November 13, 2023

Christopher Hanson
Chairman, U.S. Nuclear Regulatory Commission
One White Flint North
11555 Rockville Pike
Rockville, MD 20852-2738

Dear Chairman Hanson,

We are scientists and physicians who are or have been members of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) or the American College of Radiology (ACR). We are writing to you to express our concern about radiopharmaceutical extravasations; specifically, the effects of ionizing radiation on healthy tissue and the negative effects that large extravasations have on nuclear medicine procedures. Because of these patient safety concerns and after reading recent SNMMI and ACR public comments on extravasations, we feel it is important to share some observations with you.

SNMMI and ACR have consistently made public comments intended to minimize the importance of extravasations in nuclear medicine. We think it is likely that these comments may have discouraged the NRC from addressing extravasations like any other medical event that warrants reporting. Here are just a few examples. Supporting evidence is attached in Appendix A.

- ACR has said that radiopharmaceuticals are “without inherent properties harmful to tissues.”
- ACR and SNMMI have said that nuclear medicine technologists follow the best vascular access practices.
- ACR has said that nuclear medicine centers follow protocols for access and extravasation mitigation.
- ACR has suggested that the rate of extravasations cannot be reduced.
- SNMMI has stated that monitoring for extravasations will not lead to improvements in the administration process.

These statements are not true.

- SNMMI has stated that the 20 million patients receiving 30 million diagnostic radiopharmaceutical administrations “need not be concerned” about how to identify an extravasation or how to follow up with a physician if they suspect radiation injury.
- SNMMI has additionally suggested that these patients not be told of the risks associated with radiation, should not be effectively monitored for extravasation, and if extravasated should not have the severity of the extravasation assessed.

These suggestions contradict the society’s public statements on how extravasations affect nuclear medicine imaging procedures and their own practice guidelines. The comments are unethical. The “need not be concerned” statement is alarming and a clear indication that the nuclear medicine community does not adequately understand the purpose of medical event reporting, is not truly concerned about patient radiation protection, and cannot be relied on to report medical events based on subjective criterion.

- SNMMI suggests the "small volume" involved in radiopharmaceutical administrations should not be a concern.
- SNMMI suggests that high activity extravasations are rare and do not involve large amounts of the injected radioactive dose – "In a 1000 patient multi-center investigation into frequency of infiltration events in PET, no infiltrations of >1% of injected dose were found."
- SNMMI states "the risk of actual skin injury is significantly lower than implied in current literature…"

These comments are irrelevant, misleading, and incorrect. The volume of an administration, the frequency of extravasations, and whether patients are directly harmed by ionizing radiation are immaterial to medical event reporting. However, the amount of radiation extravasated and the resulting absorbed dose to skin and tissue do matter. Furthermore, the SNMMI is aware that NRC has seen over 50 examples of diagnostic radiopharmaceutical extravasations that greatly exceed 1% of the injected activity. Several have approached 100% of injected activity, all exceed an absorbed dose of 50 rem to 5 cc of underlying tissue or 10 cm^2 of skin, and several exceed 10 Gy, the threshold for Abnormal Occurrence reporting to Congress.

We fear that the information provided by ACR, SNMMI, and others has contributed to the Commission decision to put the burden on patients to identify and prove injury as a condition of extravasation medical event reporting. We view this decision as entirely inconsistent with NRC's radiation protection process using objective dose-based thresholds. The decision is impractical for patients for obvious reasons and undercuts any potential benefits that would accrue from eliminating the incorrect reporting exemption.

Across various statements and comments, SNMMI's position is clear. It wants its members to bear no responsibility for extravasations, does not want patients or their doctors to know if extravasations have occurred, will take no proactive steps to prevent extravasations, and will not take steps to mitigate harm to the patient when they occur. By requiring patients to self-report harm, SNMMI is encouraging NRC to continue ignoring extravasations despite the clear opportunity for improvement of the practice and patient safety.

We encourage the NRC to disregard the input from SNMMI in its entirety. Further, we recommend that extravasations be reportable like any other medical event. Quite simply, extravasations that exceed the dose threshold should be reported. 50 rem is the risk-informed level for medical event reporting, well above any normal dose to tissue from proper administration, but, depending on the radiosensitivity of the patient, likely below the level where harm could occur. Reporting these extravasations would also be consistent with NRC's own statement printed on the medical event report: "a medical event may indicate potential problems in a medical facility's use of radioactive materials. It does not necessarily result in harm to the patient." We also suggest centers be given a reporting grace period to allow them time to adopt the well-known practices that will ensure few extravasations. The result will be an improvement of practice and patient safety.

Sincerely,

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About the Authors:

Dr. Dan Sullivan is a global leader in the field of radiology. He is Professor Emeritus, Department of Radiology at Duke University Medical Center, and Founder and Chair Emeritus of the Quantitative Imaging Biomarkers Alliance (QIBA). QIBA coordinates a wide range of national and international activities related to the evaluation and validation of quantitative imaging biomarkers for clinical research and practice. Dan was in academic radiology practice for more than 40 years and was an employee of NCI/NIH for a decade. He completed radiology residency and nuclear medicine fellowship in 1977 at Yale New Haven. He then held faculty appointments at Yale University Medical Center, Duke University Medical Center, and University of Pennsylvania Medical Center, before joining the National Cancer Institute at NIH in 1997. From 1997 to 2007 Dan was Associate Director in the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI), and Head of the Cancer Imaging Program (CIP) at NCI. His areas of clinical and research expertise are in nuclear medicine and oncologic imaging, focusing on improving the use of imaging as a biomarker in clinical trials and clinical practice. Thus, he has extensive clinical experience in nuclear medicine, and has had long-standing involvements in efforts to improve the reproducibility of clinical imaging services that patients receive.

Dr. David Townsend is widely accepted as a global expert in nuclear medicine imaging. He obtained his B.Sc in Physics from Bristol University and his Ph.D. in Particle Physics from the University of London and was a staff member for eight years at the European Centre for Nuclear Research (CERN) in Geneva, Switzerland. In 1980, Dr Townsend joined the faculty of Geneva University Hospital as a physicist in the Department of Nuclear Medicine. In 1993, Dr Townsend moved to the University of Pittsburgh as an Associate Professor of Radiology and Senior PET Physicist. He was Co-Director of the Pittsburgh PET Facility from 1996-2002 and became Professor of Radiology in 2000. In 1995, Dr Townsend was Principal Investigator on the first proposal to design and build a combined PET/CT scanner. The PET/CT scanner, attributed to Dr Townsend and Dr Nutt, then President of CPS Innovations, was named by TIME Magazine as the medical invention of the year 2000. In recognition of his work on PET/CT, Dr Townsend received the 2004 Distinguished Clinical Scientist Award from the Academy of Molecular Imaging, and the 2008 Nuclear Medicine Pioneer Award from the Austrian Society of Nuclear Medicine. In 2006, he was elected a Fellow of the IEEE. He shared with Dr Ron Nutt the 2010 IEEE Medal for Innovations in Healthcare Technology. From February 2003 to 2009, Dr Townsend was Professor of Medicine and Radiology, and Director of the Molecular Imaging and Translational Research Program at the University of Tennessee, Knoxville. In July 2009, he became Head of PET and SPECT Development for the Singapore Bioimaging Consortium, Professor of Radiology at the National University of Singapore and was appointed Director of the A*STAR-NUS Clinical Imaging Research Center, Singapore in December 2010. In 2014, Dr Townsend was presented with the MILabs Advanced Imaging Scientist Award by MILabs in Utrecht, The Netherlands. He has co-authored over 170 peer-reviewed papers on nuclear physics and medical imaging technology. In 2015, Dr Townsend received the prestigious Paul C. Aebersold Award from the International Society of Nuclear Medicine and Molecular Imaging in the US for 3D PET and PET/CT development. He retired from his role in Singapore in 2018. He has been an Associate Editor of the Journal of Nuclear Medicine and an editor of the Extravasation Research Topic for the journal Frontiers in Nuclear Medicine.

Dr. Ramsey Kilani is a board-certified radiologist. He started his career in radiology as a faculty member in the Department of Radiology at Duke University and has practiced in both academic and private practice settings. He has also been an operator of over a dozen early-stage companies in the healthcare and technology spaces in the private sector in the past 20 years, and has done consulting work on behalf of a variety of entities as a Principal and Chief Medical Officer at the firm Global Security Innovative Strategies in Washington, D.C.

Appendix A - Supporting Information

Radiopharmaceutical extravasations: absorbed dose and tissue damage

In their recent comments on extravasations, the ACR and SNMMI has misled the NRC and the public regarding the dangers of radiopharmaceutical extravasations, the vascular access training levels of technologists, the implementation of extravasation protocols, and the preventability of extravasations. We provide below supporting evidence and some background, a few examples, and brief remarks for your consideration.

On August 27, 2018, the ACR wrote the NRC on the topic of modifying Training and Evaluation (T&E) requirements so referring physicians could become authorized users (AUs). In arguing against modifying T&E, the ACR emphasized the risks associated with both therapeutic and diagnostic radiopharmaceuticals. ACR stated that the responsibility of the AU is:

> "to protect patients…from ineffective, accidental, inappropriate, or otherwise unnecessary radiation exposure."

ACR specifically included **tissue extravasation** as a risk associated with both therapeutic and diagnostic radiopharmaceuticals.

In a follow-up letter to the NRC on the AU requirements, ACR built the case that medical isotopes are far more dangerous than antineoplastics agents and other hazardous materials. ACR stated:

> "All radiation has the potential for mishandling and untoward events…Many isotopes have multiple energy emissions, often including a gamma component…also of concern for safety and security."

> "Safe and effective use of radiopharmaceuticals requires a thorough knowledge and understanding of the modality and experience with the various facets and potential toxicities and dangers to patients, staff, and the public. There is a potential for increased morbidity from combined modality therapies typically employed when radionuclide therapy agents are used by providers unfamiliar with short- and long-term implications of radiation deposition in normal tissues."

The ACR completely contradicted these statements when they publicly commented on radiopharmaceutical extravasations on September 30, 2020. In this comment, ACR emphasized how contrast media and antineoplastic agents are more dangerous compared to radiopharmaceuticals. ACR stated:

> Contrast media and antineoplastic agents "are not analogous to administrations of radiopharmaceuticals, which are typically small volume, without inherent properties harmful to tissues…"

SNMMI cited a very poorly designed study that was rushed through peer review in record time[1] to support their comments that extravasations of diagnostic radiopharmaceuticals may occur but very rarely result in

[1] Knowland, J (2023). Critique and discussion of "Multicenter evaluation of frequency and impact of activity infiltration in PET imaging, including microscale modeling of skin-absorbed dose". Front. Nucl. Med., Sec. Radiopharmacy and Radiochemistry Volume 3

tissue damage. The study retrospectively reviewed records of 31,679 studies to reach their findings. SNMMI shared their conclusion in their September 2023 public comment.

> "Reported radiopharmaceutical extravasations were rare and short-term, local symptoms were observed in three patients (0.009%)…no patient had long-term adverse events with a plausible link to the radiopharmaceutical extravasation."

This study design does not support its findings. The vast majority of radiopharmaceutical extravasations are never identified at the time of the study by the nuclear medicine community and when they are, they are rarely documented.[2,3]

As you are well aware, higher doses of ionizing radiation can be harmful to healthy tissue, absorbed doses from large diagnostic and therapeutic extravasations can exceed several Gray, and licensees who routinely extravasate are not handling medical isotopes properly.

Best practices in venous access and use of protocols

SNMMI leadership has routinely communicated that radiopharmaceuticals are administered by technologists who employ best practices. In a public meeting on December 8, 2020, Ms. Tina Buehner, President of SNMMI-TS, suggested technologists use a best practice when she stated:

> "Best practices for administration of intravenous injections through IV catheters."

In their most recent comment on extravasations to the NRC, ACR suggested on September 1, 2023 that nuclear medicine follows standard of care venous access procedures. They also stated that:

> "In…nuclear medicine…extravasation management is a critical component of vascular access training, procedures, and policies."

The suggestions that nuclear medicine practices follow best venous access processes, have and use documented venous access processes/procedures, and technologists know what to do when patients are extravasated is simply not supported in the real world. A recent paper provides evidence that suggests nuclear medicine technologist do not always use IV catheters to administer radiopharmaceuticals, they do not follow best practices for vascular access, that most nuclear medicine technologists do not receive formal vascular access training, are not credentialed, and do not undergo annual competency verification for gaining vascular access.[4] Additionally, nuclear medicine practices do not have or use vascular access protocols or extravasation protocols.[4,5]

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[2] Osborne, D, Acuff, S, Noe, J and Fu, Y (2019). Use of a PACS Integrated Injection Monitoring Device to Increase Injection Quality and Infiltration Awareness. JNM 60(387).

[3] Fernandes, D, Santos, M, Pinheiro, M, Duarte, H, and Fontes, F (2023). Radiopharmaceutical extravasation in bone scintigraphy: a cross-sectional study. Nucl Med Commun.

[4] Harris, S, Crowley, J, Warden, N (2023). Radiopharmaceutical administration practices—Are they best practice? Front. Nucl. Med., Sec. Radiopharmacy and Radiochemistry Volume 3

[5] Kohl, P (2023). Transparency – a patient-centric view on radiopharmaceutical extravasations. Front. Nucl. Med., Sec. Radiopharmacy and Radiochemistry Volume 3

To be perfectly candid, there are no data to support the society's claim that licensees follow vascular access or extravasation mitigation protocols, while there is evidence that suggests the opposite. Furthermore, the vast majority of radiopharmaceuticals administered in the United States are not administered by technologist with formal training on vascular access and the associated proper access and vein finding tools.

Reduction of extravasation rates

In the same September 1, 2023 comment, ACR also cited a national benchmarking study on contrast media extravasations and quality improvement efforts to suggest that extravasations can't be reduced or prevented. ACR stated:

> "….focused large-scale, nationwide practice improvement efforts to reduce the frequency, severity, and distribution of symptomatic extravasations with non-radioactive contrast media have been unsuccessful."

The ACR failed to share with the NRC that the average starting extravasation rate for the centers participating in the national benchmarking effort was 0.28% and the median rate was 0.25%. These rates are already exponentially better than the most recent nuclear medicine extravasation rate (17.2%), averaged from published literature since 2009. Despite the already low rate of contrast media extravasations, the ACR also failed to share that while the 32 practices participating in the national benchmarking study did not see a statistically significant reduction, the average rate declined from 0.28% to 0.23% and the median rate declined from 0.25% to 0.16% during the quality improvement efforts.

In a September 2020 public comment to the NRC, leaders of SNMMI stated that they did not expect that monitoring radiopharmaceutical administrations would result in a reduction of extravasations, even though one of these leaders had co-authored a poster presentation at an SNMMI meeting that found that active monitoring did, in fact, statistically significantly reduce extravasations and that active monitoring was needed to ensure extravasations rates did not return to their previous high levels.

Nor did the SNMMI share that the largest quality improvement study ever published on nuclear medicine extravasation rates was highlighted as one of the most important presentations at their annual meeting just a few months before the public comment. The study reported that centers showed a dramatic improvement in their extravasation rates ($p<.0001$) through monitoring as part of a quality improvement project.

Process improvement efforts require monitoring, analysis of contributing factors, interventions to address these factors, and ongoing monitoring. And as you are aware, one purpose of medical event reporting is to share lessons learned with other licensees to prevent similar reports in the future. Extravasations have been proven to be reduced through actively monitoring administrations, analyzing potential contributing factors, and ensuring lessons are learned and actions are taken.

Radiation protection of patients and patient harm

In their September 2023 public comment, SNNMI stated:

> "The safety of our patients and the highest quality of care are our top priorities."

However, they also stated:

> "We support a harm based, rather than dose-based approach…"

In the same comment, they also stated that they do not support using technology to detect extravasations, and do not support assessing the severity of extravasations.

These SNMMI positions are contradictory to previous statements and inconsistent with current medical practice guidelines that guide diagnostic nuclear medicine imaging. Because diagnostic images are used to guide patient care, SNMMI knows that extravasations can be harmful to patients. In September 2020, SNMMI published a Position Statement on extravasations in which they stated:

> SNMMI "recognizes the effect that extravasation of diagnostic radiopharmaceuticals may have on the quality of diagnostic images, particularly on quantitative studies."

That is also why current SNMMI practice guidelines state that if extravasations (diagnostic or therapeutic) are suspected then providers should assess the severity of the extravasation to determine the implication to the nuclear medicine study. The assessment and steps taken to mitigate the potential damage to patients should also be documented in the radiology report.

If radiation protection and patient safety was truly a top priority of SNMMI, then they would want to identify an extravasation as soon as possible and follow their practice guidelines.

While the society's position on harm is truly irrelevant to the NRC current, dose-based medical event reporting criterion, it is illustrative that the society's position—that patients who experience diagnostic nuclear medicine procedures need not be concerned with identifying and reporting extravasation—is incongruent with their own policies and modern medicine. This position is especially discouraging since the society understands that the vast majority of extravasations are not identified now and will not be identified unless nuclear medicine practices begin to effectively monitor their administrations.

Other miscellaneous positions taken by ACR and SNMMI

The SNMMI and ACR have made other comments which are entirely irrelevant, misleading, or incorrect. These disingenuous comments suggest deliberate misinformation or plain ignorance. Neither is appropriate and both require correction.

Both societies frequently suggest that the injected volumes for diagnostic radiopharmaceuticals are small. In their September 2023 public comment, SNMMI states:

> "the smaller volume diagnostic radiopharmaceutical injections are highly unlikely to cause local symptoms…."

While this is one reason that extravasations are difficult to assess by sight or feel, it has no bearing on the severity of the extravasation. One cc of an injected diagnostic radiopharmaceutical will result in trillions of decay over the residence time of the drug in the patient. Depending on the nature of the energy emissions (e.g., positrons, internal conversion electrons, auger electrons, or low-dose x-rays) the absorbed dose to 5 cc of tissue can be several Gray.

Additionally, the SNMMI attempts to minimize the frequency of extravasations of large amounts of activity. In their September 2023 public comment, they state:

> "In a 1000 patient multi-center investigation into frequency of infiltration events in PET, no infiltrations of >1% of injected dose were found."

Reporting criterion for an event is not dependent on the frequency of the event.

In the same comment, SNMMI also questions whether patients are directly harmed by ionizing radiation.

> "the risks of actual skin injury is significantly lower than implied in current literature…"

And while their statement neglects dose to underlying tissue, it is also irrelevant to an objective dose-based medical event reporting criterion. What matters is the amount of radiation extravasated and the resulting absorbed dose to skin and tissue. Furthermore, it is public knowledge that NRC has seen over 50 examples of diagnostic radiopharmaceutical extravasations that greatly exceed 1% of the injected activity. Several have approached 100% of injected activity, all exceed an absorbed dose of 50 rem to 5 cc of underlying tissue or 10 cm^2 of skin, and several exceed 10 Gy, the threshold for Abnormal Occurrence reporting to Congress.