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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
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Ronald Lattanze
Chief Executive Officer

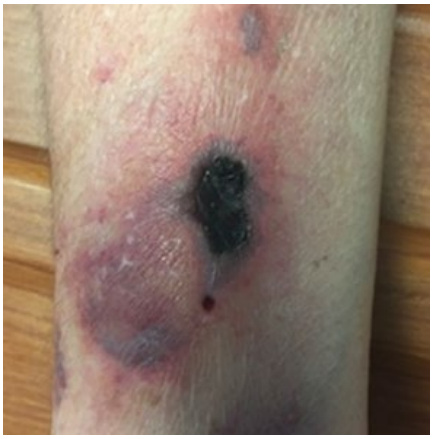
Appendix A – Analysis of the NRC findings and options and the ACMUI recommendations
Appendix B – Extravasation case studies
Appendix C – Analysis of the ACMUI "pocket" extravasation dosimetry analysis

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.



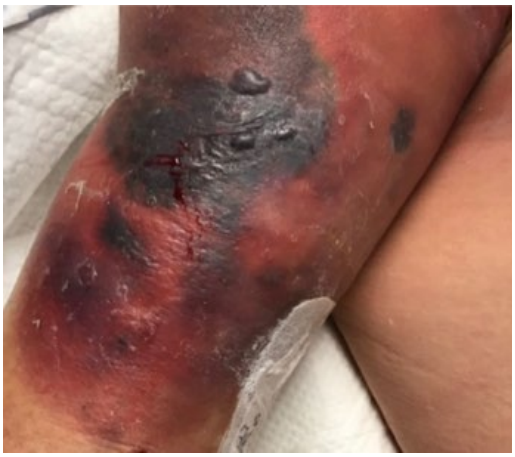
Yttrium-90 (^{90}Y) produces beta particles (average energy of 933 keV). When used as a therapy, its purpose is to kill cells. When extravasated, these beta particles travel 5-10mm while depositing their energy into the surrounding healthy tissue. The physical half-life of ^{90}Y is 64 hours—99% of the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

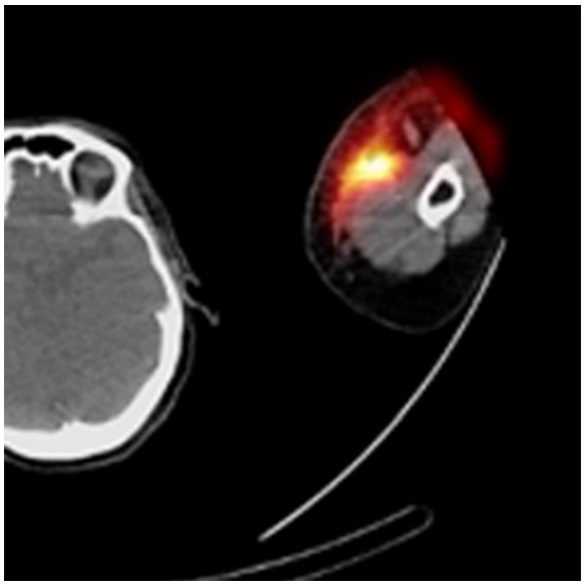


Figure 1. An extravasation of [177Lu]Lu-DOTATOC as imaged by SPECT/CT showing diffuse transition from areas of high activity to low.

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.

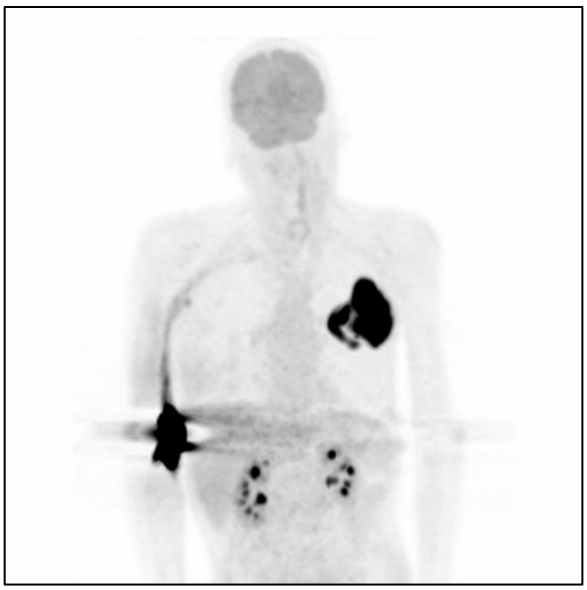


Figure 2. An 18F-FDG PET image that shows clearance of extravasate and uptake within an axillary lymph node.

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.

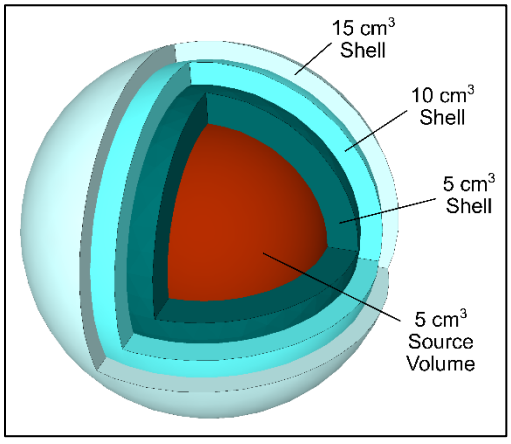


Figure 1. A cut-away view of the source volume and shells surrounding it used for simulation.

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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