

**U.S Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes
Subcommittee on Extravasation**

Subcommittee Review and Comments on

**NRC STAFF PRELIMINARY EVALUATION OF RADIOPHARMACEUTICAL
EXTRAVASATION AND MEDICAL EVENT REPORTING**

Draft Report

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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 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.

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.

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 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 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.

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 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.

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 ($r_T = r_S$). 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.

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.

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 exceedingly small number of cases of adverse tissue reactions reported in the literature.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 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.

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.
- 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.
- Some radiopharmaceuticals do not have radiation emissions that can be easily imaged by nuclear medicine gamma cameras.
- 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.

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

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.

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 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.

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 caused 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 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

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