U.S. Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
Subcommittee on Extravasations

Subcommittee Review and Comments on

NRC Staff Preliminary Proposed Rule, Implementation Guidance, and Model Procedures for the NRC's Rulemaking to Report Nuclear Medicine Extravasations

Draft Report

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EXPANDED CHARGE TO SUBCOMMITTEE:

On March 7, 2024, the ACMUI Chair, Dr. Hossein Jadvar, expanded the charge of the subcommittee on extravasations to review and provide feedback and recommendations on the U.S. Nuclear Regulatory Commission (NRC) staff's draft proposed rule, associated draft implementation guidance, and draft model procedures for reporting nuclear medicine injection extravasations as medical events.

BACKGROUND:

The ACMUI has previously discussed the topic of radiopharmaceutical extravasations and their inclusion in the medical event reporting criteria in Title 10 of the *Code of Federal Regulations* (10 CFR), Part 35, "Medical Use of Byproduct Material."

In 2019, the ACMUI re-evaluated and provided recommendations on the NRC decision to exclude infiltrations and extravasations from medical event reporting[1]. At that time, the ACMUI stated that extravasation is a practice of medicine issue that frequently occurs in otherwise normal intravenous or intra-arterial injections and is virtually impossible to avoid; and therefore, not an item that needs to be regulated by the NRC. The ACMUI noted that there was no evidence at the time for the ACMUI to recommend a reclassification of extravasations as medical events. Therefore, the ACMUI recommended that extravasations be considered a type of passive patient intervention[2].

In 2020, the ACMUI evaluated the definition of patient intervention and other actions and circumstances that are exclusive of medical events. As part of this evaluation, the ACMUI reconfirmed that exclusion of extravasation from medical event reporting was appropriate for both diagnostic and therapeutic procedures. However, the ACMUI recommended that extravasations be considered a type of passive patient intervention and that an extravasation that leads to unintended permanent functional damage be reported as a medical event under 10 CFR 35.3045(b)[3].

In 2021, the ACMUI reviewed the NRC staff's preliminary evaluation of radiopharmaceutical extravasation and medical event reporting. In their evaluation, the NRC staff sought to determine whether extravasations should be reported as medical events and, if so, what would be the appropriate reporting criteria. The ACMUI supported the reporting as medical events of extravasations that require medical attention due to a suspected radiation injury, as determined by an authorized user physician of the licensee[4]. The ACMUI stated that this option would provide the NRC with information on these extravasations, while providing an appropriate medical event criteria that could capture events that could be further evaluated for meeting the NRC's abnormal occurrence criteria. The ACMUI also stated that there is no clinical evidence that patients are being harmed because of radiopharmaceutical extravasation.

The NRC staff has drafted a proposed rule and draft implementation guidance in response to the Commission's direction in the Staff Requirement Memorandum to SECY-22-0043*,* Petition for Rulemaking and Rulemaking Plan on Reporting Nuclear Medicine Injection Extravasations as Medical Events (PRM-35-22; NRC-2020-0141)[5]. The Commission directed the staff to codify requirements for the medical event reporting of extravasations that require medical attention for a suspected radiation injury. In addition, the Commission tasked the staff to explore approaches that would reduce the reliance on patient reporting; to evaluate whether the NRC should require licensees to develop, implement, and maintain written procedures to provide high confidence that radiation significant extravasations will be detected and reported; and to create guidance to comprehensively explain and illustrate the medical event reporting criteria for evaluating and reporting all medical events, including extravasation events.

Three documents were provided by the NRC staff to the Subcommittee on Extravasations (SC) for review.

1 – the draft proposed rule (*Federal Register* notice)

2 – draft implementation guidance which includes a draft regulatory guide for the evaluating and reporting of medical events including extravasation medical events (Draft Regulatory Guide DG-8062)

3 – draft model procedures for detecting and reporting extravasation medical events

GENERAL COMMENTS:

The Subcommittee supports the publication of this draft regulation and the draft regulatory guide. They are well-written and the draft regulatory guide contains very useful information for licensees.

EXTRAVASATION AND PATIENT EDUCATION

During review of the staff's draft model procedures for evaluating and reporting extravasation medical events, the subcommittee discussed the option of requiring informed consent documents for every radiopharmaceutical injection to help reduce patient burden. However, the Subcommittee believes that extravasations can be managed effectively without informed consent, with patient education and mitigation when they occur and with reasonable policies and procedures. The subcommittee provides the following recommendations that the NRC staff should consider adding to the draft model procedures to help licensees manage extravasations incidents.

Background: United States Regulatory Commission has drafted a model procedure for management of patients that may have an extravasation of a radiopharmaceutical. The current document is entitled "Draft Model Procedures for Evaluating and Reporting Extravasation Medical Events." It is recognized that extravasations of radiopharmaceuticals may occur but occurrences that may result in a radioactive medical event are infrequent. Nuclear medicine technologists and other health care staff monitor patients for extravasation, and they are managed in real time as they occur.

Identification: Most vascular events involving radiopharmaceutical extravasation will be identified at the time of administration. When extravasation occurs, patients generally indicate that they feel pain, discomfort, or burning, and there may be swelling depending on the volume of radiopharmaceutical that was extravasated. Health care staff will use this information to identify the extravasation and should mitigate immediately.

Management: Management of vascular events include discontinuation of the administration and, as necessary, resuming the administration with appropriate vascular access at another site. Appropriate notifications to the authorized user, radiation safety officer, and others as necessary shall be completed. With the intravenous catheter in place, the vesicant may be aspirated safely and appropriately. The area affected should be clearly delineated. Further mitigation efforts may include elevation of the affected extremity, application of warm compresses, wrapping the location of extravasation and limitation of activity for the affected extremity. Analgesics may be given for pain management, if necessary. Consultations from dermatology or other providers may be appropriate and follow-up care should be arranged. Radiation safety or nuclear medicine staff can perform radiation measurements or serial gamma camera imaging to indicate clearance of the radiopharmaceutical. Radiation safety staff or other appropriate individuals can perform a radiation dose assessment, as needed.

Post-vascular event documentation and follow-up care: After a significant radiopharmaceutical extravasation, the incident should be recorded in the electronic health record and facility's incident reporting system. Follow-up phone calls or medical visits shall occur at established timepoints, and appropriate documentation recorded in electronic health record. Healthcare personnel should assess continued pain, erythema, swelling or ulceration. Extravasation wound assessments shall be performed and documented. Medical practitioner(s) and/or authorized user(s) shall provide appropriate treatment and care as necessary. If indicated, patients may be referred to plastic surgery for continued care and skin grafting as necessary.

Patient Education: Most radiopharmaceutical extravasations will not result in physical injury to the patient. Nevertheless, it is important in known extravasation occurrences that patients self-monitor and health care facilities monitor patients appropriately. In order to perform this effectively, health care organizations should educate patients adequately and provide written information or include written information in discharge instructions. It is recommended that health care facilities proactively prepare for potential extravasations by establishing policies and procedures which can be developed by researching available information from medical professional societies (e.g., the Society of Nuclear Medicine and Molecular Imaging).

Patient Information or Discharge Instructions: Formal written informed consent is not required prior to a diagnostic or therapeutic procedure involving radiopharmaceutical administration. Each facility should develop their own patient education documentation and home instructions, particularly for radiopharmaceuticals administered therapeutically. It is recommended that the patient education document or discharge instructions include the definition of an extravasation, indicate symptoms and possible outcomes. Health effects that may be indicative of radiation injury and require follow-up care are blistering, changes in pigmentation, ulceration, discoloration, reddening of skin, increasing pain, and any loss of sensation around the extravasation site. Mitigation instructions should include elevation, compresses, compression, and other treatments that may be effective (how long, how often, and when these actions should be taken shall be included). The healthcare facility should provide contact information for follow-up care which include locations, hours, and phone numbers. After hours care and instructions should be included, and medical emergencies should be addressed appropriately. Patients should take an active role in extravasation occurrence management and their own well-being, but health care organizations cannot rely on patients to perform this appropriately. Facilities should take an active role in contacting the patient, scheduling follow-up visits, making referrals, scheduling consultations, and providing effective care.

Conclusion: Radiopharmaceutical extravasations are uncommon but can occur rarely. Health care facilities should proactively plan for these occurrences. They should discuss the potential effects of extravasation with the patient when it occurs, and patient education should be provided to all patients when appropriate. If an extravasation

occurs without initial recognition by health care staff providing the radiopharmaceutical administration or by the patient, patient education should assist with identification, management, and minimization of the impact from a potential injury when a radiopharmaceutical extravasation occurs.

SPECIFIC COMMENTS ON DRAFT PROPOSED RULE:

1. Definition of Extravasation

"As proposed in this rule, the NRC defines extravasation to mean the unintentional presence of a radiopharmaceutical in the tissue surrounding the blood vessel following an injection." The subcommittee believes that this is overly specific and excludes other possible injection errors that may occur such as during intraarterial injections, intrathecal injections as well as injections intended to be into a specific body cavity or space (i.e., pleural, peritoneal, etc.)

2. Page 1

"This proposed rule would affect medical licensees that administer radiopharmaceuticals for diagnostic and therapeutic purposes."

3. Page 5

"As proposed in this rule, the NRC defines extravasation to mean the unintentional presence of a radiopharmaceutical in the tissue surrounding a blood vessel, spinal cord or body cavity into which it was intended following an injection."

4. Page 10

"Revising the definition for "extravasation" to mean the unintentional presence of a radiopharmaceutical in the tissue surrounding a blood vessel, spinal cord or body cavity into which it was intended following an injection;"

5. Page 11

"This proposed rule would affect all NRC and Agreement State medical licensees who administer radiopharmaceuticals for diagnostic and therapeutic purposes."

6. Page 13

"Moreover, since an extravasation can occur during almost any radiopharmaceutical ~~IV~~ injection, imposing a dose-based criterion would require monitoring millions of administrations per year, which would result in significant regulatory burden for medical licensees for only a marginal increase in radiation safety. In light of the above information on the potential risks posed by extravasations of radiopharmaceuticals, the NRC believes such a dose-based requirement would be inappropriate."

7. Page 14

"...written directive and intended by an authorized user (AU) is administered to a patient. While there may be some delay time, normal biological processes may transport the dose to the intended target."

8. Page 17

"For example, extravasations from I-131-iodocholesterol resulting in an erythematous plaque and Thallium-201". Both radiopharmaceuticals mentioned are not currently commercially available in the US. The subcommittee suggests this sentence be removed.

9. Page 20
"Upon consideration of this feedback, in this proposed rule the NRC defines the term "extravasation" in § 35.2 as the unintentional presence of a radiopharmaceutical in the tissue surrounding a blood vessel, spinal cord or body cavity into which it was intended following an injection."

10. Page 26
"The conclusion from the analysis is that this proposed rule and associated guidance would result in a cost to the industry (NRC and Agreement State medical licensees that administer radiopharmaceuticals for diagnostic and therapeutic purposes),"

11. Page 30
"Who will be required or asked to respond: NRC and Agreement State licensees who administer radiopharmaceuticals for diagnostic and therapeutic purposes."

12. Page 42
"Extravasation means the unintentional presence of a radiopharmaceutical in the tissue surrounding a blood vessel, spinal cord or body cavity into which it was intended following an injection."

SPECIFIC COMMENTS ON THE DRAFT REGULATORY GUIDE:

13. Section 1.1.1: Add a statement about whether it is reportable if an unintended dosage was administered and the licensee didn't fill out a written directive when they should have (i.e., there was no "prescribed" dosage). This would address situations where the administered dose was >20% different from the intended dose but the physician failed to complete a written directive.

14. Section 4: Instead of referencing the best practices via ML number, the Subcommittee recommends listing the best practices explicitly in the regulatory guide as there are only five short best practices.

15. Appendix B: Add example of microsphere medical event.

16. Appendix B: Two of the examples use Lutathera. The subcommittee recommends limiting to one example per radiopharmaceutical, or describing the radiopharmaceuticals generically (i.e., a beta-emitting radiopharmaceutical).

SPECIFIC COMMENTS ON THE DRAFT MODEL PROCEDURES:

17. Page 1
Informed consent should not be required for either diagnostic or therapeutic nuclear medicine procedures. Patient education whether done verbally and/or in printed format is the appropriate method of communication between patient and physician.

18. Page 1
Guidelines for observation of unexpected sensations by the patient or other developments observed by the medical staff or the patient should be developed by each facility in accordance with recommendations from the professional medical societies such as the Society for Nuclear Medicine and Molecular Imaging (SNNMI), the American College of Radiology (ACR), the American Society for Radiation Oncology (ASTRO), and the American Association of Physicists in Medicine (AAPM).

Respectfully Submitted,
Subcommittee on Extravasations,
Advisory Committee on the Medical Uses of Isotopes
U.S. Nuclear Regulatory Commission

REFERENCES:

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

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

3. Advisory Committee on the Medical Uses of Isotopes, Subcommittee on Patient Intervention, Final Report, April 6, 2020, available at ADAMS Accession No. ML20097F476.

4. Advisory Committee on the Medical Uses of Isotopes, Subcommittee on Extravasations, Final Report, September 16, 2021, available at ADAMS Accession No. ML21288A125.

5. Staff Requirement Memorandum to SECY-22-0043, Petition for Rulemaking and Rulemaking Plan on Reporting Nuclear Medicine Injection Extravasations as Medical Events (PRM-35-22; NRC-2020-0141), December 12, 2022, available at ADAMS Accession No. ML22346A112.