AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

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Secretary
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001
ATTN: Rulemaking and Adjudications Staff

Submitted by electronic mail to Rulemaking.Comments@nrc.gov

Re: Preliminary Proposed Rule: Reporting Nuclear Medicine Injection Extravasations as Medical Events [Docket ID NRC–2022–0218]

The American Association of Physicists in Medicine (AAPM)[1] is pleased to submit comments on the preliminary proposed rule language for rulemaking on the reporting of nuclear medicine extravasations as medical events. AAPM appreciates this opportunity to provide feedback directly to the U.S. Nuclear Regulatory Commission (NRC) on this important topic.

INTRODUCTION

AAPM supports the use of good scientific practices to risk-inform the NRC's policies and regulations, and this certainly applies when discussing extravasations. We recognize that since the filing of the petition for rulemaking, a vast set of perspectives have come forth to energize the conversation. AAPM appeals to the NRC to select a sound regulatory approach supported by scientific evidence and attributable risks.

Therapy vs. Diagnostic—Extravasations of nuclear medicine procedures cannot be evaluated practically for every performed procedure. Unquestionably, biological consequences from injected radiopharmaceutical therapies can occur, and there is value in bringing this to people's attention. AAPM supports the effort to require practices in preventing, managing, and reporting therapeutic medical events. Conversely, over a half-century of performing diagnostic radiotracer studies have yet to demonstrate deterministic harm to patients. AAPM leans heavily on this point to say that any increase in regulatory burden would be unreasonable for the minimal doses spared during diagnostic procedures. Instead, the monitoring, training, and quality assurance for these can be suitably managed at an institutional level. As such, we strongly recommend this rulemaking only capture therapeutic applications of radiopharmaceuticals.

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[1] The American Association of Physicists in Medicine (AAPM) is the premier organization in medical physics, a broadly-based scientific and professional discipline encompassing physics principles and applications in biology and medicine whose mission is to advance the science, education and professional practice of medical physics. Medical physicists contribute to the effectiveness of radiological imaging procedures by assuring radiation safety and helping to develop improved imaging techniques (e.g., mammography CT, MR, ultrasound). They contribute to development of therapeutic techniques (e.g., prostate implants, stereotactic radiosurgery), collaborate with radiation oncologists to design treatment plans, and monitor equipment and procedures to insure that cancer patients receive the prescribed dose of radiation to the correct location. Medical physicists are responsible for ensuring that imaging and treatment facilities meet the rules and regulations of the U.S. Nuclear Regulatory Commission (NRC) and various State regulatory agencies. AAPM represents over 9,000 medical physicists.

Medical Events—Medical event reporting arose from commendable intentions, but along the way it strayed from having a positive association to being viewed by users as negative and punitive. If licensees had more transparency and learning opportunities from the events being reported, it may feel more collaborative and that we are in this safety effort together. Medical event reporting brings many negative connotations: rapid reporting to regulators, public exposure on the NRC's event log, legal and reputational risks, reactive regulatory inspections, possible non-compliances, threats for enforcement and financial penalties. These are counterproductive to building a strong safety focused industry. Instead, medical event rules should foster learning, quality improvement opportunities, reducing future risks, and developing techniques to limit radiation injury. Reporting would largely benefit from a cultural and educational overhaul for both licensees and regulators.

Dose vs. Activity—With nuclear medicine procedures it is not currently possible to plan precise dose distributions, the material is at the mercy of biological redistribution. All that we can do is ensure the activity prescribed is delivered to the bloodstream as intended. For therapeutic procedures, if >20% of the planned activity misses the bloodstream then it should classify as an event. If the NRC revises its 1980 policy exempting all extravasations to only exempt diagnostic procedures, therapeutic treatments will need to be reported based on written directive and medical event procedures established by licensees. In that case, rulemaking is largely unnecessary. Should rulemaking proceed, the language could be made clearer and more explicit for handling radiotherapeutic extravasations.

This rulemaking presents an opportunity to create a well-conceived and balanced way of addressing extravasations. Through it, we stand to improve delivery techniques and to establish more accurate treatments for patients. However, applying these requirements to all nuclear medicine procedures would be overly burdensome and provide minimal safety gains. AAPM urges the NRC to limit the scope of this rulemaking to only encompass therapeutic written directive required (10 CFR 35.300) procedures.

DEFINITIONS

1. What term should the NRC use (*e.g.,* extravasation, infiltration) when describing the leakage of radiopharmaceuticals from a blood vessel or artery into the surrounding tissue?
AAPM defers to other professional organizations with physician, or authorized user (AU), representation for the final selection of medical terminology. Within context to the NRC, *"extravasation"* is suitably defined.

"Extravasations" are a subset of infiltrations that involve a vesicant, chemical irritants capable of damaging tissue in relatively short order. Thus, *"extravasation"* is an appropriate term to use if only considering deterministic harm or *"suspected radiation injury"*. *"Extravasation"* should be reserved exclusively for written directive required procedures (10 CFR 35.300), and it should not be used to describe diagnostic (10 CFR 35.200).

2. What criteria should the NRC use to define ''suspected radiation injury''?
Same as the first question, this would be best answered by physician or AU groups. Additionally, identifying *"suspected radiation injury"* would need to occur on a case-by-case basis by the AU. It is unclear if the NRC is seeking scenarios where only visible injury and tissue damage can occur due to radiation, or if the intention is to include situations with a potential to cause injury. If the former, we must limit our scope to where injury is even possible, essentially therapeutic applications.

Thresholds for deterministic effects can vary quite a bit from person to person, let alone when considering the tissue or organ affected. This makes it challenging to select any one activity, activity concentration in tissue, or other dose related metrics. Ideally, an absorbed equivalent dose could be

identified for the tissue in question, then each radiopharmaceutical, under set circumstances (arbitrary at this time) could have an evaluated amount of activity required to achieve the dose. Then a guide could be drafted, like how RG 8.39 exists for patient release, to focus on extravasations and possible radiation injury thresholds.

The following details should be considered when suspecting a radiation injury:

1) If available, post-treatment images to show distribution and dispersion over time of the radiopharmaceutical.
2) Radiation survey measurements near the extravasation site could also prove helpful.
3) Any symptoms that could indicate a radiation injury (erythema, hair loss, tissue peeling, ulceration nausea, vomiting, diarrhea, etc.).
4) Time between a suspected radiation exposure and the onset of symptoms.
5) Estimation of the radiation dose received by the individual (organ or tissue).
6) Appropriate management and follow-ups post the suspected radiation injury.
7) Any known or suspected history of radiation exposure to an individual (organ or tissue).

Case-by-case evaluations must occur, with final determinations made by the AU. It would be difficult (and inappropriate) to blanketly classify all therapeutic extravasations as triggering *"suspected radiation injury"*.

3. What techniques or methods should be included in the definition of ''medical attention''?
Again, this is best answered by the AU physicians. Nurses and physicians alike receive training on procedures following extravasations.

"Medical attention" could be tied to intervention of a *"suspected radiation injury"*. If the actions are prophylactic, they would not count as an intervention and thus not be considered as *"medical attention".*

Once the suspected injury threshold is exceeded, actions that may be deemed as *"medical attention"*:

1) Immediate assessment for any symptoms of a radiation injury.
2) Document and report the details of the incident.
3) Immediate measures taken to minimize tissue damage. Strategies may include encouraging the lymphatic system to clear the extravasate (massage, warming, moving the affected limb, etc).
4) Consult professionals for management and treatment.
5) Follow-up monitoring and care.

PROCEDURES

4. What steps could the licensee take to minimize the chance of a radiopharmaceutical extravasation occurring?
AAPM recognizes that certain steps can reduce chances for radiopharmaceutical extravasation; however, the specifics of what procedures a site elects to implement would be overly specific for a regulation. Instead, the NRC could require licensees to have a policy for identification, assessment, and reduction of extravasations. Example policy components could be offered via regulatory guidance documents (i.e., IV with an advance volume before therapeutic injections, mandatory annual training on venipuncture for anyone starting IVs for radiopharmaceutical administration).

Techniques and Tools—These are no different than the administration of any other drug. Many organizations have published best practices for injected pharmaceuticals, it should be similar for radiopharmaceuticals. Extravasation risk may be reduced by using the established methods in

medical literature for obtaining and verifying IV access prior to injection or infusion. Additionally, certain tools and techniques for vein visualization, catheter insertion, securing, and stabilization of the IV to the vein will help reduce the chance.

Quality Improvement—Quality assurance and quality control programs prove time and time again that they are effective at making improvements, across all types of industries. The idea of doing better, measuring outcomes, and evaluating results is one sure way to reduce chances of future extravasations. A facility will learn and become better through tracking when and how extravasations occur. Until a baseline is established, it will be impossible to know if things are heading in a positive direction.

Teamwork and Collaboration—Nurses, technologists, physicians, administrators, and physicists all play a role in this. Reducing extravasation events is not purely a question for physicists, but one that should be asked of the entire nuclear medicine care team. Through a more holistic discussion, we may discover alternative and better solutions.

Training and Education—Note that Centers for Medicare and Medicaid Services (CMS) requires board certification or licensure of personnel to be eligible for Medicare Improvements for Patients and Providers Act (MIPPA). This means that many facilities are likely evaluating their training across the entire care team, as required for payment and accreditation reasons. Expanding training and education materials to cover procedural enhancements and administration considerations would be helpful.

5. What steps should the licensee take when an extravasation is suspected or discovered?
First, if we apply the term extravasation as discussed in question 1, this answer would only be applicable to written directive related procedures, or essentially therapies. The steps a licensee takes would be an elaboration from what was answered already in questions 2 and 3:

1) If not completed, stop the infusion immediately.
2) Assess the incident, immediate measures taken to minimize tissue damage.
3) Take actions to adjust or mitigate any negative consequences.
4) Notify team of healthcare and radiation professionals, such as the AU, the radiation safety officer (RSO), and medical physicists. Consult with professionals as needed.
5) Inform the patient about the situation. Note, this will be an easier conversation if a discussion took place prior to the treatment, at the time of consent.
6) Perform post-treatment imaging or survey measurements to show distribution and dispersion over time of the radiopharmaceutical. Surveying the contralateral anatomical structure (i.e., the other arm) from the extravasation site could help confirm activity is trapped in an extravascular space.
7) Consider evaluating the extravasation site with medical imaging techniques (gamma camera, X-rays, MRI, ultrasound, etc.).
8) Quantify the extravasation activity, distribution volume, and calculate the radiation dose received by the individual (organ or surrounding tissue).
9) With consultation of the team in step 4), further assessment to determine if any symptoms or radiation injuries are suspected. If so, estimate the timeline until onset. *[Note, this would be the "discovery" point per the current preliminary proposed rule, triggering reporting.]*
10) Advise patient on how to monitor for symptoms that could indicate a radiation injury (itchy, swelling, erythema, hair loss, tissue peeling, ulceration, necrosis, nausea, vomiting, diarrhea, etc.).
11) Ask about previous known or suspected history of radiation exposure to an individual (organ or tissue).
12) Follow-up routinely to monitor, advise, and provide care as necessary post any suspected radiation injury.

13) Document in detail over the course of these steps and make a complete record of the incident.
14) Continue follow-up monitoring and documentation until a full recovery or a permanent result occurs.

Many hospitals performing these procedures will not have a full-time medical physicist or RSO on site. Licensees should confirm access to these experts and their services in the event that an extravasation occurs.

6. What techniques, technologies, or procedures (*e.g.,* post-treatment imaging, visual observation, patient feedback) should be used to help identify an extravasation during or immediately after a radiopharmaceutical injection?
Post-treatment imaging (small amounts), direct visual observation (large amounts), radiation surveys of the injection/infusion site, and patient feedback regarding swelling or stiffness are well established. If it is not already performed, post-treatment images should be collected in cases with indications or symptoms suggesting an extravasation.

7. What techniques, technologies, or procedures (*e.g.,* post-treatment imaging, survey measurement) should be used to better characterize an extravasation after radiopharmaceutical treatment?
Post-treatment imaging and radiation surveys of the injection/infusion site are about the best bet. If it is not already performed, post-treatment images should be collected. This is assuming a gamma camera is available with sensitivity for therapeutic isotopes delivered. Imaging the site provides the possibility for first order activity quantification.

8. What information should licensees provide to nuclear medicine patients on how to identify an extravasation and how to follow up with their physician if they suspect a radiation injury?
This question is best answered by physicians, but licensees should lean on established and proven medical practices for communicating with patients. Contact information for the licensee, with ways of communicating to the AU and RSO, would be needed so that the patient may raise questions or concerns.

Extravasations—It is improbable that a patient would be able to identify an extravasation that was not previously caught by, or in the presence, of the healthcare team. As such, providing information to identify an extravasation would only raise unnecessary concern and worry from the patient.

Radiation Injury—Due to the delayed effects produced by radiation injury, it is worthwhile to inform and educate a patient on what to look out for following therapeutic procedures. Possible symptoms (itchy, swelling, erythema, hair loss, tissue peeling, ulceration, necrosis, nausea, vomiting, diarrhea, etc.) and the timelines for onset would make it reasonable for a patient to self-monitor.

9. When should a reportable extravasation be counted as ‘‘discovered’’ for the purposes of notification (*e.g.,* when medical attention is administered, when the physician identifies that the injury is from radiation)?
This is again a question best answered by the AU. When a reportable extravasation is considered *“discovered”* is dependent on the facility’s burden for investigation and the subsequent resources that can be applied to evaluate the incident. Per the preliminary proposed rule language, AAPM suggests the time *“discovered”* coincide with an AU confirmation of *“suspected radiation injury”*. This time is potentially hours to days from the moment when the extravasation is first identified.

10. The NRC requires that licensees notify the referring physician and the individual who is the subject of a medical event no later than 24 hours after discovery of the medical event.

When should licensees be required to provide notification of an extravasation medical event to the referring physician and the individual?
If an extravasation meets the definition of a reportable medical event by way of *"suspected radiation injury"*, it is reasonable to treat it the same as any other medical event in terms of notifications.

11. Who (*e.g.,* patient's primary physician, authorized user, nuclear medicine technician) should be able to identify an extravasation that could result in a ''suspected radiation injury''?
The whole team should be trained for awareness and identification of extravasations to the extent practical. However, the clinical decision for a *"suspected radiation injury"* is the responsibility of the AU.

12. What topics should the NRC include in guidance to assist licensees to accurately identify, characterize, and report extravasation events in a timely manner?
Licensees, and thus patients, would benefit more if the guidance focused predominantly on prevention and management of extravasations rather than identifying, characterizing, and reporting them. Extravasations should be uncommon with good injection/infusion techniques. Additionally, they should cause for minimal adverse outcomes if identified quickly and managed according to available medical recommendations and guidelines.

Guidance for identification, characterization, and reporting examples would assist licensees from a regulatory compliance perspective. As discussed in question 2, providing a calculation method that gives set parameters (tissue volume, activity concentration, biological dispersion rates, etc.) and tables of dose thresholds for various radiopharmaceuticals would be helpful in quickly discerning if *"suspected radiation injury"* is possible.

HEALTHCARE INEQUITIES

13. What regulatory actions could help ensure that extravasations in patients affected by healthcare inequities are accurately assessed and reported?
Healthcare disparities are vast within the U.S., and unfortunately many factors are outside of a patient's control (location, race, financial/insurance status, education, etc.). Licensees should take steps to adequately inform and empower patients to communicate (in their primary language and at the patient's education level) with their healthcare team. There may not be a regulatory action per se that the NRC could impose to resolve this systemic issue, but the Commission might consider drafting a policy statement. This could be like the *Safety Culture Policy Statement* but instead focus on reducing or eliminating healthcare inequities across NRC licensed facilities.

14. Are vascular access tools and other technologies (*e.g.,* ultrasound guided vein finders) likely to reduce the potential for an extravasation in all patients, particularly in patients of color?
Yes, our understanding is that ultrasound guidance can be effective for patients with difficult veins. In asking a few technologists, we found mixed opinions. It was clear that these devices require experience and training to reduce the likelihood of extravasations. Additional tools would expand costs and training, and thus they are not a single catch-all solution.

CUMULATIVE EFFECTS OF REGULATION

1. Given current or projected CER challenges, how should the NRC provide sufficient time to implement the new proposed requirements, including changes to programs and procedures?
There is a substantial length of time before we arrive at a final rule. The rulemaking process and public engagement steps should be sufficient for licensees to develop and train on procedures to evaluate and report extravasation medical events. However, since the final rule is subject to change, AAPM recommends at least 12 months from the published date until it is evaluated for compliance.

2. If CER challenges currently exist or are expected, what should be done to address them?
Funding and resources for any additional requirements must be addressed and offset in some way. If the rule takes away from nuclear medicine's ever-thinning margins, it risks pushing licensees toward termination. Closure of these facilities would make it harder for patients to seek care. The NRC should consider appealing to CMS so that licensee activities for extravasations can be reimbursable.

Regulatory Shift—Just because reporting timelines, methods, and regulatory response activities exist for the current medical events does not necessarily mean that the same should apply for extravasation medical events. Instead, consider if the NRC required medical events per 10 CFR 35.3045(a)(3) to only be recorded. These recorded events could be reviewed during facility inspections. Suspected injuries could prompt record keeping, patient tracking and follow-up, and other licensee response activities to an event. A separate reportable level of extravasations could then be established that is associated with observable radiation injuries.

3. What other (NRC or other agency) regulatory actions (e.g., orders, generic communications, license amendment requests, inspection findings of a generic nature) influence the implementation of the proposed rule's requirements?
The NRC should create a regulatory guide, that could be published in advance of the final rule. This guidance would allow licensees to test out and refine their procedures before they are evaluated against the rule for compliance.

Generic communications about the upcoming changes and expectations might help prompt licensees to start developing procedures and methods for monitoring extravasations. Once the rule is final, respective regulatory programs may request licensees to submit extravasation procedures for tie-down to the license. These amendments would add burden to both the licensees and regulatory agencies. AAPM would suggest these procedures not be submitted for licensing, but rather that they are evaluated during inspection activities.

4. What are the unintended consequences, and how should they be addressed?
Unintended consequences can never fully be known, but care should be given when expanding the regulatory requirements for nuclear medicine procedures. Adding treatment steps, technology standards, administrative responsibilities, and regulatory burden will only further stress an already taxed healthcare system. The NRC must judiciously evaluate the benefits of this rulemaking compared to the costs and consequences that will be imposed to licensees of all sizes.

If achieving compliance requires more technological investment, more staff hours, changes to existing procedures, increased reporting, and more recordkeeping, then it will absolutely affect licensees. Naturally, this will impact smaller clinics disproportionately to the larger and well-funded nuclear medicine departments. Either way, it stands to drive some facilities away from offering services all-together, thus reducing access to these life-changing procedures.

SUMMARY
AAPM is grateful for the opportunity to examine these questions and the complex issues surrounding extravasations. Our response underscores the importance of striking a careful balance between regulatory measures and the practical realities for licensees. AAPM strongly supports advocating for the safety and well-being of patients; however, this rulemaking requires an approach that distinguishes between therapeutic and diagnostic procedures. Moreover, we recognize concerns to address healthcare inequities and stress the significance of clear, practical guidance for healthcare professionals.

AAPM hopes that the NRC finds our response to be insightful. We ask that these comments receive due consideration while making changes to the proposed rule for the reporting of nuclear medicine extravasations as medical events. If we can provide any additional information, please contact AAPM's Senior Government Relations Manager, David Crowley (david@aapm.org).

Sincerely,

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