

**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

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 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

References:

1. Medical Use of Byproduct Material; Final Rule (67 FR 20250, April 24, 2002).
2. Certification of the Minutes of the March 24-25, 1999, Meeting of the Advisory Committee on the Medical Uses of Isotopes," July 9, 1999, available at ADAMS Accession No. ML20137X873.
3. Kim JT, Park JY, Lee HJ, Cheon YJ. Guidelines for the management of extravasation. *J Educ Eval Health Prof.* 2020;17:21. doi: 10.3352/jeehp.2020.17.21. Epub 2020 Jul 16. PMID: 32668826; PMCID: PMC7431942.
4. Hall NZJ. Impact of FDG extravasation on SUV measurements. *J Nucl Med.* 2006;47 suppl 1:115P.
5. Osman MM, Muzaffar R, Altinyay ME, Teymouri C. FDG dose extravasations in PET/CT: frequency and impact on SUV measurements. *Front Oncol.* 2011;1:41.
6. Ruibal A. Correction for FDG PET dose extravasations: Monte Carlo validation and quantitative evaluation of patient studies. *Med Phys.* 2014;41(5):052502.
7. Chatterton BE, Vannitamby M, Cook DJ. Lymph node visualisation: an unusual artefact in the 99mTc-pyrophosphate bone scan. *Eur J Nucl Med.* 980;5(2):187.
8. Jeannette Jackson-Rose, Chemotherapy Extravasation: Establishing a National Benchmark for Incidence Among Cancer Centers, *Clin J Oncol Nurs.* 2017 Aug 1;21(4):438-445.
9. Thomas M. Dykes, Intravenous Contrast Extravasation During CT: A National Data Registry and Practice Quality Improvement Initiative, *Journal of the American College of Radiology* Volume 12, Issue 2, February 2015, Pages 183-191.
10. See *supra* fn. 4.
11. Osborne, Dustin; Kiser, Jackson W.; Knowland, Josh; Townsend, David; Fisher, Darrell R. "Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements" *Health Physics.* 120(3):339-343, March 2021.
12. 1. J. van der Pol, et al. Consequences of Radiopharmaceutical Extravasation and Therapeutic Interventions: A Systematic Review. *Eur J Nucl Med Mol Imaging.* 2017; 7:1234-1243.
13. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017 U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.
14. Advisory Committee on the Medical Uses of Isotopes, Subcommittee on Extravasation, Final Report, October 23, 2019, available at ADAMS Accession No. ML19316E067.

15. Delbeke, D., and Segall, G.M. "Status of and Trends in Nuclear Medicine in the United States." *J Nucl Med* (2011) 52:24S–28S.



UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

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) 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.

¹ "Medical Use of Byproduct Material; Policy Statement, Revision" (65 FR 47654; August 3, 2000).

² On May 18, 2020, the NRC received PRM-35-22, requesting a rulemaking that would require medical event reporting for certain nuclear medicine injection extravasations. The docket for PRM-35-22 is available at <https://www.regulations.gov/docket?D=NRC-2020-0141> and the petition is also available in the NRC's Agencywide Documents Access and Management System (ADAMS) at Accession No. ML20157A266.

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 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

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

³ “Misadministration Reporting Requirements; Final Rule” (45 FR 31701, May 14, 1980).

⁴ In 2002 the NRC replaced the term “misadministration” with “medical event” to properly convey that byproduct material was not administered as directed.

⁵ “Misadministration Reporting Requirements; Proposed Rule” (43 FR 29297, July 7, 1978).

⁶ 45 FR at 31703.

⁷ SECY-80-26, “Effective Amendments of 10 CFR Part 35 to Require Reporting of Misadministrations of Byproduct Material,” January 16, 1980 (ML12237A576, non-public).

⁸ “Quality Management Program and Misadministrations; Final Rule” (56 FR 34104, July 25, 1991).

⁹ National Council on Radiation Protection and Measurements, Commentary No. 7, “Misadministration of Radioactive Material in Medicine – Scientific Background” 1991; ISBN 0-929600-22-3.

¹⁰ Stochastic effects occur by chance and which may occur without a threshold level of dose, whose probability is proportional to dose and whose severity is independent of the dose. The main stochastic effect is cancer.

¹¹ The 1991 rule also added the requirement for a quality management program for therapeutic administrations and certain uses of radioactive sodium iodide. This change was made to provide high confidence that the byproduct material or radiation from byproduct material will be administered as directed by an authorized user physician.

¹² “Medical Use of Byproduct Material; Final Rule” (67 FR 20250, April 24, 2002).

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.

DISCUSSION:

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, 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.

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

¹³ "Certification of the Minutes of the March 24-25, 1999, Meeting of the Advisory Committee on the Medical Uses of Isotopes," July 9, 1999, available at ADAMS Accession No. ML20137X873.

¹⁴ "Medical Use of Byproduct Material—Medical Event; Definitions and Training and Experience" (83 FR 32759, July 16, 2018).

¹⁵ See *supra* fn. 9.

¹⁶ 21 CFR 314.80, "Postmarketing reporting of adverse drug experiences."

¹⁷ 42 CFR 482.21, "Condition of participation: Quality assessment and performance improvement program."

¹⁸ Delbeke, D., and Segall, G.M. "Status of and Trends in Nuclear Medicine in the United States." *J Nucl Med* (2011) 52:24S–28S.

¹⁹ "Status of Medical Events FY 2019," March 20, 2020, available at ADAMS Accession No. ML20115E343.

²⁰ Wong, T.Z., et al., "Quality Improvement Initiatives to Assess and Improve PET/CT Injection Infiltration Rates at Multiple Centers," *J Nucl Med Technol*, 2019, 47:326–331.

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.

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.

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.

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."

²¹ Energy Reorganization Act of 1974, as amended (Public Law 93-438), Section 208.

²² "Regulation of the Medical Uses of Radioisotopes; Statement of General Policy" (44 FR 8242; February 9, 1979).

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.

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.

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 percent.²³ The author noted that any visualized increased uptake of the radiopharmaceutical at the injection site was considered to

²³ See *supra* fn. 20.

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.

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.

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, 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.

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.

²⁴ Hall, N., et al., "Impact of FDG extravasation on SUV measurements in clinical PET/CT. Should we routinely scan the injection site?" *J Nucl Med*, 2006, 47(supp1):115.

²⁵ Transient, mild erythema can occur within hours of external beam radiotherapy, likely due to capillary dilation shortly after patient exposure to radiation. The threshold for this type of tissue reaction is around 2 Gy. However, the more conventional, sustained hyperpigmentation or erythema associated with radiotherapy typically does not occur until 2 to 4 weeks into treatment with an associated threshold of 6 to 10 Gy.

²⁶ See fn. 34-36 *infra*.

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 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

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 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,

²⁷ "Teleconference Meeting of the Advisory Committee on the Medical Uses of Isotopes, December 18, 2008, Meeting Summary," December 18, 2008, available at ADAMS Accession No. ML090340678; "Meeting of the Advisory Committee on the Medical Uses of Isotopes, Meeting Summary," May 8, 2009, available at ADAMS Accession No. ML091730001.

²⁸ "Advisory Committee on the Medical Uses of Isotopes, Subcommittee on Extravasation, Final Report," October 23, 2019, available at ADAMS Accession No. ML19316E067.

²⁹ "Summary of December 8, 2020, U.S. Nuclear Regulatory Commission Public Meeting on Radiopharmaceutical Extravasations," March 16, 2021, available at ADAMS Accession No. ML21005A436.

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

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 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.

³⁰ See page 86 of December 8, 2020 public meeting transcript at ML21012A446.

³¹ Medical professional societies opposed to the petition include the Society of Nuclear Medicine and Molecular Imaging, American College of Nuclear Medicine, American College of Radiology, American Society of Radiation Oncology, Health Physics Society, American Society of Nuclear Cardiology, American Association of Physicists in Medicine, and American Pharmacists Association. The Association for Vascular Access supported the petition.

³² SNMMI commented on PRM-35-22 with the American Society of Nuclear Cardiology and the American College of Nuclear Medicine, the comment is available at ADAMS Accession No. ML21013A178.

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.

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).

OPTIONS:

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

³³ OAS, North Carolina, Arkansas, and North Carolina Radiation Protection Commission comments are available at ADAMS Accession Nos. ML21019A494, ML21019A495, ML20336A268, and ML21015A409.

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 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

³⁴ Bonta, D.V., Halkar, R.K., Alazraki, N., “Extravasation of a therapeutic dose of 131I-metaiodobenzylguanidine: prevention, dosimetry, and mitigation,” *J Nucl Med*, 2011, 52(9): 418–422. doi:10.2967/jnumed.110.083725.

³⁵ Tylski, P., Vuillod, A., Goutain-Majorel, C., Jalade, P., “Dose estimation for an extravasation in a patient treated with Lu-DOTATATE.” *Physica Medica*, 2018, 56(1):32-33.

³⁶ Benjegerdes, K.E., Brown, S.C., Housewright, C.D., “Focal cutaneous squamous cell carcinoma following radium-223 extravasation.” *Proc (Bayl Univ Med Cent)*, 2017, 30(1):78–79.

cause skin injury would likely otherwise go undetected. Monitoring for extravasation would 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 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.

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 occurrences are excluded from medical event

³⁷ 10 CFR 35.3045(a)(1)(iii)—A dose to the skin or an organ or tissue other than the treatment site that exceeds by: (A) 0.5 Sv (50 rem) or more the expected dose to that site from the procedure if the administration had been given in accordance with the written directive prepared or revised before administration; and (B) 50 percent or more the expected dose to that site from the procedure if the administration had been given in accordance with the written directive prepared or revised before administration.

³⁸ 10 CFR 35.40, "Written directives," and 35.41, "Procedures for administrations requiring a written directive."

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 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.)

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

³⁹ Van der Pol, J., et al., “Consequences of radiopharmaceutical extravasation and therapeutic interventions: A systematic review,” *Eur J Nucl Med Mol Imaging*, 2017, 44(7):1234–1243.

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 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 caused 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 effects.

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.

SUMMMARY:

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.

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.