U.S. Nuclear Regulatory Commission,  
Washington, DC 20555–0001  
ATTN: Rulemakings and Adjudications Staff  
Docket ID NRC–2022–0218

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) appreciates the opportunity to comment on the preliminary proposed rule language for a rulemaking on the reporting of nuclear medicine injection extravasations as medical events. We believe it’s important to share the medical expertise of SNMMI’s 15,000 members and to provide good data based on strong science.

The safety of our patients and the highest quality of care are our top priorities. Patients must have access to valuable nuclear medicine procedures. We also must ensure that patients who would benefit from nuclear medicine procedures are not apprehensive or resistant to safe, often lifesaving procedures because of “radiation paranoia” or a “chilling effect” that can result from misinformation. We support a harm based, rather than dose-based approach, as has been recommended by the NRC.

There are two new important and relevant studies. These studies demonstrate both the infrequency and lack of severity of extravasations in nuclear medicine. We are confident that the frequency of extravasations is not 3% - 23%, as has been discussed by the NRC. When looking back at the literature, studies with these results are largely based on small cohort studies which may apparently overestimate the incidence of these events with the small denominator of total patients. Newer large cohort studies are more likely to have data which is reliable.

In October 2022, the Journal of Nuclear Medicine, an independent highly regarded peer reviewed medical journal, published “Adverse clinical events at the injection site are exceedingly rare following reported radiopharmaceutical extravasation in patients undergoing $^{99m}$Tc-MDP whole body bone scintigraphy: A 12-year experience (Parihar AS, Schmidt L, Crandall J, et al. J Nucl Med. 2022; 63 (supplement 2) 2767).”

This study looked at 31,679 patient records retrospectively from 2010 to 2022.
“**Results:** Retrospective review of the records of 31,679 $^{99m}$Tc-MDP WBBS showed RPE documented in 118 studies (0.37%). Medical records were not retrievable for 22 patients, yielding the final cohort of 96 patients with reported RPE. The median follow-up duration was 18.9 months (IQR: 7.8-45.7 months). Short-term events were noted in four patients, of whom one was asymptomatic. Of the three symptomatic patients, two experienced mild discomfort at the injection site, and one had tender swelling. Three of the four events had a prior intravenous contrast extravasation for a contrast-enhanced computed tomography scan performed earlier during the day, and a $^{99m}$Tc-MDP injection later at the same site likely leading to RPE. None of the long-term local events had any plausible link with the RPE event.

**Conclusion:** Reported RPE were rare and short-term, local symptoms were observed in three patients (0.009%), all of which were likely related to the prior higher volume intravenous contrast extravasation. The smaller volume diagnostic RP injections for WBBS are highly unlikely to cause local symptoms on their own. No patient had any long-term adverse event with a plausible link to the RPE.


The primary objective of this study was to gain data on the frequency and significance of injection infiltration events in clinical PET/CT practice through quantitative analysis of 1000 subjects from 10 US imaging sites. The secondary objective was to gauge the true risk associated with dose infiltrations through detailed, anatomically specific Monte Carlo estimates of radiation dose to the highly proliferative epidermis, and the less radiation sensitive dermal and subcutaneous hypodermal tissues.

**Results:** In a 1000 patient multi-center investigation into frequency of infiltration events in PET, no infiltrations of >1% injected dose were found. The majority of visualized activities at injection site were external contamination, or injection apparatus.

Only 6/1000 injections had activities in excess of 6 μCi, none > 50 μCi. Frequency appears very low when cannula injections are used.

A first of its kind, skin dosimetry Monte Carlo model was developed and tested that includes the actual skin anatomy, which turned out to be critical in terms of dose distribution.

**Conclusion:** The risk of actual skin injury is significantly lower than implied in current literature due to the magnitude of beta dose absorption in the relatively radiation resistant hypodermis and dermis and sparing of the sensitive epidermis.
In addition, when referencing data on CT and MRI procedures, we would expect that our rate of infiltration would mirror that of CT or MRI since our technologists have similar training. A large cohort study of 502,391 injections yielded a rate of extravasation in CT and MRI was 0.11% (541/502391); the % was 0.13% during CT and 0.06% during MRI (Shaqdan K, Aran S, Thrall J, et al, Clin Radiol. 2014; 69:1264-72). This is more in line with the data from larger cohort studies in nuclear medicine. We feel that the estimates used by the NRC of 3-23% to be inflated.

It is also interesting that since the dawn of nuclear medicine many decades ago that we do not have data to suggest that increased cancer at sites of injection of diagnostic or therapeutic radiopharmaceuticals has occurred.

Clearly, it’s essential to minimize and work to prevent serious extravasation events, but accurate estimates of both frequency and severity are an important factor when deciding whether there is an immediate need for regulatory measures.

**Definitions:**

1. **What term should the NRC use (e.g., extravasation, infiltration) when describing the leakage of radiopharmaceuticals from a blood vessel or artery into the surrounding tissue?**

There remains inconsistency regarding the nomenclature surrounding what to call injected activity that inadvertently enters the tissue space. Historically, the terms infiltration and extravasation have been used interchangeably in nuclear medicine literature. However, in the general medical literature “extravasation” has a specific definition and refers to injectates that are vesicants – chemicals that are irritants capable of causing tissue damage. In context, this has typically meant they may be capable of causing blistering, tissue sloughing or necrosis. Although radiation can do this in high enough doses, in the diagnostic space, at least in PET, this does not seem likely, and so we would suggest the term infiltration be used when there is no reasonable expectation of tissue damage. Extravasation would be a better term to describe events where deterministic tissue damage actually occurs. With this differentiation, a clearer distinction between the seriousness associated with an injected radiopharmaceutical inadvertently entering the tissue space would be immediately clear.

2. **What criteria should the NRC use to define “suspected radiation injury?”**

This can be a difficult assessment. Not all radiopharmaceuticals are created equally.
In general, diagnostic radiopharmaceuticals would be expected to be exempted from this definition. More damage could be expected with therapeutic infiltrations, but even then there have been case reports of no clinically significant injury (Clin Nucl Med 2021;46: 144–145, Clin Nucl Med 2017;42: 639–640, Clin Nucl Med 2017;42: 639–640), though some have resulted in injury (J Nucl Med 2011; 52:1418–1422). We would refer the NRC to the recent SNMMI Board approved white paper related to best practices in the safe administration of radiopharmaceuticals. (Grady EE, Bartel TB, et al, Safe Administration of Radiopharmaceuticals: A White Paper Developed by the Society of Nuclear Medicine and Molecular Imaging Committee on Quality and Patient Safety. Under review for publication). In this paper, we suggest that if infiltration/extravasation of therapeutic radiopharmaceuticals is suggested that the infusion be discontinued, physician notified, confirmed via imaging, and evaluated for additional attention if needed.

3. **What techniques or methods should be included in the definition of ‘medical attention’?**

Medical attention should include evaluation by the authorized user for signs/symptoms which should indicate surgical evaluation such as swelling, numbness, blanched skin, tight skin, discolored/bruised skin, evidence of neurologic or circulatory impairment or moderate to severe pain in the suspected area (Eur J Nucl Med Mol Imaging. 2017;44:1234-1243). Appropriate referral to dermatology or surgical colleagues.

SNMMI supports reducing reliance on the patient to report adverse tissue reactions to an authorized user physician. We support licensees developing and implementing written safety procedures to prevent extravasations, which is already the case in most facilities. We do not support requiring a device to “detect” extravasations.

4. **What steps could the licensee take to minimize the chance of a radiopharmaceutical extravasation occurring?**

Like any drug, processes and procedures need to be in place to ensure safe administration. Having access to protocols specifically for injection of vesicant agents decreases errors and extravasations. Departments should review these procedures to ensure their clinical professionals are trained and aware of the specific therapeutic procedures to reduce errors. There is precedence for best practices and standardized procedures with chemotherapy.

We strongly suggest that the NRC regulations should avoid any clinical content regarding vascular access procedures, devices/catheter type and bore, monitoring methods, evaluation and follow-up methods which could have unintended consequences on patients’ health and safety, best practices from the SNMMI have already been developed in this regard.

5. **What steps should the licensee take when an extravasation is suspected or discovered?**
6. **What techniques, technologies, or procedures (e.g., post-treatment imaging, visual observation, patient feedback) should be used to help identify an extravasation during or immediately after a radiopharmaceutical injection?**

The treating physician/authorized user or their designee should evaluate the injection site physically as well as on post-therapy imaging (if able to be performed) to determine if an extravasation has occurred and may contact a physicist for measurement/relevant calculations as well as a dermatologist or surgical colleague for further evaluation.

7. **What techniques, technologies, or procedures (e.g., post-treatment imaging, survey measurement) should be used to better characterize an extravasation after radiopharmaceutical treatment?**

The treating physician/authorized user or their designee should evaluate the injection site physically as well as on post-therapy imaging to determine if an extravasation has occurred and may contact a physicist for measurement/relevant calculations as well as a dermatologist or surgical colleague for further evaluation.

Any radiation-attributable extravasation injury should meet the Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 for medical intervention. This is an NIH promulgated, nationally accepted metric leveraging the radiation expertise of AUs.
8. What information should licensees provide to nuclear medicine patients on how to identify an extravasation and how to follow up with their physician if they suspect a radiation injury?

Patients receiving diagnostic radiopharmaceuticals need not be concerned.

At the time of a radiopharmaceutical therapy, patients should be coached to alert the treating physician/AU and technologist or other nearby staff about potential discomfort at the site of injection. Should this occur, the site should be evaluated, and infusion stopped as warranted. In this event, patients should be coached to look out for swelling, numbness, blanched skin, tight skin, discolored/bruised skin, evidence of neurologic or circulatory impairment or moderate to severe pain in the suspected area. Additional imaging and further evaluation of this region should be performed as soon as suspected.

Patients who have uneventful infusions should not be concerned. If post-therapy imaging is performed, the site of injection can be further evaluated if included in the field of view. Coaching patients to be looking for symptoms after uneventful infusions may lead to unnecessary fear/concern about the radiopharmaceutical therapy. Patients should always have contact information for the facility for any post-therapy questions if they arise.

9. When should a reportable extravasation be counted as “discovered” for the purposes of notification (e.g., when medical attention is administered, when the physician identifies that the injury is from radiation)?

Medical attention is needed in the setting of swelling, numbness, blanched skin, tight skin, discolored/bruised skin, evidence of neurologic or circulatory impairment or moderate to severe pain in the suspected area of recent therapeutic radiopharmaceutical administration. Additional imaging and further evaluation of this region should be performed as soon as suspected. It should also be expected that any events determined to require notification be those that meet the Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 for medical intervention. This is an NIH promulgated, nationally accepted metric leveraging the radiation expertise of AUs. Otherwise, there may be many false positive reports, which would unnecessarily overwhelm the NRC.

10. The NRC requires that licensees notify the referring physician and the individual who is the subject of a medical event no later than 24 hours after discovery of the medical event. When should licensees be required to provide notification of an extravasation medical event to the referring physician and the individual?

If this meets the CTCAE grade 3 or 4 definition, 48-72 hours may be more appropriate for time
of discovery to reporting so the site can assess for localized washout of the therapeutic radiopharmaceutical has occurred as has been demonstrated in prior publications (Clin Nucl Med 2021;46: 144–145, Clin Nucl Med 2017;42: 639–640, Clin Nucl Med 2017;42: 639–640). In that event, it will likely be a clinically insignificant infiltration. We again highlight that not all infiltrations cause localized injury.

11. Who (e.g., patient’s primary physician, authorized user, nuclear medicine technologist) should be able to identify an extravasation that could result in a “suspected radiation injury?”

A licensed nuclear medicine technologist followed up by the treating physician/AU or their designee.

12. What topics should the NRC include in guidance to assist licensees to accurately identify, characterize, and report extravasation events in a timely manner?

We would again direct the NRC to the SNMMI white paper on this topic.

**Healthcare Inequities**

13. What regulatory actions could help ensure that extravasations in patients affected by healthcare inequities are accurately assessed and reported?

We are disturbed and concerned about the many healthcare inequities across the country. However, in the study, “Frequency and significance of injection infiltration and associated dosimetry in clinical PET/CT: A multi-center investigation” data was parsed on 1000 patients based on race. There was no meaningful evidence that infiltration rates or quantities were higher in darker skinned individuals.

14. Are vascular access tools and other technologies (e.g., ultrasound guided vein finders) likely to reduce the potential for an extravasation in all patients, particularly in patients of color?

Yes, but even with these tools extravasations can occur.

Thank you for your consideration of our recommendations and feedback. Please feel free to reach out with any questions or if you’d like additional information.

Sincerely,

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