasation events that meet the public health and safety significance AO criteria. Additionally, all reporting options would involve some amount of regulatory burden on licensees, however, as discussed in the "cons" below, some options involve significantly more regulatory burden on licensees (and regulators) than others.	
Option 1, "No Action," would maintain the status quo, and extravasations would continue to be excluded from medical event reporting. This option would continue to support the Commission's 1980	

position that extravasation commonly occurs in otherwise normal injections and is impossible to avoid. Pros: • Extravasations may not merit medical event reporting for a number of reasons: (1) even with best venipuncture practices, they can still be caused by many factors beyond the control of the technician, such as anatomical and physiological conditions or patient action, (2) the occurrence of an extravasation does not mean the administration deviated from the written directive or the physician's intent, and an extravasated injection could still result in the intended medical benefit and clinical outcome, i.e., diagnostic scan or radiotherapy treatment, (3) extravasation does not indicate a potential problem in a medical facility's use of radioactive materials, and (4) extravasations are rarely significant from a radiation safety or clinical perspective. • This option aligns with the medical community's position that extravasation is a practice of medicine issue that does not need to be regulated and is best addressed at the institutional level. • Unlike the reporting options discussed below, there would be no additional regulatory burden placed on licensees and regulators. Cons: • The "no action" option means that extravasations resulting in patient harm would continue to go unreported as medical events. Therefore, an extravasation event of public health and safety significance would not meet the AO criteria. • Without medical event reporting requirements for extravasation, the prevalence and impact of extravasation are difficult to determine with certainty. Data from published literature and the petitioner shows extravasation of a radiopharmaceutical at the injection site may result in a high radiation dose to that area. At a minimum, the radiation dose depends on the amount of radioactivity extravasated, the volume of fluid containing the radioactivity, and the rate at which the extravasated radiopharmaceutical is cleared from the extravascular space and reabsorbed by the blood stream. However, a high radiation dose does not equate to radiation injury. While radiation injury after parenteral administrations of radiopharmaceuticals is probably	Again, the best practices rate of extravasations is <<1% as evidenced by chemotherapy in a similar patient population. According to vascular access experts like the Association for Vascular Access, nuclear medicine departments are not currently using the best venipuncture practices. Radiopharmaceuticals are intended for intravenous delivery. If it were intended to be a subcutaneous injection, the procedure guidelines would say so. Therefore, delivering dose to injection site tissue is contrary to intent. While every case of extravasation does not represent a significant lapse in their use of materials, regular occurrences do indicate a potential problem with the facility's use of radioactive materials. **The NRC is reinforcing the misperception that extravasations are rarely significant from a radiation safety or clinical perspective. There is abundant evidence that extravasations can and do cause harm.** The rate is unknown because administrations are not monitored and extravasations are not reported, imaging is not repeated, dosimetry is not performed, patients are not followed, their physicians are not informed, etc. This is a preventable event and when a center routinely, significantly extravasates, it clearly indicates that they have a problem handling radioactive material. This situation is exactly what medical event reporting was designed to address.

unlikely, extravasation incidents have been described in published case studies with patients receiving skin doses in the range of deterministic effects following extravasation of, for example, I-131 • metaiodobenzylguanidine,34 Lu-177 dotatate,35 and Ra-223 dichloride.36	
Option 2, "50-rem dose threshold" would require medical event reporting for extravasations that exceed a localized dose equivalent of 50 rem. This option would include both diagnostic and therapeutic radiopharmaceutical administrations. Licensees would need to monitor every administration for extravasation because extravasations that do not impact image quality or require taking an image over the injection site soon after administration or using some type of radiation detector device to monitor the administration. If an extravasation were detected, the licensee would then need to perform a radiation dose calculation to determine if it exceeded the 50-rem dose threshold for reporting. Pros: • The 50-rem dose threshold for both diagnostic and therapeutic administrations may incentivize practitioners to improve injection quality. • This option would be consistent with the existing 50-rem dose threshold for reporting other types of medical events. • A regulation specifically addressing reporting requirements for extravasations would be clearer than requiring reporting under the current regulations. Cons: • The 50-rem dose threshold may be too low. The NRC's medical event reporting criteria are set at conservative levels that would rarely cause patient harm, and this low threshold for reporting could result in hundreds of thousands or more of harmless extravasation events reported annually. NRC and Agreement State regulators would expend resources to evaluate and sort through these reports to screen for more significant events of interest that could provide valuable information on extravasation root cause and corrective actions. • This option would impose significant regulatory and financial burden on licensees to monitor all radiopharmaceutical administrations in order to detect even minor extravasations. There is not an	There is no medical, clinical, or scientific logic that justifies why radiopharmaceutical spills on the skin are ME reportable, but extravasations are not. An equivalent dose under the skin is far more dangerous because it cannot be mitigated as easily as wiping off the skin. Nuclear medicine already makes a very large investment in time and money to ensure high quality scans. However, there is no quality check for the variable that arguably has the greatest ability to negatively affect the image and patient safety. Monitoring for extravasation should not be any more of a burden than the existing quality measures. Monitoring can add less than a minute to the patient procedure, provides significant information about the quality of the administration, and enables immediate mitigation in case of extravasation. In the event that there is an extravasation, monitoring data can dramatically reduce the amount of additional work that is required for dosimetry. A grace period before an ME reporting mandate goes into effect would allow centers to dramatically improve their administration quality. Centers that routinely significantly extravasate can drive down their rate through quality improvement programs during the grace period. Applying the know-how from the chemotherapy and contrast CT experiences should allow the rate to fall to 2 out of 1,000 patients. Approximately 12,000 per year would require dosimetry. Many of these would be less than the reporting threshold, leaving approximately 36 per day that might exceed the reporting criteria. And depending upon rulemaking (see below), most could be reviewed periodically, rather than reported within 24 hours. The solutions to reducing extravasations are known; removing the exemption will give motivation to apply them to nuclear medicine.

equivalent regulatory requirement to monitor for the other medical use modalities. Additionally, this option would require dosimetry to determine if extravasations exceeded the 50-rem dose threshold. The dosimetry for extravasation could be complex, and there is currently no standardized model or software program to perform this dosimetry.	The logic that resulted in the 50-rem threshold applies as well here as in other situations. A regulation specifically addressing extravasations would allow for extravasation-specific deadlines for ME reporting, distinct from the current deadlines. For example, a low frequency extravasation center could be allowed to report their events quarterly or annually, and high frequency extravasation center could be required to report weekly until their rate improves. The burden on centers should be to improve their extravasation rates, so that they do not need to report ME frequently. This is the only result that serves to protect patients from extravasations. Centers with professionally-appropriate extravasation rates (e.g., <<1%) will not be burdened. Again, reasonably accurate estimation of dose to representative volumes is not difficult. In practice, and depending on how the information is gathered, only a handful of dose calculations would need to be made annually in a center that rarely extravasates.
Option 3, "Administration site dose for procedures requiring a written directive," would require that for procedures requiring a written directive, extravasations resulting in a dose 50 rem greater and 50 percent or more than the expected dose to the administration site be reported as medical events. This option would be similar to reporting requirements in 10 CFR 35.3045(a)(1)(iii),37 except it would be specifically applicable to extravasation. The NRC staff is determining whether the written directive regulations38 can be used to account for a reasonable skin dose at the administration site from a normal therapeutic radiopharmaceutical administration in order to screen out expected or possible side effects from radiopharmaceutical therapy. This accounting for administration site dose would be similar to the situation for yttrium-90 (Y-90) microsphere lung shunt occurrence and medical event reporting. For Y-90 microsphere procedures, if lung shunting is evaluated prior to treatment in accordance with manufacturer procedures, the resultant dose to the lungs is not considered a medical event. Furthermore, Y-90 lung shunt	If a radiotherapy is administered properly, the expected dose to tissue will be similar to a diagnostic dose. For a therapeutic beta-emitter like Lutathera the expected dose to arm tissue will be ~1 mGy. An extravasation of 177-Lu will result in a dose to arm tissue that is far greater than the current reporting limit of 500 mGy (0.5 Sv) and indicate that center is potentially having an issue handling radioactive materials.

occurrences are excluded from medical event reporting even if the dose from the lung shunt is more than expected, because lung shunts are a known potential complication of the procedure. In order to fully assess this reporting option, the NRC staff needs additional information on unintended dose at the administration site from parenteral administrations of therapeutic radiopharmaceuticals and what dose levels could be expected. One published study reviewed by staff discussed that the unintended dose at the administration site from therapeutic extravasations can result in adverse tissue reactions more commonly than diagnostic extravasations. Specifically, the 2017 study39 reviewed 3,016 radiopharmaceutical extravasations: 3,006 involved diagnostic radiopharmaceuticals and ten involved therapeutic radiopharmaceuticals. Only three of the 3,006 diagnostic extravasations required medical follow-up due to skin irritation and tissue swelling around injection site, whereas five of the ten therapeutic extravasations required medical follow-up due to ulceration around the injection site. Pros: • The written directive requirement in this option would exclude diagnostic procedures, which account for most radiopharmaceutical injection procedures and are considered low risk. Furthermore, if authorized user physicians can account for an expected dose from minor extravasation or leakage at the administration site, then only extravasations exceeding this dose by 50 rem and 50 percent would be required to be reported as medical events, which could screen out less significant extravasations. • The reporting criteria in this option may yield more useful lessons-learned information than Options 2, 5, and 6. Compared to this option, Option 2 may result in too many harmless extravasations being reported, and Options 5 and 6 may result in not enough extravasations being reported to gather useful information. • This option would maintain consistency in the medical event reporting regulations because extravasation would be reported at the same dose criteria as other medical events involving procedures requiring a written directive. Cons: • This option would result in additional regulatory burden on licensees. Authorized user physicians would need to determine an	This summary of van der Pol misses the key takeaway from this publication. The authors note that centers do not routinely publish their extravasation experiences. One cannot draw the conclusion that therapeutic extravasations occur more frequently than diagnostic extravasations when neither are monitored or tracked. Only three of the 3,016 diagnostic extravasations demonstrated tissue reactions because ONLY THREE PATIENTS had dosimetry performed and were followed. None of the other diagnostic extravasations had dosimetry or patient follow-up, so nothing is known about the results for the patient. **The NRC is reinforcing the misperception that diagnostic extravasations are low risk. There is abundant evidence that diagnostic extravasations can and do cause harm.** The NRC has more than three dozen case reports from Lucerno, collected from a handful of centers, that show substantial dose to tissue from diagnostic extravasations, well in excess of the ME threshold.

expected dose to the administration site for therapeutic procedures and plan for this in the written directive; licensees would be required to have procedures in place to determine whether an extravasation has occurred; and if an extravasation occurred, conduct dosimetry or somehow otherwise determine whether the dose exceeded the 50-rem and 50 percent reporting criteria. (Although this regulatory burden would be significantly less than the burden associated with Option 2, and would only apply to procedures requiring a written directive.)	This option will not allow the NRC to meet its AO reporting obligation because it would exclude most of the nuclear medicine administrations including those extravasations that result in >10Gy dose to tissue.
Option 4, "Extravasation events that require medical attention" would be a non-dose-based option for reporting extravasations that result in a radiation injury. If a patient requires medical attention due to skin damage near the administration site, and the damage is determined to be caused by radiation, then this extravasation would require medical event reporting. This option would not require dosimetry to determine whether an extravasation should be reported, however, dosimetry may be required if the extravasation appears severe enough to trigger the AO criteria. Pros: • Unlike Option 3, this option would capture extravasations of both diagnostic and therapeutic radiopharmaceuticals that result in radiation injury to a patient. • This option would not require monitoring of administrations or dosimetry to determine whether an extravasation meets the criteria of a medical event. • This option aligns with other agencies' reporting requirements for clinical patient safety, such as the FDA and CMS. • Similar to Option 3, this option may yield more useful lessons-learned information, such as root cause and corrective actions, than Options 2, 5, and 6, because it would only require reporting of extravasations that result in radiation injury to a patient. Cons: • This option relies on the patient to self-report adverse tissue reactions to their physician, and if their physician is not the authorized user who was responsible for the administration, then this information would need to be relayed to the authorized user. Not all patients would seek follow-up for adverse tissue reactions.	This option shifts the responsibility for ensuring the proper performance of the nuclear medicine procedure from the licensee to the patient. The patient is poorly equipped to recognize radiation-induced injury that is likely to occur days, weeks, months, or years after the procedure. Neither the patient, nor their physician, will have been informed of the extravasation, and so are unlikely to connect the injury to their nuclear medicine encounter. For these reasons, few of the otherwise qualifying extravasation events would be reported to nuclear medicine, resulting in significant underreporting of ME. With such delayed identification, the root cause analysis would likely be more difficult to determine. This reporting mechanism is unlikely to improve performance of nuclear medicine centers and result in underreporting of ME. Dosimetry may not be possible. In sum, this option will not allow the NRC to meet its AO reporting obligation. Finally, this option would absolve the licensee from taking any mitigation steps to minimize the potential damage to the patient.

• This option relies on the physician's subjective assessment of radiological harm, which would represent a change in paradigm from the existing medical event reporting criteria, which are non-subjective and dose-based.	
Option 5, "Extravasation events that cause a significant dose" would require medical event reporting for extravasations that meet the 10 Gy (1,000 rad) dose threshold requirement for AOs. Similar to Option 4, Option 5 would not require monitoring of radiopharmaceutical administrations. Instead, this option would initially rely on patients to self-report to their physicians if they have any adverse tissue effects, like erythema, which could begin to occur at extravasated doses lower than 10 Gy. After the patient reports the adverse tissue effect to his or her physician, the authorized user physician would determine if the adverse tissue effect was cause by radiation and, if so, perform dosimetry to determine if the extravasated dose was 10 Gy or higher. Pros: • The 10 Gy dose threshold is a dose of public health and safety significance that would screen out diagnostic injections and less significant extravasations. • Compared to Option 4, adding a dose threshold for reporting would be clearer to licensees than relying solely on a subjective assessment of radiological harm. • This option would not require monitoring of radiopharmaceutical administrations. Cons: • This option would require dosimetry to confirm if an extravasation resulted in a dose to the administration site 10 Gy or greater, although this dosimetry would likely be less complex than that needed for the lower dose threshold options (i.e., Options 2, 3). • The 10 Gy dose threshold associated with AOs may be too high. Deterministic skin effects can start at about 6 Gy, and the 10 Gy dose threshold may screen out lower dose extravasations that cause patient harm. • This option has a similar con as Option 4 related to relying on patients to self-report adverse tissue affects.	This option has all the same defects described in Option 4.
Option 6, "Extravasation events that cause permanent functional damage" would require extravasations that result in permanent	

functional damage to be reported as medical events. This would be similar to the current reporting requirements for events caused by patient intervention that result in unintended permanent functional damage as determined by a physician. This option could be modified to also include extravasations that require medical intervention to prevent permanent functional damage (e.g., a skin graft). Pros: • Similar to Option 4, this option does not rely on a dose threshold for reporting, nor does it require dosimetry. • Of all the reporting options, this option would result in the least regulatory burden on licensees and regulators. • This option is responsive to the ACMUI recommendation to require medical event reporting of extravasations that result in permanent functional damage. Cons: • Permanent functional damage is a very high threshold. It is expected that extravasation events would never be reported if permanent functional damage is the threshold, and, without a lower threshold for reporting, even significant extravasation events that meet the AO criteria will not be tracked and operational experience on extravasations will not be shared. However, as noted above, this reporting threshold could be lowered by including extravasations that require medical intervention to prevent permanent functional damage.	This option has all the same defects described in Option 4, with the additional defect that it completely ignores AO reporting.
<u>SUMMMARY</u>: The NRC's medical event reporting regulation is intended to identify the causes of the events in order to correct them, prevent their recurrence, and allow the NRC to notify other licensees of the events so they too can avoid them. As noted in the "Background" section, the NRC does not consider an extravasation to be the incorrect route of administration or incorrect intent of a physician's directive. The NRC staff recognizes that in following a physician's direction for a prescribed dosage, even the most skilled clinician may occasionally not place the needle far enough into the vein, have the vein roll off to the side, or push the needle through the vein, resulting in some leakage of the radiopharmaceutical into the surrounding tissue during the IV administration.	<u>Summary</u> • There is no benefit to the patient from an extravasation, but there might be harm, depending on the dose. • The NRC should consider that the professionally acceptable rate of extravasations is <<1%. This the rate achieved by chemotherapy and contrast CT practitioners through quality improvement efforts. The rate for nuclear medicine is not well known, but published data indicate that it one to two orders of magnitude higher. The NRC should find this rate completely unacceptable. • Extravasations are much more common in nuclear medicine because nuclear medicine routinely employs practices that are no longer acceptable in chemotherapy and contrast CT administrations AND the

The staff's review of published literature illustrates that extravasation of diagnostic radiopharmaceuticals has rarely caused patient harm. It is more likely that the extravasation could impact image quality. In those instances where the extravasation impacts image quality, the patient may need to reschedule and return for a repeat procedure. In this case, the dialogue related to why the patient needs a repeat injection and scan occurs between the patient and the medical provider. However, extravasations of therapeutic radiopharmaceuticals are more likely to result in adverse tissue effects (e.g., erythema or ulceration) at the administration site. There are other times when a patient may receive an unintentional dose of greater than 0.5 Sv (50 rem) to tissue or an organ and the occurrence is not considered a medical event under NRC regulations. For example, the medical event criteria for permanent implant brachytherapy excludes sources that were implanted in the correct site but later migrated outside the treatment site, and as noted under Option 3 above, the medical event criteria for Y-90 microspheres exclude events caused by shunting if shunting was evaluated prior to treatment. The NRC staff is evaluating whether the dose consequence from extravasation is significant enough to merit regulatory reporting and, if so, what reporting criteria is appropriate for extravasation. ACMUI input on the considerations and options discussed in this memorandum will be used to inform the NRC staff's recommendation to the Commission on this issue.	NRC has allowed extravasations to be hidden from patients, doctors, and regulators since 1980. • The pervasive belief that diagnostic extravasations are harmless is wrong. NRC must stop perpetuating this falsehood. NRC has received dozens of examples of high doses to patient tissue from diagnostic extravasations, some of which should have been reported as AO. The only reason they were not is because of the 1980 exemption. The NRC cannot continue to claim ignorance, echoing the talking point of the nuclear medicine community. • The nuclear medicine community has made it clear that they have not and will not take patient exposure to extravasations seriously. They will not invest the effort to reduce extravasations until regulation requires them to do so. • Monitoring is work that the nuclear medicine licensees will have to do, but it is work they should have been doing for the last 40 years. It is the only way to ensure immediate mitigation for the patient, useful ME reporting with dosimetry, and AO reporting compliance. • Concerns about volume of ME reports and difficulty with dosimetry are mere puffery and should not be taken seriously. Centers that routinely exceed 0.5 Sv should be more concerned about the unacceptable frequency of poor patient care than volume of ME reports. And patients should know that such a center should be avoided.

ACMUI Subcommittee Response to NRC Staff Preliminary Evaluation

Original Text	*Analysis*
Draft Report July 30, 2021 Subcommittee Membership: Vasken Dilsizian, M.D. Richard Green Melissa Martin (Chair) Michael Sheetz Megan Shober NRC Staff Resource: Lisa Dimmick **Subcommittee Charge:** To review the U.S. Nuclear Regulatory Commission (NRC) staff's Memorandum "Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting" dated April 1, 2021 and provide feedback and recommendations.	
Introduction: The Advisory Committee on the Medical Uses of Isotopes (ACMUI) Subcommittee on Extravasation appreciates NRC staff for their thorough evaluation of the issues surrounding this topic and the proposed options for consideration. Overall, we feel that the evaluation is comprehensive, balanced, and accurately covers the issues and problems related with determining whether radiopharmaceutical extravasations should need to be reported as medical events, and if so, what are the appropriate criteria. One of the main issues is that since the NRC currently excludes extravasation of radiopharmaceuticals from its Medical Event reporting regulations, those extravasation events that result in patient harm and meet the public health and safety significance for an Abnormal Occurrence (AO) do not need to be reported. Since the medical AO criteria requires it first to be a Medical Event, it would be desirable to have some medical event criteria to capture those extravasation events that could result in patient harm so that they can be further evaluated for meeting the AO criteria, and if so, for reporting as an AO. The following discussion will expand on this issue and the NRC staff's evaluation determining whether: (1) extravasation merits regulation considering the objectives of the NRC's medical use policy statement, (2)	The original exemption was based on incorrect assertion that extravasations are virtually impossible to avoid. In fact, they can be virtually eliminated, as chemotherapy infusion practitioners have demonstrated. An extravasation merits medical event reporting because extravasations inadvertently irradiate patient tissue and skin with doses that exceed reporting limits. The definition of a medical event (ME) is statutory. The dose threshold for ME reporting is already established. Consequences resulting from the dose (ie, patient harm) is not a criterion for ME reporting.

the dose consequence from extravasation is significant enough to merit reporting; and (3) extravasation can be prevented with technology.	
Discussion: *Applicability of Extravasation to Medical Event Reporting* The purpose of the Medical Event reporting requirement is to allow NRC to evaluate if there was a breakdown in the licensee's program for ensuring that byproduct material or radiation from byproduct material was administered as directed by the Authorized User (AU), or if there was a generic issue that should be reported to other licensees, thereby reducing the likelihood of other medical events.1 The Medical Event reporting rule is intended to capture "errors" on the part of the licensee that exceed a certain dose threshold. To classify an extravasation as an "error" is not consistent with the original intent for Medical Event Reporting. The NRC does not consider extravasation as the wrong route of administration.2 Also, the 0.5 Sv tissue dose threshold that was implemented in 2002 was intended to eliminate errors in diagnostic administrations from being reported as Medical Events because they did not rise to the level of causing any patient harm. This 0.5 Sv dose threshold was not intended to be applied to very small volumes of tissue, such as that surrounding an extravasation, which do not result in patient harm. Medical Event reporting of patient specific extravasations will not likely contain a root cause analysis or provide generic causal information that will be applicable to other licensees in helping them to prevent future extravasations. Exempting extravasation from existing Medical Event reporting requirements has been consistent with the other reporting exemptions, such as patient intervention, shunting and stasis with yttrium-90 microspheres and migration of implanted brachytherapy and radioactive seed localization seeds. Furthermore, with the Medical Event regulatory reporting and patient notification requirements, there must be consideration of the psychological harm to the patient if his/her administration procedure results in an extravasation and is labeled as a Medical Event. Even though "Medical Event" does not necessarily imply clinically significant problems with the procedure, public perception is it constitutes a medical error.	There is no medical or clinical benefit to an extravasation. The radiopharmaceutical is intended to enter circulation, not the tissue at the administration site. Tissuing the dose is, by definition, unintended, and therefore should be considered an error. If the dose to tissue meets the 0.5 Sv criterion for an ME, then it is an ME. In fact, since an extravasation is an inadvertent irradiation to patient tissue that can exceed reporting limits and is an event which can be prevented, it is exactly the type of event that the original misadministration language intended to address. ACMUI is suggesting that patient harm is necessary to be a ME, but harm is not in the ME definition. Lucerno has provided clinical evidence that extravasations are not limited to very small volumes of tissue. Lucerno has also provided clinical evidence that diagnostic extravasations can result in very high dose to tissue and skin, as well as patient harm. **The ACUMI is reinforcing the misperception that "diagnostic extravasations do not cause patient harm"—there is abundant evidence that diagnostic extravasations can and do cause harm.** These statements demonstrate a lack of understanding of the energy emissions that are present in the most routinely used diagnostic radioactive isotopes (18F and 99mTc). When a diagnostic radiopharmaceutical is administered properly, the benefits of a nuclear medicine study certainly outweigh the radiation risk to the patient. However, when a diagnostic radiopharmaceutical is inadvertently injected into the patient tissue, the absorbed dose can easily exceed reporting thresholds, adverse tissue effects thresholds, and increases the chance of cancer later in life. This is a preventable event, and when a center routinely, significantly extravasates it clearly indicates that they have a problem handling radioactive material. This situation is exactly what medical event reporting was designed to address. If the ACMUI is so confident that extravasations of diagnostic radiopharmaceuticals do not cause harm, we propose a human challenge

Nonetheless, the Subcommittee recognizes that, in rare cases, extravasated radiopharmaceuticals have caused serious tissue injuries to patients, and in these situations the consequences of radiation damage are of interest to NRC from the standpoint of public health and safety. Exempting extravasations from all Medical Event reporting requirements does not allow NRC to collect information on radiation-induced injuries. This emphasizes the importance of developing a truly appropriate and relevant definition of Medical Event for extravasation of radiopharmaceuticals.	study with the ACMUI member as subjects. Each subject can choose to have either 10 mCi of positron emitting FDG or 20 mCi of 99mTc MDP injected into their tissue. They can flush the FDG with 10 cc of saline, but not the MDP, since that is routinely injected via straight sticks in the US at this time. We will then observe what happens to their tissue over the ensuing weeks or months. Serial images will be captured every 5 minutes post-injection to confirm the extravasation and to capture biological clearance. Dosimetry will be performed, estimating the dose to the affected area and to 5 cc of tissue in the immediate proximity of the injection site. We will know the injected activity and the activity and tissue volumes throughout the uptake period. Despite the ACMUI oft repeated line that diagnostic extravasations do not cause harm, it is unlikely that any IRB or RSO would allow such a study to proceed, ***because that amount of activity in tissue is not harmless.*** Extravasation rates can and should be reduced. Perfection (extravasation rate of 0%) may not be achievable, but achieving a rate of <<1% in nuclear medicine is certainly achievable, as this has already been achieved in the field of chemotherapy infusion with a similar patient set. The know-how exists; it simply must be applied in nuclear medicine. A combination of tools, training and technique will be required, the same needed for any quality improvement process. The ACMUI's casual dismissal of root cause analysis reveals only their lack of understanding of quality improvement processes. The ME regulation already allows the licensee to skip informing the patient if doing so would be detrimental; this is not a reason to continue the exemption. Furthermore, this type of paternalistic thinking has no place in the medical community today. It is the inherent right of a patient is to be informed when they experience improper care at the hands of a clinician.
Medical Practice Issue Performing an intravenous injection is a medical procedure that requires a certain technical skill to choose the appropriate infusion equipment, locate the vein and position the needle in the vein to infuse the radiopharmaceutical. However, even the most skilled individual will occasionally not place the needle far enough into the vein, have the vein roll off to the side, or push the needle through the vein, resulting in	Prescribing nuclear imaging and determining the dose of radiopharmaceutical required for the nuclear medicine study or therapy are examples of practice of medicine issues. Since there is no medical or clinical benefit to an extravasation, they should be avoided. Chemotherapy infusion practitioners have shown that extravasations can be virtually eliminated, occurring <<1% of the time. The rate of nuclear medicine

some leakage of the radiopharmaceutical into the surrounding tissue during the injection. Even with correct insertion of the needle into the vein and flushing after radiotracer administration, there may be a small amount of "radioactive" leakage at the venous puncture site when the needle is removed from the vein until the puncture site is plugged through normal physiological processes. Patient anatomy also plays a large part in obtaining a successful injection. Factors such as age, body habitus, hydration, and prior medical treatments can all affect the ability to obtain a complete injection without leakage or tear in the vein wall. In a publication on "Guidelines for the Management of Extravasations", it states: "The purpose of these practice guidelines is to offer and share strategies for preventing extravasation and measures for handling drugs known to cause tissue necrosis, which may occur even with the most skilled experts at intravenous (IV) injection".3 For example, we have all had blood drawn where we thought the phlebotomist was an ace, only to see black and blue discoloration around the needle stick site the next day. This is the same thing that can happen with an injection. Therefore, a successful injection is dependent on a combination of acquired technical skills and the ability to navigate, to the extent feasible, the patient's anatomical landscape and physiological conditions. Because of all these factors, injecting a radiopharmaceutical is truly a medical practice issue. In addition, extravasation of diagnostic radiopharmaceuticals rarely affects the sensitivity and quantification of the study, or compromises patient care and management decisions because of the generally small amount of extravasate, and that it is reabsorbed via the lymphatic channels. If the amount of extravasation results in poor quality images, making it technically unreliable for clinical interpretation, the study is usually repeated on another day. This is no different than repeated procedures due to wrong imaging protocol or improper positioning. All nuclear medicine facilities should have comprehensive quality control measures in place to monitor and track extravasations to improve the quality and safety of patients undergoing medical procedures involving the use of radiopharmaceuticals. Monitoring for extravasation may decrease the frequency of extravasation but will not prevent it from occurring. While there should be a quality assurance policy to monitor and improve the extravasation rate at an institution, as there exists for	extravasations is 1 or 2 orders of magnitude higher, as referenced in the petition. The difference? The application of quality improvement processes to optimize tools, techniques, and training. Routinely, inadvertently irradiating the patient's tissue with a dose greater than 0.5 Sv is a regulatory issue because it indicates the center has a problem handling radioactive material properly. This kind of issue is precisely what ME reporting was designed to surface. The ACMUI notes that extravasations may occur even with the most skilled experts at IV injection. This fact has been confirmed by infusion nurses who have received extensive training and who use the most advanced tools to help them gain venous access. That is why, for peripheral IV chemotherapy administrations, the extravasation rate is 0.18%. But nuclear medicine technologists do not receive the most advanced training. They are not using the most advanced tools and they are not using best practices. As a result, many nuclear medicine technologists extravasate at an unacceptably high rate. They do not handle radioactive material as well as it should be handled. The ACMUI cannot support with evidence the statement that extravasations <u>rarely</u> affect a study. To know this, the study would need to be repeated, and the study interpretations and clinical ramifications compared. They state that studies that are unreliable as a result of extravasation are usually repeated the next day. These are two examples of the ACMUI making claims that cannot be supported with any evidence,

many types of medical procedures, this should be conducted as part of a medical quality improvement initiative, and not subject to regulation by the NRC.	since there is no evidence. The petition cites numerous publications that describe how extravasations can and do effect patient care. We agree—all centers should have comprehensive quality control measures in place for extravasations. Lucerno's experience is that all centers have extensive quality control programs for nuclear medicine, but a rare few have included extravasations in the program. The NRC exemption enables this omission, much to the patient's detriment. The ACMUI continues to be confused regarding the purpose of monitoring of administrations. The purpose of monitoring is to identify when extravasations occur so that mitigation steps for the patient can be taken and dosimetry performed. Furthermore, knowing the actual rate of occurrence and investigating root causes allows a quality improvement program to decrease the rate of occurrence, with the goal of reducing the rate of occurrence. The petition does not suggest regulating how a center approaches their quality assurance policy. The petition only ensures that there is transparency about the reporting of extravasations. When patients are inadvertently irradiated with a dose equivalent greater than 0.5 Sv, the NRC should know this. It may mean that the center needs a quality assurance policy or an improved execution of their existing policy.
Frequency of Extravasations In a review of four studies involving a total of 2613 patients, the reported frequency of radiopharmaceutical extravasation was an average of 17% (range 10.5-21%).4, 5, 6, 7 However, this data is simply not consistent with the reported extravasation rates for chemotherapy (0.09%)8 or IV contrast (0.24%)9 involving 739,812 and 454,497 infusions, respectively. These are similar types of injections to that being performed for radiopharmaceuticals and therefore the extravasation rates should be similar. One reason these studies show a higher extravasation rate for radiopharmaceuticals is that the criterion to be counted as an "extravasation" in these studies was any visualized increased uptake of tracer at the injection site. It does not take much activity to be visualized on a gamma camera or PET scanner image, so any leakage of the	The extravasation rate data is indeed not consistent between nuclear medicine and chemotherapy infusions or contrast CT. We agree that the rates should be similar; however, we disagree with the ACMUI's assertion that the difference is simply due to the fact radiopharmaceutical extravasations are easier to see. In fact, the authors of one of the references cited by the ACMUI believes that extravasations may be underreported by ~30% due to the fact that injection sites are often outside the imaging field of view. Chemo and contrast CT rates are low because they have to report extravasations when they happen, and they know when extravasations happen because patients complain from immediate pain and discomfort. Furthermore, the latest United States'

radiopharmaceutical out of the vein at the injection site would be classified as an extravasation. For non-radiopharmaceuticals, the criterion for extravasation needs to be pain, swelling or redness resulting from a relatively larger volume of injectant, which is a significantly different standard. For the one study that quantified the amount of activity in the extravasation, over 98% of the time the amount of activity was less than 1% of the injected dose.10 So, while visualized increased uptake of the radiotracer at the injection site may occur approximately 10-20% of the time, it will rarely be enough activity to interfere with the study or cause any patient harm, nor will it necessarily indicate poor technique on the part of the individual performing the injection.	benchmarking study for chemotherapy extravasation conducted in 2015 and referenced by the ACMUI (8) specifically states that the numerator (number of extravasations) includes cases where the infusion nurse suspected that the administration was not ideal. Even if patients did not complain about the burning effects of chemotherapy, if nurses were aware of anything suspicious about the administration, they classified it as an extravasation. The ACMUI reference to the national benchmarking publication and the study from the University of Santiago are examples of how the ACMUI does not appear to understand the references they cite. The ACMUI suggests that the chemotherapy extravasation rate is 0.09%. That rate is the average rate of peripheral IV administration and port administration extravasations rates. Since ports are contraindicated for administering radiopharmaceuticals, an apple-to-apple comparison between nuclear medicine patients and chemotherapy patients should consider the 0.18% rate. The University of Santiago study incorrectly assumes that the static image is an adequate proxy for the severity of the extravasation. That is not true. With the exception of MDP extravasations, biological clearance can dramatically reduce the amount of radioactivity present near the injection site by the time an imaging occurs. What the University of Santiago observed in their ~1800 images does not reflect the true nature of the extravasations that occurred. Chemo and contrast CT clinicians have different training compared to nuclear medicine technologists. These areas are continually pursing quality improvement even though they are 0.24% or less. Technology exists that can help clinicians differentiate between a few microcuries of a radiopharmaceutical and a massive extravasation that will result in a dose of 10 Gy to the tissue. The extravasations that matter are the severe ones. Again, the ACMUI cannot support with evidence the statement that extravasations <u>rarely</u> interfere with a study or cause patient harm because the extravasation rate is not tracked, studies are not repeated, and patients are informed, much less followed.

Determining the Dose from Extravasation To accurately calculate the dose to surrounding tissue from an extravasation, factors such as tissue volume, geometry, and clearance rate all need to be considered. This would require serial gamma camera or PET scanner images over the injection site to determine the clearance rate and region of interest quantification of the activity, along with determination of the extravasated tissue volume and geometry. Many gamma camera systems do not have the software to perform these measurements. If one assumes an overly simplistic and conservative model such as a 1 cc spherical volume and no biological clearance from the site, a 0.5 Sv dose threshold is quickly exceeded. Using this model, it would only take 150 uCi of Tc-99m or 30 uCi of F-18 (which is less than 1% of the typical activities administered for these radionuclides) to reach the 0.5 Sv dose threshold. A recent article "Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements" by Dustin Osborne, et al, states that a dedicated radiopharmaceutical injection monitoring system can help characterize radiopharmaceutical extravasations for calculating tissue and skin doses.11 However, the dosimetric models and methodology used for the dosimetry calculations do not accurately reflect the geometric infiltrate/tissue configurations of an extravasation. Underestimating the amount of self-absorption within the infiltrate and underestimating the distance between the source and the skin will grossly overestimate the tissue and skin doses. For subdermal tissue dose calculations, it is convenient to assume that the infiltrated radiopharmaceutical is uniformly mixed within the tissue mass for different geometrical configurations and that the dose to the tissue is calculated assuming the source and target regions are the same (rT = rS). However, during an infiltration, the injected liquid will push between layer(s) of tissue, not uniformly mix within the tissue, so the source and target regions are not the same. A more accurate dosimetry model would represent the infiltrated radiopharmaceutical as a sphere, ellipsoid, or disk, with the dose to target tissue being calculated at the surface of the source material. With this configuration, the energy absorbed fraction will be significantly less due to self-absorption within the infiltrate.	The ACMUI assertion that dosimetry for extravasations is too complex should be dismissed as puffery. Nuclear medicine is extraordinarily complex. Nonetheless, the field has developed standards and practices which allow it to be practiced with consistency. At times (e.g., using SUV as surrogate for kinetics) standard practices incorporate simplifications and approximations which make them easier to follow. Peer reviewed publications already offer solutions. Biological clearance can be estimated practically by using external counting detectors or other measures (e.g., images or ionization chambers). Tissue volume assumptions can be chosen realistically, avoiding too-small volumes. In the cited paper, the authors used "representative volumes" of tissue. The goal of dosimetry following extravasation is to make as reasonable an estimate as possible without undue complexity. Spherical volumes have historically been used for dosimetry calculations because they represent a reasonable shape while minimizing additional measurements and calculations. The distance between the infiltrate and the skin will dramatically change the resulting skin absorbed dose. This logically explains why erythema and other skin effects are not commonly reported following extravasation of radioactive isotopes with energy emissions that do not travel far in water/tissue. In these cases, it is reasonable to expect that dose to the infiltrated tissue is higher than that to the skin. No reference or evidence is given to support this "pocket extravasation" theory. While there is no evidence that these self-contained extravasations exist, there is ample evidence that they do not. When imaged, extravasations do not appear as highly concentrated, well-defined volumes. Instead, they are amorphous and gradually transition from areas of high activity to low. Also, the fact that extravasations undergo biological clearance is an indicator that they are mixing within tissue. If they remained sequestered, there could be no re-uptake by the lymphatic system. This "pocket extravasation" theory is further analyzed in Appendix C.

For skin dose calculations, it is important to accurately determine the distance between the infiltrated source and the sensitive basal cell layer. The sensitive basal layer lies within the upper epidermis layer of the skin. The infiltrated material would lie below the dermis and hypodermis layers of the skin (consisting mostly of connective and fatty tissue), putting it at a distance of at least several millimeters (several thousand microns) away. With this configuration, most of the radiation dose would be absorbed by the overlying dermis and hypodermis layers and not reach the sensitive basal layer. Regardless of the geometric model used, one must also quantify the amount of activity in the extravasate and determine its effective half-life. Obtaining all these parameters takes time and would be particularly challenging to most licensees. The result would be that most licensees would assume "worst-case" assumptions which would result in doses readily exceeding a 0.5 Sv threshold.	It is unclear why the ACMUI is unconcerned with significant dose to tissue other than the skin. For ME purposes, 0.5 Sv is the criterion. Again, reasonable simplifications and approximations have been published and can be used to create a reasonable dosimetry estimate without complexity. There is no reason a licensee must use worst case assumptions. Furthermore, the overall incremental work that must be done to perform dosimetry of extravasations, beyond what clinicians should already be doing when they suspect an extravasation, would take less than 5 minutes. This work can be accomplished with software that is available now and is free.
Radiation-induced Injury from Extravasation Extravasation of diagnostic radiopharmaceuticals will rarely, if ever, result in any patient harm, even if the tissue dose exceeds 0.5 Sv, as evidenced by the exceeding small number of cases of adverse tissue reactions reported in the liturature.12 Also, the stochastic risk from the extravasated dose to the surrounding tissue will likely be negligible compared to the stochastic risk from the radiation dose to other more radiosensitive tissues of the body irradiated from the radiopharmaceutical administration for the diagnostic or therapeutic procedure. While exceedingly rare, there have been reports of patients who developed severe tissue damage following extravasation of radiopharmaceuticals (almost exclusively from therapeutic radiopharmaceuticals). When this occurs, the effort involved in assessing the event and determining a potential dose to affected tissue is warranted. The NRC already receives reports of radiation-induced tissue injuries from other licensed activities (for example, patients receiving radiation therapy with a high dose rate remote afterloader who develop tissue erythema after the radiation source is unexpectedly in contact with the skin). From a clinical perspective, the tissue injury from an external	**The ACUMI is reinforcing the misperception that diagnostic extravasations rarely if ever cause patient harm.** There is abundant evidence that diagnostic extravasations can and do cause harm. Again, patient harm is not a criterion for ME reporting and Lucerno has provided dozens of examples of patient with extravasations that greatly exceeded the ME reporting threshold. An extravasation will increase the stochastic risk for the patient. The increase in the stochastic risk should be compared to that of tissue that was not extravasated, not to other more radiosensitive tissues. Reports of adverse tissue reaction is to be expected to be limited when effects are delayed in time, patients and their physicians are not told, and the patient is not followed. There exists today no mechanism to capture these reports, so the limited number of reports is unsurprising.

radiation source adjacent to skin and a tissue injury from an extravasated radiation source present similar radiation consequence. Although typically used for chemotherapy extravasation, the U.S. Department of Health and Human Services uses the Common Terminology Criteria for Adverse Events to grade injuries from infusion site extravasation.13 A scale like this could be used to determine qualitative criteria for extravasation event reporting to NRC.	Tissue damage is an inadequate gauge of extravasation severity. For example, a 99m-Tc extravasation may result in a high dose to the patient tissue with no visible sign of damage to the skin (based on the distance that the 99m-Tc emissions travel as they deposit energy). While a qualitative scale may have utility in describing patient effects, it is not sufficient, nor should it be used to determine ME reporting.
Subcommittee Comments on the Draft Options: In 2019, the ACMUI Subcommittee on Extravasations recommended reporting as Medical Events extravasations which caused unintended permanent functional damage.14 Since that time, the Subcommittee has continued to deliberate the topic as additional research and practices have come to light. As presented in the NRC Staff preliminary evaluation, rulemaking options 2-6 would require that certain extravasations be reported as medical events; these options would add regulatory burden on licensees (and regulators). The Subcommittee examined the following considerations:	
• Medical event reporting, when appropriate, is an effective regulatory tool for NRC to collect information on adverse consequences of using radioactive material in medicine.	ME reporting, by definition, includes events that reveal that center has a problem handling radioactive material properly. These events may or may not have immediate adverse consequences for patients.
• Data about the frequency, severity and causes of radiation injury are necessary to support NRC's radiation safety mission.	
• Complexities and uncertainties in radiation dosimetry make it difficult to provide precise estimates of radiation doses to small tissue volumes near injection sites.	Again, the ACMUI objection to dosimetry should be dismissed as puffery. Reasonably accurate estimation of dose to representative volumes is not difficult.
• Some radiopharmaceuticals do not have radiation emissions that can be easily imaged by nuclear medicine gamma cameras.	Imaging is not the only way to measure radiation emissions; external detectors are very useful.
• Numerous clinical trials are underway for novel therapeutic radiopharmaceuticals. Potential consequences of extravasating therapeutic material, particularly alpha-emitting radiopharmaceuticals, may warrant a framework for regulatory oversight.	Clinical studies of therapeutic radiopharmaceuticals should be actively monitored for extravasations for both safety and efficacy reasons.
At this time, the Subcommittee has decided that the best regulatory strategy with regard to extravasation is to focus on qualitative consequences of radiation-induced injury. The Subcommittee supports Option 4. This would provide NRC with information on the types of	The ACMUI-recommended strategy offers no hope to patients of mitigating the effects of extravasations except in the case where the extravasation is so severe that it is immediately apparent. Aside from these obviously severe cases, meaningful dosimetry cannot be performed.

radiation injuries caused by extravasation, and the frequency of such injuries. The Subcommittee recognizes the challenges associated with a qualitative reporting standard but believes that this strikes the best balance between radiation safety, patient harm, and complex dosimetry.	NRC's current non-compliance with abnormal occurrence reporting to Congress is not addressed by this strategy. While it will provide the NRC with some information on injuries, Option 4 puts the burden on patients to know to whom they should report harm that could occur months or years after their extravasation—an extravasation that they were not told had occurred. In all likelihood, the patient harm will not be associated the previous nuclear medicine procedure, and therefore will not be reported to nuclear medicine and no ME report will ever be filed. While we appreciate the ACMUI acknowledging that something should be reported, this option does nothing to protect patients, does not provide the data to improve the practice of nuclear medicine, and makes very little difference relative to the status quo.
Option 1, "No Action," would maintain the status quo, and extravasations would continue to be excluded from medical event reporting. This option would continue to support the Commission's 1980 position that extravasation commonly occurs in otherwise normal injections and is difficult to avoid and predict. The Subcommittee does not support Option 1. The Subcommittee believes that extravasations of high consequence should be reported to regulatory authorities.	
Option 2, "50-rem dose threshold," would require medical event reporting for extravasations that exceed a localized dose equivalent of 50 rem. This option would include both diagnostic and therapeutic radiopharmaceutical administrations. Licensees would need to monitor every administration for extravasation. The Subcommittee does not support Option 2. Option 2 would create a significant burden on licensees to monitor every administration to "detect" or "see" if an extravasation occurred. This would require taking an image over the injection site immediately after administration or using a radiation detector device to monitor the injection. Considering there are over 20 million diagnostic and therapeutic nuclear medicine procedures performed in the United States every year15, this would add significant time and require increased effort to perform. If an extravasation were detected, the licensee would then need to perform a	It would be helpful for the ACMUI to define "**significant burden**" that monitoring would require. How does this burden compare to that of all the other routine quality control, quality assurance, preventative maintenance, calibration, training, and investment in tools and time that an average licensee expends to ensure that patients are not inadvertently irradiated with excess radioactivity? To ensure that the NRC understands the "extraordinarily complex" dosimetry, we suggest we demonstrate this process to the medical and

radiation dose calculation to determine if it exceeded 0.5 Sv and required reporting as a Medical Event. This dose calculation, which is extraordinarily complex and for which there is no standardized model or software program to perform, would take even more time and effort on the part of the licensee. As similarly pointed out by the NRC Staff in their evaluation, assuming an extravasation rate of only 1 percent, it would result in over 200,000 potential medical events each year (over 500 per day). There simply are not enough resources on part of either licensees or regulators to handle this workload, and any attempt to process this workload would significantly and negatively impact other more important patient care and safety issues.	dosimetry staff so they can see that appropriate, patient-specific dosimetry of extravasations can be performed within a few minutes for free. This dosimetry follows processes described in a peer-reviewed publication and uses realistic assumptions. The ACMUI's predictions suggest that all 200,000 extravasations would exceed ME criteria and therefore need to be reported. That is not realistic.
Option 3, "Administration site dose for procedures requiring a written directive," would require that for procedures requiring a written directive, extravasations resulting in a dose 50 rem greater and 50 percent or more than the expected dose to the administration site be reported as medical events. This option would be similar to reporting requirements in 10 CFR 35.3045(a)(1)(iii), except it would be specifically applicable to extravasation. Subcommittee does not support Option 3 as it excludes all diagnostic administrations, and the dosimetry methodology is not standardized at this time.	
Option 4, "Extravasation events that require medical attention," would be a non-dose-based option for reporting extravasations that result in a radiation injury. If a patient requires medical attention due to skin damage near the administration site, and the damage is determined to be caused by radiation, then this extravasation would require medical event reporting. This option would not require dosimetry to determine whether an extravasation should be reported, however, dosimetry may be required if the extravasation appears severe enough to trigger the AO criteria. The Subcommittee supports Option 4.	
Option 5, "Extravasation events that cause a significant dose," would require medical event reporting for extravasations that meet the 10 Gy (1,000 rad) dose threshold requirement for AOs. Similar to Option 4, Option 5 would not require monitoring of radiopharmaceutical administrations. Instead, this option will initially rely on patients to self-report to their physicians if they have any adverse tissue effects, like erythema, which could begin to occur at extravasated doses lower than	

10 Gy. After the patient reports the adverse tissue effect to his or her physician, the authorized user physician would determine if the adverse tissue effect was cause by radiation and, if so, perform dosimetry to determine if the extravasated dose was 10 Gy or higher. The Subcommittee does not support Option 5. To be consistent with other types of medical events, the threshold for medical event reporting should be lower than the threshold for reporting an abnormal occurrence.	
Option 6, "Extravasation events that cause permanent functional damage," would require extravasations that result in permanent functional damage to be reported as medical events. This would be similar to the current reporting requirements for events caused by patient intervention that result in unintended permanent functional damage as determined by a physician. This option could be modified to also include extravasations that require medical intervention to prevent permanent functional damage. The Subcommittee does not support Option 6. Permanent functional damage is an extremely high threshold for reporting damage and may not provide NRC with enough information on the types of radiation injuries patients may experience. Although in 2019 the Extravasation Subcommittee supported what is now Option 6, the Subcommittee at that time believed that such reporting could be accomplished, via policy change, using existing Medical Event reporting requirements. With NRC now considering rulemaking specific to extravasations, the Subcommittee supports a broader reporting requirement.	
Conclusion and Recommendations: 1. The Subcommittee supports Option 4. This would provide NRC with information on the types of radiation injuries caused by extravasation, and the frequency of such injuries. It would also establish appropriate medical event criteria to capture those extravasation events that could result in patient harm so that they can be further evaluated for meeting the AO criteria, and if so, reported as an AO. 2. Monitoring for extravasation will not prevent them from occurring. While there should be a quality assurance policy to monitor and improve the extravasation rate at an institution, as there exists for many types of medical procedures, this should be conducted as part	Option 4, for the reasons stated above, would not provide much useful information about the frequency of extravasations. Aside from immediately apparent, most severe cases, Option 4 provides for no mitigation for the patient, no meaningful dosimetry, no effective solution to AO underreporting, and little motivation for nuclear medicine to improve the quality of administration. Again, the purpose of monitoring is to identify when extravasations occur so that mitigation steps can be taken and dosimetry performed. Centers should already have programs that drive quality improvement. Whether

of a medical quality improvement program, and not subject to regulation by the NRC. 3. Requiring extravasations that result in a localized tissue dose exceeding 0.5 Sv to be reported as Medical Events would create significant licensee and regulatory burden with no additional benefit to patient safety. 4. There is no clinical evidence that patients are being harmed, either from excess radiation dose or compromised diagnostic studies because of radiopharmaceutical extravasation. Respectfully Submitted on July 30, 2021, Extravasation Subcommittee Melissa Martin, Chair	the center follows QI practices or not, frequent ME reports indicate to the NRC that a center has a problem handling radioactive material. Licensees who regularly experience extravasations exceeding 0.5 Sv and fail to correct their problems might feel burdened by additional regulation. Licensees who correct their extravasation problems would experience no regulatory burden. The NRC and the ACMUI have been presented with abundant evidence that diagnostic extravasations can and do cause harm. Ignoring the published clinical evidence does not make this patient care and patient safety issue disappear.
[References]	Lucerno has previously provided the NRC with references that support the statements above.

Appendix C – Analysis of the ACMUI "pocket" extravasation dosimetry analysis

Josh Knowland[1]

The Nuclear Regulatory Commission (NRC) has had a policy of exempting all radiopharmaceutical extravasations from medical event reporting even if existing reporting thresholds are otherwise met. During 2020 and 2021, NRC staff have been investigating the topic and whether the exemption policy should be retained since the original premise of the exemption has been proven to be incorrect, since the exemption creates regulatory inconsistency, and since the nuclear medicine community has increased the use of positron- and beta-emitting radiopharmaceuticals. On April 1, 2021, NRC staff wrote a memorandum[2] to the Extravasation Subcommittee of their Advisory Committee on Medical Uses of Isotopes (ACMUI). The memorandum, which was not publicly available at the time, was intended to

> *"…summarize the U.S. Nuclear Regulatory Commission staff's preliminary evaluation of whether and how radiopharmaceutical extravasations should be reported as medical events, and to request feedback and recommendations from the Advisory Committee on the Medical Uses of Isotopes (ACMUI) on this preliminary evaluation."*

On August 11, 2021, the memorandum was released publicly along with a draft response from the ACMUI's Extravasation Subcommittee. In their response to the NRC staff, the subcommittee members stated that,

> *"For subdermal tissue dose calculations, it is convenient to assume that the infiltrated radiopharmaceutical is uniformly mixed within the tissue mass for different geometrical configurations and that the dose to the tissue is calculated assuming the source and target regions are the same (rT = rS). However, during an infiltration, the injected liquid will push between layer(s) of tissue, not uniformly mix within the tissue, so the source and target regions are not the same. A more accurate dosimetry model would represent the infiltrated radiopharmaceutical as a sphere, ellipsoid, or disk, with the dose to target tissue being calculated at the surface of the source material. With this configuration, the energy absorbed fraction will be significantly less due to self-absorption within the infiltrate."*

No citation was provided for the "pocket" extravasation mechanism described by the subcommittee members, and I have not found any reference to this idea in the literature. If this mechanism were to occur during radiopharmaceutical extravasation, the resulting radiation dose to tissue could be dramatically affected. The purpose of this work was to investigate the hypothesis further and discuss its applicability to the overall discussion of reporting radiopharmaceuticals as medical events.

[1] Josh Knowland is an engineer with over 14 years of experience designing medical technology to improve the safety and effectiveness of diagnostic and therapeutic radiation. He is the VP of Product Development at Lucerno Dynamics.

[2] U.S. Nuclear Regulatory Commission Staff Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting for ACMUI Review. ADAMS Accession Number ML21223A085.

Manifestations of Extravasation

The ACMUI subcommittee members describe a situation where extravasated radiopharmaceutical is administered through an intravenous access catheter over a period of time and then re-forms into a sphere, ellipsoid, or disc that is deposited between layers of tissue and remains sequestered there unable to diffuse through the interstitial space of tissue. If this were the case, then cases of extravasation visible on nuclear medicine images should appear visually as compact and well-defined with no biological clearance by the patient's lymphatic system.

I have been unable to find any images or descriptions in the literature of such an occurrence. On the contrary, images of radiopharmaceutical extravasations commonly show areas of infiltration with edges that are not well-defined. For example, Arveschoug et. al(*1*), report on a case of [^{177}Lu]Lu-DOTATOC extravasation which included the transverse SPECT/CT image shown in Figure 1.

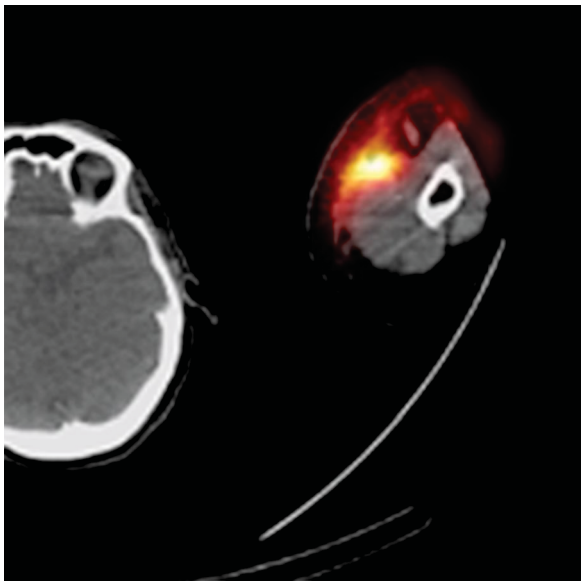


Figure 1. An extravasation of [177Lu]Lu-DOTATOC as imaged by SPECT/CT showing diffuse transition from areas of high activity to low.

The extravasation image shows one area within the arm with significantly more activity present than other areas. However, the transition between high activity and very low background tissue activity is gradual—just as would be expected from concentration-based diffusion within tissue.

With respect to biological clearance of activity trapped between layers of tissue, published images are also not supportive. In a case report published by Kiser et. al(*2*), an area of higher activity is visible extending beyond the initial extravasation site (Figure 2). The location and shape are consistent with drainage through the lymphatic vessels.

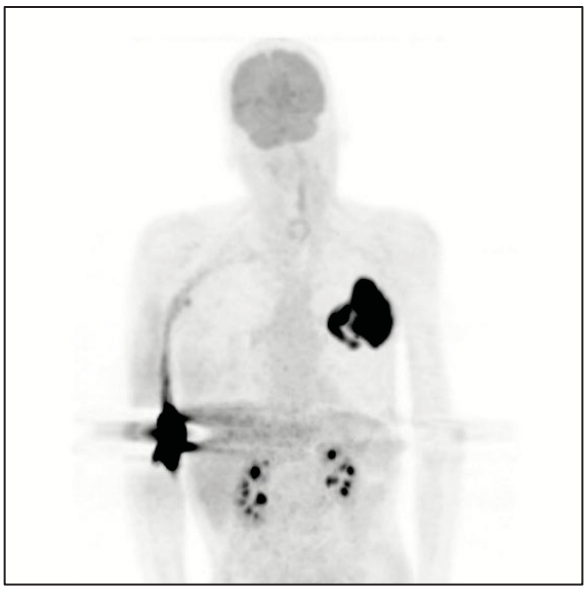


Figure 2. An 18F-FDG PET image that shows clearance of extravasate and uptake within an axillary lymph node.

Yucha et. al, published results of a study(*3*) designed to analytically characterize intravenous extravasations. In the study, arm tissue was intentionally infiltrated with saline using a method consistent with cephalic vein extravasation. The authors recorded induration measurements and magnetic resonance imaging was used to quantify the amount of infiltrate remaining at the IV site. Of particular significance to the question of "pocket" extravasations, the authors stated that,

> *"Immediately after infiltration, there were clearly definable borders of induration noted on visual inspection. Most often, the infiltrate assumed a circular shape. After 20 minutes, the borders became unclear and accurate measurement was difficult. After 40 minutes it was impossible to accurately judge the borders of the infiltrate. The infiltrate appeared to be totally resolved within 1 hour."*

Similarly, work by Fisher et. al, shows that direct injection into tissue will result in dispersion of the injectate throughout that tissue(*4*). Through direct tumor injection of a therapeutic radiogel composite material, they showed that "…activity distributed interstitially rather than vascularly." I contacted Dr. Fisher, the lead author of the study and asked about the ACMUI subcommittee's "pocket" extravasation hypothesis. He replied,

> *"I read the ACMUI explanation on bolus (or pocket) extravasation, and I think it could occur, but if so, rarely. The fast assimilation of injectate into tissue, the observed interstitial distribution, and personal experience with direct interstitial administration argue against the bolus or pocket distribution theory. For about 25 years, I have been injecting mice, rabbits, cats, and dogs with a radiopharmaceutical comprising a polymer solution in phosphate buffered saline as the injectate carrier for 1-2 micrometer yttrium phosphate microparticles. I and my colleagues have shown that direct interstitial injections infiltrate tissue, displacing extracellular fluids, with fluid clearance via the lymphatic system. I have PET/CT and microCT images confirming such interstitial biodistribution, thus we have rejected outright the bolus or pocket distribution theory. In my view, the appropriate terms are infiltration and assimilation by natural processes, together with redistribution and clearance."*

Finally, if the "pocket" extravasation hypothesis were accurate, subdermal lymphoscintigraphy procedures would not be possible as the injectate would, in fact, not be cleared through the lymphatic system as required. According to EANM and SMMI Practice Guidelines(*5*),

> *"Widely used techniques include peritumoral, subdermal, periareolar, intradermal, and subareolar injections. All enable axillary SLNs [Sentinel Lymph Nodes] to be identified accurately, and satisfactory SLN detection rates have been reported for all injection approaches. Results of multiple studies have confirmed that the method of injection does not significantly affect the identification of axillary SLNs."*

From investigations of dosimetry following radiocolloid injections, Bronskill reported(*6*) that,

> *"Radiation dosimetry for IRL [interstitial radiocolloid lymphoscintigraphy] applies to the general problem of interstitial deposition of radioactivity in a site from which it is slowly cleared. Extravasation of intravenous injections for routine nuclear medicine procedures also falls into this category."*

Bronskill goes on to describe asymptotically increasing measurements of the injection site distribution over time—a phenomenon which would not occur in the case of a "pocket" extravasation.

Dosimetry Calculation

The subcommittee members state that the self-absorption of "pocket" extravasations will result in a significantly lower energy absorbed fraction within surrounding tissue. Within the context of the discussion, it is safe to assume that their implication is that the resulting dose to surrounding tissue could never rise to the level of the medical event reporting threshold of 0.5 Sv. Since no representative calculation of energy absorbed fraction or tissue absorbed dose was provided, I have performed Monte Carlo simulations to test the idea.

Using the GEANT4 Application for Emission Tomography (GATE) Monte Carlo framework[3], I simulated a spherical source volume of water containing 1 mCi of ^{18}F ions distributed uniformly. The source volume was surrounded by water in which all interaction events were recorded. From the 1 mCi of source activity, energy deposited per unit time (MeV/mCi•sec) within various volumes of a spherical shell surrounding the source volume (Figure 3) was calculated and converted to units of absorbed dose (Gy/mCi•sec). Based on the above discussion, it was assumed that a "pocket" extravasation would undergo no biological clearance, thus the time-integrated activity calculation incorporates only the physical half-life of the isotope (109.7 min). Table 1 details the values I calculated for total absorbed dose to tissue surrounding a "pocket" extravasation.

As shown in Table 1, an extravasation of only 1 mCi of ^{18}F-FDG would result in 0.52 Gy of tissue absorbed dose within the 5 cm^3 surrounding the "pocket" extravasation.

According to published methods(*7*), the 5 cm^3 source volume itself would receive approximately 2.7 Gy, so the subcommittee members are correct in stating that the energy absorbed fraction for surrounding tissue would be lower in cases of "pocket" extravasation. However, their implication that tissue absorbed doses would be negligible is unsubstantiated by these dosimetry calculations.

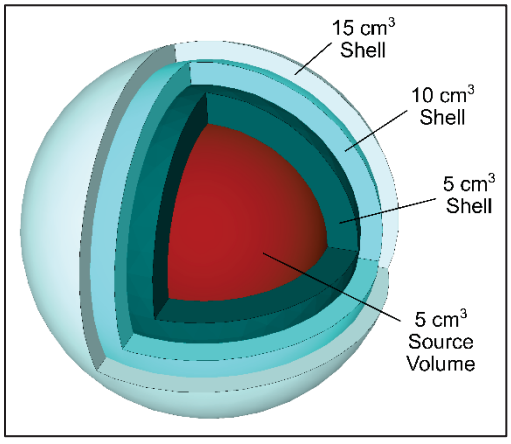


Figure 1. A cut-away view of the source volume and shells surrounding it used for simulation.

Table 1. Monte Carlo simulation results.

Tissue Shell Volume(cm^3)	Absorbed Dose per Unit Activity Extravasated (Gy / mCi)
5	0.52
10	0.40
15	0.33
20	0.29
25	0.26
30	0.23
35	0.21
40	0.20
45	0.18
50	0.17

[3] http://www.opengatecollaboration.org/

Conclusion

The purpose of this work was to investigate the hypothesized "pocket" extravasation mechanism proposed by members of the ACMUI's Extravasation Subcommittee. Through an analysis of nuclear medicine imaging and lymphoscintigraphy, I have shown that the mechanism of action proposed by this hypothesis is highly unlikely. Furthermore, I have shown through Monte Carlo simulation that while the absorbed dose to surrounding tissue for cases of "pocket" extravasation would be lower, the medical event reporting threshold of 0.5 Sv is still achievable even for relatively minor extravasation of certain radiopharmaceuticals.

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SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

August 31, 2021

Kelly Jamerson
Nuclear Regulatory Commission
Submitted electronically to Kellee.Jamerson@nrc.gov

Dear Ms. Jamerson:

On behalf of the Society of Nuclear Medicine and Molecular Imaging (SNMMI),[1] I appreciate the opportunity to comment on both the Advisory Committee for the Medical Uses of Isotopes (ACMUI) Subcommittee on Extravasations' draft report and the Nuclear Regulatory Commission (NRC) Staff's Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting. The regulatory treatment of nuclear medicine extravasation is a very important issue in our field with the potential impacts affecting the availability of nuclear medicine services for decades to come.

After the petition for rulemaking (PRM-35-22) was filed, SNMMI responded first with a position statement and with additional comments later in the year. The Petitioner, the manufacturer of a device used to measure extravasation of radiopharmaceuticals, filed a petition seeking NRC rule changes to its benefit and the public's detriment. There are approximately 20 million nuclear medicine procedures performed annually in the US with no evidence of significant patient harm from extravasation of these radiopharmaceuticals. Additionally, a systematic review of more than 3,000 reported cases of extravasation of diagnostic radiopharmaceuticals (world-wide) revealed that only 3 cases resulted in patient symptoms that required follow-up.[2] This outstanding level of safety supports the effectiveness of current regulations coupled with qualified medical practitioners.

To summarize our position, the reporting of nuclear medicine extravasations is a practice of medicine issue and not a patient safety issue. Therefore, extravasations are best managed on an institutional level at the discretion of the authorized user and do not require additional NRC regulation. SNMMI recognizes the effect that extravasation of diagnostic radiopharmaceuticals may have on the quality of diagnostic images, particularly on quantitative studies, and is actively addressing this as the quality-control issue that it is, rather than a patient safety issue.

[1] SNMMI's more than 15,000 members set the standard for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals and meetings, and leading advocacy on key issues that affect molecular imaging and therapy, research, and practice.

[2] van der Pol J., Vöö S, Bucerius J., & Mottaghy F.M. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. (2017). *Eur J Nucl Med Mol Imaging. 44*(7), 1234-1243. doi: 10.1007/s00259-017-3675-7. Epub 2017 Mar 16. PMID: 28303300; PMCID: PMC5434120.

SNMMI appreciates the NRC putting forth qualitative (non-dose-based) options and focusing medical event reporting on the extremely rare and clinically significant extravasations. Conversely, a quantitative medical event reporting mandate would result in widespread clinical, financial, and professional burdens on healthcare providers and the field of nuclear medicine without benefit to patients. Such a quantitative policy would almost certainly limit access of patients to life-saving nuclear medicine procedures. It is also important to note that the Petitioner's tool uses non-standard dosimetry to determine if extravasations should be reported to the NRC. In fact, the tool has not been endorsed by physician societies and radiation physics organizations. Hundreds of healthcare organizations opposed the manufacturer's proposed rule change in their public comments to the NRC.

Therefore, after reviewing both reports, while we feel the current regulations are assuring patient safety, the SNMMI recommends Option 6, a non-dose-based option with a higher and more clearly-defined threshold for medical event reporting than Option 4 (the other non-dose-based option).

Option 6 would require medical event reporting of extravasations determined by a physician to meet the significant harm standard of 10 CFR §35.3045(b). Though the ACMUI Subcommittee on Extravasations recommends Option 4,[3] SNMMI has the following concerns about this option:

A. The phrase "medical attention" is ambiguous. Taken to the extreme, "medical attention" could conceivably include basic IV access care (e.g., compresses, etc.) for temporary injection site bruising, erythema or swelling. If Option 4 is to be seen as a viable option, the manner and intensity of "medical attention" that would trigger medical event reporting requirements must be clearly defined.

B. The injury assessor should be a physician with radiation medicine expertise (i.e. an Authorized User (AU) or AU-eligible physician) who can differentiate normal injection site changes from radiation-caused damage. Option 6 would provide for this physician determination of harm standard whereas Option 4 does not specify the qualifications for the "radiation damage assessors."

C. Option 4 would require further rulemaking to create a new Medical Event type. Alternatively, Option 6 may likely be implemented through sub-regulatory policy as the language already present in 10 CFR §35.3045(b)[4] does not specifically exclude extravasations.

[3] Option 4 would require reporting if "a patient requires medical attention due to skin damage near the administration site, and the damage is determined to be caused by radiation."

[4] "A licensee shall report any event resulting from intervention of a patient or human research subject in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician."

SNMMI appreciates the ACMUI and NRC's consideration of this statement. Though we hope the ACUMI aligns themselves with Option 6, we are also open to supporting Option 4 if amendments addressing our concerns in A and B (above) are made. As always, we are ready to discuss any of these comments or to meet with the NRC on the above issues. In this regard, please contact Julia Bellinger, Director of Health Policy at jbellinger@snmmi.org or (703) 326-1195.

Respectfully Submitted,

Richard L. Wahl, MD
President, SNMMI

PATIENTS
FOR SAFER NUCLEAR MEDICINE

August 31, 2021

To Whom It May Concern:

We contact you on behalf of nuclear medicine patients across the United States to respectfully ask the Nuclear Regulatory Commission to adopt the recommendations made in the petition in Docket: NRC-2020-0141. We believe that patients, their physicians, and the NRC should all be made aware of radiopharmaceutical extravasations that exceed the medical event reporting limit.

The Patients for Safer Nuclear Medicine Coalition is comprised of numerous advocacy organizations, across several therapeutic areas, representing thousands of patients across the US. We are dedicated to ensuring the safety of nuclear medicine procedures, which are commonly used to support cardiology, neurology, cancer, and many other types of patients.

Radiopharmaceutical extravasations can inadvertently irradiate patient tissues with doses that far exceed the reporting limit (0.5 Sv) and the threshold that the nuclear medicine community says will lead to adverse tissue reactions (1.0 Sv). We also know that these significant extravasations that exceed the reporting limit happen far more often than they should, even though they are preventable.

In addition to contributing to injury, significant extravasations can also lead to misdiagnosis and incorrect course of treatment for patients. When it comes to cancer, for example, a significant extravasation can compromise diagnostic images, leading to a misdiagnosis that can take a patient down the wrong treatment path. Similarly, when it comes to cardiology and neurology patients, a significant extravasation can lead to doctors making decisions for treatment based on inaccurate images. The idea that information regarding a significant extravasation should continue to be kept from the patient and their physician is simply unacceptable.

We further believe the NRC should be aware of significant extravasations. The agency is responsible for protecting patients during procedures involving the use of isotopes. Unfortunately, the current problem is compounded by a lack of reporting. There is no way to address this serious issue when information is incomplete or unavailable in the first place. Patients have the right to know which nuclear medicine centers have issues in the proper administration of medical isotopes.

By adopting the recommendations included in the petition in Docket: NRC-2020-0141, we can begin to tackle this serious problem while continuing to make strides forward in the diagnosis and treatment of patients. On behalf nuclear medicine patients, we thank you for considering our request.

Sincerely,

The Patients for Safer Nuclear Medicine Coalition

From: drwpeddoc@aol.com
To: Jamerson, Kellee
Subject: [External_Sender] Comments on the extravasation issue
Date: Tuesday, August 31, 2021 12:36:38 PM

I am a practicing physician with a deep understanding of the topic of extravasations. I have patients who have had nuclear medicine studies and have accompanied family members who required nuclear medicine diagnostic procedures. I appreciate that the NRC is studying this issue and for allowing me to comment. I believe the NRC has identified a serious problem and has the opportunity to limit unintended and unnecessary radiation exposure for millions of Americans. I doubt there is another situation where just requiring an industry to follow best practices could reap so many benefits.

It is undisputed that radiopharmaceuticals are being administered incorrectly in far too many cases. Call it what you will, when these radioactive materials do not go in the vein cleanly, it means something was not given as intended. Institutions that have tracked extravasations and focused on fixing the problem have improved their rates to levels much lower than what is occurring and accepted today. The assumption that the majority of these extravasations are trivial and do not cause harm is unproven and should not be accepted by the NRC.

The ACMUI's response is embarrassing, but not unexpected. As a physician who interacts with scores of patients face-to-face every day, I am offended by the ACMUI's attempts to evade telling patients that they have inadvertently received a high dose of radiation to their tissue as a result of an extravasation. Patients deserve and appreciate transparency in all their interactions with physicians. I have read their past statements on the issue and at least they are consistent. Their goal in this process has been to avoid regulation, not to improve safety. Concerning extravasations, they have misled the NRC in the past and are trying to do so again. Now that the NRC is aware of the extent of the problem, the ACMUI seeks to limit oversight rather than provide a plan that would improve the safe administration of radiopharmaceuticals.

The NRC has the responsibility of assuring the safe administration of these radioactive materials. The NRC is aware that these materials are being incorrectly administered on a frequent basis. After reviewing the NRC medical staff's preliminary findings, Option 2 is the option that patients and referring physicians need enacted now, not months from now.

The regulatory burden of addressing this issue is limited by the institutions themselves. As they lower their extravasation rates their burden decreases. The 40-year pass that has been given for not reporting extravasations has meant that these institutions have ignored the issue. The opportunity to lower the rate by improvement in training, use of technology and different materials has always been there, but has never been consistently implemented by most centers. That regulation is necessary to address the issue is a sad state of affairs, but is not a reason to avoid regulation.

The NRC is aware that institutions could dramatically improve their rate of misadministration if they focused energy into the effort. I encourage the NRC to expeditiously enact regulations that force them to do so. Failure to do this is a failure to protect patients.

Sincerely,
Rob Williams, MD

New Day
FOUNDATION
FOR FAMILIES FIGHTING CANCER

In Honor of Matt Kell & Cathy Spehn

245 Barclay Circle, Suite 300, Rochester Hills, MI 48307 • FoundationForFamilies.org
A 501(c)(3) Non-Profit Organization • Tax ID# 26-0609040

August 10, 2021

Dear Kellee,

I am contacting you on behalf of cancer patients throughout Michigan to ask for your help. A petition in Docket: NRC-2020-0141, now before the NRC, includes recommendations regarding radiopharmaceutical extravasations that exceed the reporting limit. I support this petition.

It is estimated that an extravasation occurs once every 56 seconds in the U.S. Surprisingly, patients do not have to be informed when this happens. Neither do their physicians, nor the NRC for that matter. I hope you will agree that this policy needs to change. Simply put, patients have a right to know about medical procedures that directly impact them.

My stake in this issue is deeply personal. I started the New Day Foundation for Families in 2007 with my husband Michael. We both lost our first spouses to cancer, giving us an intimate understanding of the emotional and financial toll cancer takes. New Day Foundation is committed to helping those with cancer navigate the financial and emotional burdens.

I know how hard it is. I have been there. That is why I am asking you to take action that can help ease the burden on cancer patients. A reporting requirement for extravasations – which are preventable – will help shed light on the issue, keep patients and their doctors better informed, and help ensure the course of treatment presented to a patient is the best available option.

The current problem is compounded by a lack of reporting. There is no way to tackle this very serious issue when information is incomplete.

Thank you for your time and attention. I hope you will seriously consider supporting the petition in Docket: NRC-2020-0141 and help cancer patients feel more secure as they navigate what can be an overwhelming process of diagnosis and treatment. Please feel free to contact me with any questions.

With hope and gratitude,

Gina Kell Spehn
Co-Founder and President

August 30, 2021

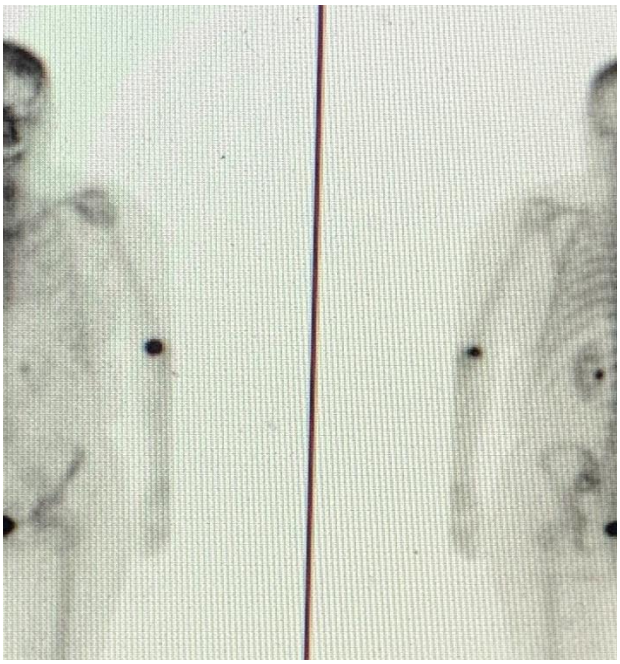
Dear Chairman Hanson, Commissioner Wright, Commissioner Baran, and Ms. Jamerson,

On July 11, 2021, I sent you comments intended for an upcoming NRC ACMUI meeting on radiopharmaceutical extravasations. As you may recall, I expressed the patient perspective regarding the effects of radiopharmaceutical extravasations. I shared my disappointment in the attitudes of clinicians to these medical errors and also questioned their understanding of the radioactive drugs they are using. I also challenged the NRC to survey authorized users with questions that would shed light on the real issue.

Unfortunately, later that month, I was extravasated myself during a nuclear medicine procedure. I would like to explain what happened and then comment on the recent meeting material that the NRC medical staff and the ACMUI posted online in advance of the postponed July 15 meeting that is now scheduled for September 2.

As I mentioned in my previous letter, I am a metastatic breast cancer patient. As a result, I also am a regular nuclear medicine patient. During my latest round of imaging, I was extravasated during a bone scan procedure. During the injection of 22.5 mCi of 99mTc MDP, I felt an unusual sensation. I noticed it because it felt different from previous injections I have had. I immediately suspected that I had been extravasated, only because I know a lot about this issue. I would guess that most patients would not have suspected extravasation, since they don't even know what an extravasation is. I asked my technologist and suggested she had just extravasated me. Even though I am well-versed in this issue, I didn't quite know what to do. Neither did my technologist, which surprised me. My care is provided by a leading academic center in the United States. Finally, I asked the technologist how do I know that the injection is in my vein? After examining the site closely, she noticed a slight swelling and decided to image my arm right then. She removed my IV and we went to a camera and imaged the arm and sure enough I was extravasated. She then imaged my other arm and saw activity indicating some of the MDP had made it into circulation.

As I mentioned, patient advocacy is my vocation. But I admit that I did not consider what to do next. I should have asked the technologist to try and mitigate the amount of absorbed dose my tissue would receive. But I didn't. As a result, no additional flushing with saline was done to disperse the radioactivity. No warm compress was provided to try and increase blood flow. No massage was done. I was not told to raise my arm or move my arm to try and increase vascular flow. Even though I had attended the May 2021 webinar when vascular access experts explained mitigation, I did nothing. More disappointing to me was that the technologist did nothing. She just wrapped up the procedure and I waited several hours for my imaging. The following day, I had another imaging procedure. I requested a vascular access expert use an ultrasound device to guide the access procedure. Same arm, different vein. No extravasation. The image from that procedure was flawless, but as you can see, my bone scan was not flawless. I have attached cropped versions of my images for your consideration.



What was the absorbed dose to my arm tissue? Why did mitigation not happen? Why did I not receive any instructions on what to look for in the days or weeks to come. I know that the energy emissions from 99mTc will not likely reach my skin, so I shouldn't expect to see skin damage, but what is happening to my tissue? When I reviewed the questions I asked you in my previous correspondence, I can now answer some of them about the center that performs my nuclear medicine procedures.

- My center does not actively monitor injections. As a patient, I had to suggest that I had been extravasated.
- My center takes no steps to mitigate the radiation dose when they extravasate.
- My center obviously does not know what threshold should be worrying, since they didn't bother to perform dosimetry to assess my absorbed dose and compare it to a threshold.
- While the extravasation was noted on my radiology report, perhaps because I brought it to the attention of the technologist, there is no estimation of the dose to my tissue from the extravasation in my medical record.
- I am requesting that my oncologist ask for a nuclear medicine physician to compare my July extravasated bone scan image quality to my April not extravasated bone scan image to see if they think I should repeat the procedure.
- I was not followed by anyone in nuclear medicine to see if I have had any adverse tissue reactions.

Unfortunately, I am experiencing adverse tissue reactions. In the days and weeks that followed this extravasation, the injection site has been painful. In fact, the pain woke me up at night. Even worse, extreme fatigue is one side effect of my current treatment for my cancer and now my sleep has been affected by a preventable misadministration of a radioactive drug. And I still don't know how much damage that isotope has caused to my arm tissue. I understand it could be weeks or months or even longer for that to show up and frankly, I have more important things to worry about.

Since I was registered for the upcoming NRC/ACMUI meeting, I received notification that the September 2 meeting material was available online. Now, my disappointment with clinicians and the ACMUI regarding extravasations extends also to your organization.

On April 1, 2021, the NRC medical staff submitted a report on their preliminary findings to the ACMUI subcommittee on extravasations. I have several concerns from a patient perspective.

The NRC staff states that the purpose of the regulation is "to reduce unnecessary radiation exposure to patients" and that the purpose of medical event reporting is "to identify the causes of events in order to correct them, prevent their recurrence, and allow the NRC to notify other licensees of the events so they too can avoid them." They go on to say that "Medical events may not necessarily cause patient harm, but the NRC requires their reporting because they have the potential to cause harm and they may indicate a potential problem with how a medical facility administers radioactive materials or radiation from radioactive materials." Yet, the rest of the report appears focused on finding excuses why the NRC should allow the community to continue to avoid addressing extravasations. Let me be clear what a patient thinks:

- A center that routinely extravasates is more likely to have significant extravasation than a center that rarely extravasates at all. It is important that patients are aware of which centers extravasate frequently and which centers rarely extravasate.
- Extravasations are not routinely caused by patients – the NRC should know this by now! We are the same patients who undergo chemotherapy and contrast CT injections. Those nurses or technologists have to undergo infusion training. They have to be observed gaining access by trained vascular access experts. They have to prove their skills again to trained vascular access professionals annually. Technologists do not. Nor do they have to report when they make a mistake. Extravasations are caused by technologists who do not use the latest technology, do not employ the proper technique, and who do not have the requisite training. Ultra sound guided techniques are available and should certainly be used when radiopharmaceuticals are involved. Stop blaming me for my extravasation. Stop blaming patients
- Standardized uptake values do matter. My oncologist waits for my SUV measurements to help guide my treatment. Incorrect quantification is unacceptable when it can be eliminated. Nuclear medicine physicians can talk all they want about the variability of these values (some caused by extravasations), but patients, medical oncologists, and radiation oncologists use these quantitative values. I think Cardiologists use quantification, too.
- Doses greater than 0.5 Sv or absorbed doses of more than 0.5 Gy, need to be reported. My tissue and my skin should not be getting any dose more than what it gets when my administration is done properly. The NRC has already determined that 0.5 Sv is the right reporting threshold. It may not cause harm, but it does indicate a potential problem. If a center is constantly extravasating and irradiating patient tissue with 1-2 Sv then something is wrong at that center. And the higher the absorbed dose the greater the chance a patient can develop cancer down the line. Furthermore, I would not want my imaging procedure to be done there.
- I have met with the Chairman of the OAS. The OAS is not skeptical about extravasations; they know that extravasations should be reported and want the NRC to eliminate the reporting exemption, period. Please ask the OAS board to confirm.

Many of the options that your staff listed for the consideration of the ACMUI scare me. It is hard to believe that the staff would even list a *no action* option or a *permanent functional damage* option. Other options mention excluding diagnostics, worrying about regulatory burden of a center that routinely extravasates with doses greater than 0.5 Sv, not performing dosimetry on extravasations like mine, asking patients to be responsible for self-reporting when most of them have no idea what has happened to them, asking physicians to subjectively assess extravasations (have you seen the clinicians' comments to the petition?), suggesting extravasation doses less than 10 Gy be ignored, or mentioning financial burden when centers already spend lots of money to provide quality in all other aspects of the procedure are just a few examples that make it clear that your staff is not following the medical policy statement.

I have read the ACMUI positions for the past few years and even back to 2008 and 2009. I have read the clinician comments to the NRC. The community is not going to voluntarily address this issue. A regulatory option is needed. Let me suggest the option patients care about. We want an option that will ensure our technologists are trained to the same level as chemotherapy infusion nurses and also trained on mitigation steps in case they extravasate. We want an option where our administrations are monitored. We want an option that lets us know immediately if we have been extravasated. We want the option that makes centers perform dosimetry on extravasations, so we know how bad the extravasation was and whether or not we should reimage and whether or not we will have a tissue reaction later. We want an option that makes centers check on us and not send us home without instructions on what to do if symptoms develop. We want an option that drives centers to stop extravasating.

It is extremely disturbing for a patient to see an organization whose goal is to prevent unintentional irradiation of patients, allowing extravasations to continue. This issue is so simple to patients. We do not want to be extravasated. But when it happens, we want to know. Centers that routinely extravasate and ones that routinely extravasate really large amounts of radioactivity need to stop. This is the role of the NRC. I hope my message gets delivered to your staff. Thank you so much for considering my request.

Sincerely,

Pam Kohl

July 11, 2021

Dear Chairman Hanson, Commissioner Wright, and Commissioner Baran,

My name is Pam Kohl. Thank you for providing this opportunity to comment on the topic of radiopharmaceutical extravasations. I am a metastatic breast cancer (MBC0 patient. I am involved with several MBC groups and as a result I am a very-well informed breast cancer advocate. I have written the NRC before and also submitted a comment for a recent petition to make the reporting of significant extravasations required just like any other misadministration that meets medical event reporting criteria.

Recently, I participated in a webinar on the topic of radiopharmaceutical extravasations, sponsored by AltusLearn. I provided the patient perspective. As part of this webinar, I was fortunate to work with several other presenters. Dr. David Townsend, the co-inventor of the PET/CT scanner, described the physics of how an extravasation negatively affects a camera image. I believed him. Dr. Jackson Kiser then showed how an extravasation absolutely affected his ability to interpret images. As a cancer patient, who relies on my PET/CT scans to help assess my treatments and guide my care, this was sobering to hear. Dr. Darrell Fisher, who used to be a member of the ACMUI, then precisely described the energy emissions of isotopes that are routinely used to assess my treatment. He made it perfectly clear that if these isotopes are extravasated, patients can receive very high radiation doses to their tissue. Dr. Marjan Boerma then discussed how ionizing radiation actually affects healthy tissue and how these effects can often take weeks or months to be discovered. The final two presenters were Nancy Warden and Stephen Harris, two nurses who gain venous access for a living. They are experts who are called when hospitals struggle with certain patients. I am one of those patients and it is not unusual for my clinical team to stick me several times as they try to gain access or before calling for help. Nancy and Stephen described their experiences with nuclear medicine patients and shared an example of a diagnostic and a therapeutic extravasation that harmed patients.

This experience made me think hard, especially when I continue to see comments from the medical societies that are very distressing. In a recent Health Imaging article, the American College of Radiology was quoted as saying that significant extravasations are “inconsequential.” I can assure you from the patient perspective, this position is not only wrong, but also insulting. This is the same group that publicly commented that there is nothing inherently harmful in a radiopharmaceutical administration. In this same Health Imaging article, the Society of Nuclear Medicine and Molecular Imaging assured the writer that significant extravasations are not a patient safety issue. How can the society representing nuclear medicine not understand the patient consequences of dumping radiation into the tissue? It makes me wonder if these clinicians truly understand the nature of the drugs they are using. Hopefully, none of these commenters are authorized users of radioactive material.

As I think about the countless nuclear medicine procedures I have experienced, I consider another point that Dr. Townsend made in the webinar. He described in great detail all the quality control efforts that are routinely performed to ensure the quality of nuclear medicine procedures. He noted that the one area of the imaging process that has the potential to have a very large impact on quality is the administration of the radiopharmaceutical, but that he was not aware of any routinely used quality assurance efforts for this process. He is right. In all my procedures, I was not aware of any monitoring of the quality of the administration.

And this leads me to the main reason I am addressing you today. Reflecting on the points from the webinar and all I know about this topic, I have assembled some questions. I think these questions should be sent to every authorized user and they should be required to respond. This will allow the NRC to better understand the issue.

1. What is the frequency of diagnostic and therapeutic radiopharmaceutical extravasations at your institution?
2. In determining these extravasation rates, does your institution actively monitor the administration process with a method that can know for sure if an extravasation happens or does your institution review images later to assess the quality of nuclear medicine administrations today?
3. If your institution actively monitors nuclear medicine administrations today,
a. what process is used to confirm that the administration was ideal or extravasated and are these processes different between diagnostic and therapeutic administrations?
b. when extravasation is identified, at what time in the administration process do you know of an extravasation is happening?
c. what steps are taken to mitigate the effects of a diagnostic extravasation? A therapeutic extravasation?

4. If your institution monitors nuclear medicine administrations today by reviewing images sometime after the procedure,
a. what percentage of diagnostic images (including all nuclear medicine procedures) capture the injection site in the imaging field of view?
b. does your institution image the injection site after therapeutic administrations?
c. when the injection site is not included in the field of view or imaging is not performed post therapeutic administration, how does your institution determine if the administration was extravasated?

5. At your institution, what specific tissue dose and skin dose thresholds are considered harmful (possibly leading to adverse tissue/skin reactions) to the patient? Are the clinicians aware of these limits?

6. What dosimetry method is used to measure the dose to tissue/skin at your institution? Does this method capture the biological clearance of extravasations? If so, how is this done?

7. If patients receive a tissue/skin dose higher than what your institution has determined will lead to adverse tissue/skin reactions,
a. are the extravasations and the estimated dose to tissue included in the patient's electronic health record?
b. is this information also shared with the patient and their referring physician?
c. how long are patients followed for the delayed radiation injury effects?
d. Are these reported to the FDA as adverse events or are they reported to Joint Commission as a sentinel event?

8. What percent of diagnostic extravasations at your institution require repeat imaging? What percent of therapeutic extravasations require repeat administration to ensure the target received the prescribed dose?
a. What is the process to determine whether or not the procedure should be repeated?

b. How are the costs of these repeat procedures addressed?
c. If the patient or a payer does not pay for the repeated procedure isn't there a financial disincentive for the institution to repeat the procedure?

9. What role does your institution's radiation safety committee play in nuclear medicine extravasations?

10. Does your institution employ a quality improvement process for radiopharmaceutical administrations? If so, please describe how this process works and can you share the trending information over the past 3-5 years?

11. Do reports of radiopharmaceutical extravasation go to the same executive in your institution as CT, chemotherapy, or general floor IV extravasations? If not, where do these reports go?

12. Does the organization that accredits your nuclear medicine program analyze radiopharmaceutical extravasations? What specifically is audited when it comes to radiopharmaceutical administrations?

Thank you for considering this request.

Sincerely,

Pam Kohl
Pamkohl52@gmail.com
Raleigh, North Carolina

Cc: David Crowley, Chairman, Organization of Agreement States

THE PINK FUND
REAL HELP NOW

August 23, 2021

To Whom It May Concern:

I am a breast cancer survivor and founded an organization called The Pink Fund in 2006. The Pink Fund provides 90 days of non-medical financial aid to cover the basic costs of living expenses for those with cancer. Since its founding, The Pink Fund has made over $4 million in bill payments on behalf of breast cancer survivors in active treatment.

I am contacting you to ask for your help. I respectfully ask that you adopt recommendations in Docket: NRC-2020-0141 regarding reporting of radiopharmaceutical extravasations.

It is estimated that extravasations may harm up to 500,000 patients a year in the U.S. but does not have to be reported to the patient or entered into their medical record. An extravasation may affect the images of a PET/CT scan, which can lead to inaccurate staging of a cancer diagnosis and improper treatment. It is my belief that patients have a right to know about medical procedures that directly impact them.

A reporting requirement for extravasations will keep patients and their doctors better informed. Please support patients and require reporting of extravasations.

Thank you for your time and attention. Please feel free to contact me with any questions.

Sincerely,

Molly MacDonald
Founder, CEO
The Pink Fund
SurThrivor®
Crain's Detroit Business Notable Woman in Healthcare 2020
AARP Purpose Prize Fellow 2019/20
Northwood University Distinguished Woman Award 2019/20
Patient Champion Award North America eyeforpharma 2019

Venus Ginés, MA CHWI, and CEO/Founder,
14 Sunnyvale Lane, Manvel, Tx 77578 EIN#58-2577989
venusgines@gmail.com – 281-489-1111 www.diadelamujerlatina.org

September 3, 2021

To Whom It May Concern:

I am the founder of Día de la Mujer Latina, a non-profit (501c3) organization in the state of Texas and globally acknowledged for its successful outreach strategies within the Latino Community and I'm a breast cancer survivor.

On behalf of myself and the Latino community I serve, I ask the Nuclear Regulatory Commission to adopt the recommendations made in the petition in Docket: NRC-2020-0141. Patients, their physicians, and the NRC should all be made aware of radiopharmaceutical extravasations that exceed the reporting limit.

The use of nuclear medicine is an invaluable tool that helps with early detection and identifying the best courses of treatment. However, this tool can work against cancer patients when a significant extravasation occurs, including an inarguable impact on diagnostic images. This can hamper the ability to correctly diagnose and effectively treat cancer.

We believe strongly that a patient can only successfully advocate on her own behalf when she has as much information as possible about her diagnosis. By keeping information about extravasation from the patient and her doctor, you are harming the ability for this patient to receive the best possible counsel and treatment options available to her.

Your support of the petition will help drive attention to this little-known, but very serious medical issue and potentially contribute to a reduction in the number of significant extravasation cases.

The patients we serve already face what can be an overwhelming physical, emotional, and financial burden. A cancer diagnosis is an extraordinarily difficult and instantly life-changing event. These patients deserve to have all of the information about their condition. By adopting the recommendations made in the petition in Docket: NRC-2020-0141, the NRC will help cancer patients get the best possible care and treatment. Thank you for considering our request.

Sincerely,

Venus Ginés

Venus Ginés, M.A. P/CHWI
President/Founder, Día de la Mujer Latina® Inc

VASCULAR WELLNESS
ADVANCING HEALTHCARE. EMPOWERING NURSES.

July 9, 2021

Dear Chairman Hanson, Commissioner Wright, and Commissioner Baran:

We appreciate the opportunity to provide a written comment regarding the July 15, 2021, NRC/ACMUI meeting. We represent Vascular Wellness, a company focused on improving quality and safety in healthcare. Our nurse clinicians are experts in the general field of vascular access services focusing on the placement, support and education around ultrasound guided vascular access procedures including central venous catheters. We provide these services for hundreds of healthcare providers in the Southeastern United States including many hospitals. Through our work, we assist nuclear medicine technologists and recently became aware of the petition for rulemaking (PRM)-35-22.

We have reviewed the petition, the associated public comments, meeting transcripts, and peer-reviewed articles through the lens of our vascular access experiences. Since gaining vascular access is a process that is critical to the success of nuclear medicine imaging and therapeutic procedures, our knowledge and experiences make us uniquely qualified to comment on the merits of this petition. Other than our concern for patient care, we have no material vested interest in this matter. Our core business focuses on vascular access via central lines and central lines are not the primary means for vascular access for nuclear medicine imaging.

Extravasations are preventable
Extravasations are exempted from reporting based on the NRC belief that radiopharmaceutical extravasations are "virtually impossible to avoid." *This belief is absolutely incorrect!*
Radiopharmaceutical extravasations are almost completely preventable. As a result, extravasations that meet or exceed medical event reporting criteria should be reported like any other medical event.

Extravasations are not caused by patients
We place ultrasound guided Peripheral IVs (non-ultrasound guided PIVs being the primary approach for most nuclear medicine related vascular access procedures), Midlines, PICCs, Small Bore lines, and Large Bore lines including Vas Caths for Dialysis. Across all of these lines including the advanced procedures and acknowledging that we get contacted for the most difficult of cases, we still successfully gain proper access approximately 98% of the time. Given this, we firmly believe that *patients are not the cause of extravasations*.

Insufficient training, lack of appropriate tools, lack of policies, and inadequate monitoring of the administration process are the causes of high extravasation rates. In our experience, nuclear medicine technologists rarely use the tools and techniques that vascular access professionals train and rely on to prevent extravasations including the expert use of an ultrasound machine to provide needle visualization which forms the basis for our high success rates. Technologists seem to rarely monitor for whether extravasations occur. As a result, they are unable to stop an extravasation early in the process and mitigate the pernicious effects of ionizing radiation to patient tissue.

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Patient harm is not immediate, but comes later

While we are not dosimetry experts who can determine if a dose meets reporting criteria, we do recognize patient harm. In routine practice, we have seen numerous examples of the latent effects of ionizing radiation to tissue. While we understand that an improperly administered radiopharmaceutical results in detrimental effects to images that guide care and to the successful delivery of therapies, the harm we typically see is physical patient injury. We see disturbing adverse tissue reactions in patients of all ages including children. And these injuries usually begin to appear several days or many weeks after the radiopharmaceutical administration. The administering technologist, radiation safety officer, physicist, or interpreting physician are often completely unaware that an extravasation has happened and almost certainly will not see these injuries. But we see them and have non-personally identifiable information (PII) photos of multiple radiopharmaceutical extravasation injuries.

We do not believe that these cases are reported. Individuals who or organizations that claim diagnostic or therapeutic extravasations do not cause harm are misleading themselves and the NRC. Diagnostic and therapeutic radiopharmaceutical extravasations are real, disturbing, tissue-damaging cases that routinely happen every day.

Administering radiopharmaceuticals without proper training, tools, and monitoring represents an irresponsible handling of nuclear material that should be of immediate concern to the Nuclear Regulatory Commission. We encourage you to approve the petition immediately. This will lead to measuring and monitoring of a process that is critical to nuclear medicine and patient care. It will drive providers to improve their processes. The benefits of this effort far outweigh the costs. Preventing extravasations saves time and money and ensures that the nuclear medicine images and therapies are as good as they can be. Monitoring for extravasations ensures immediate mitigation to minimize absorbed dose. Prevention and monitoring efforts will help improve patient care and minimize wasteful spending on repeated imaging, ineffective treatments, and costs associated with inadvertent tissue irradiation. These are the right things to do for patients and for nuclear medicine.

If you are interested in learning more, we would welcome the opportunity to speak with you about this topic and to share the photos of real cases. Thank you for your consideration of our request.

Sincerely,

Nancy W. Williams, RN, VA-BC, BSN, MBA
Chief Clinical Officer & Chief Operating Officer

Alan R. Etkin, JD
President

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YSC YOUNG SURVIVAL COALITION

To Whom It May Concern:

Young Survival Coalition (YSC) strengthens the community, amplifies the voice and improves the quality of life of young adults affected by breast cancer. As an organization representing the voice of thousands of young adults diagnosed with breast cancer, we urge the NRC to adopt the recommendations included in Docket: NRC-2020-0141. We respectfully ask that you do whatever is in your power to support this action.

The use of nuclear medicine is an invaluable tool that helps with early detection and identifying the best courses of treatment. However, this tool can work against cancer patients when extravasation occurs, including an inarguable impact on diagnostic images. This can hamper the ability to correctly diagnose and effectively treat cancer.

We believe strongly that a patient can only successfully advocate on her own behalf when she has as much information as possible about her diagnosis. By keeping information about extravasation from the patient and her doctor, you are harming the ability for this patient to receive the best possible counsel and treatment options available to her.

Incidents of extravasation, while obviously harmful, are also preventable. Your support of the petition will help drive attention to this little-known, but very serious medical issue and potentially contribute to a reduction in the number of extravasation cases.

The patients we serve already face what can be an overwhelming physical, emotional, and financial burden. A cancer diagnosis is an extraordinarily difficult and instantly life-changing event. These patients deserve to have all of the information about their condition. By adopting the recommendations made in the petition in Docket: NRC-2020-0141, the NRC will help cancer patients get the best possible care and treatment. Thank you for considering our request.

Thank you for your attention to this very important issue facing the young adults we serve.

Sincerely,
Mary Farrell Ajango
Director of Community Advocacy and Partnerships

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Young women facing breast cancer together.