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Reporting Nuclear Medicine Injection Extravasations as Medical Events

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Reporting Nuclear Medicine Injection Extravasations as Medical Events; Notification of Docketing and Request for Comment

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General Comment

See attached file(s)

Attachments

2020-11-30 Iryna Barvi NRC Comment

Docket ID NRC-2020-0141

Dear NRC Representative,

I am an employee of the Petitioner, Lucerno Dynamics. I have been reviewing many of the public comments over the past several months. The comments that are opposed to the petition consistently reference the findings of the NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI). Therefore, I have thoroughly researched the ACMUI position on extravasation to try and better understand the merits of their position. My research dates back to the early 2000s, when the ACMUI supported the move to make NRC regulations more risk-informed. As part of this more risk-informed regulatory strategy, the ACMUI agreed with rasising of the medical event reporting dose threshold to 0.5 Sv to tissue.

In 2008, the NRC suggested the ACMUI reconsider the extravasation exemption as the result of a case filed by the Boston VA regarding a positron-emitter diagnostic extravasation. The NRC was rightfully concerned about the trend to positron-emitting diagnostics since the year 2000 and the future use of alpa- and beta-emitters in radiotherapeutic administrations. The ACMUI held two meetings, December 2008 and May 2009 on extravastions. The ACMUI also reconsidered the topic in 2019. And earlier this month also held a meeting with the NRC Commissioners on this topic. Here are my findings:

ACMUI 2008 meeting transcript

- While discussing the case the NRC presented regarding the Boston VA FDG extravasation that exceeded medical event reporting limits, one of the ACMUI's members stated that "there were no identified adverse effects. There was nothing to suggest any kind of a radiation injury." It appears that members are not aware that if the skin had been affected, radiation injury would not be visible for several days, and tissue injury would not be visible for months or years. The patients should be followed for a very long period to see the effect of extravasations.
- The same member believed that "diagnostic dosages, like technetium-99m, that were typically used in nuclear medicine at the time are gamma emitters of relatively low energy and low risk and wouldn't exceed the dose thresholds that are in the medical event criteria." This comment suggests that the members do not understand the radiation energy spectrum of technetium-99m. If extravasated, a not inconsequential amount of non-gamma energy would be deposited locally. Multiple cases of diagnostic extravasations that resulted in high doses to tissue have been shared with the NRC. The NRC is now aware that not only therapy extravasations but also diagnostic extravasations, can lead to high absorbed doses in patient tissue.
- Members also stated that "infiltrations, are an integral part of the procedure, and so their occurrence must be viewed as expected." The occurrence of extravasations should not be viewed as expected, because their frequency can be reduced. Nothing that can potentially cause patient harm can be viewed as expected if there is an opportunity to improve.
- Advisory member states that "the NRC would be flooded with more medical events than it could manage." This is absolutely not an appropriate excuse to exempt reporting when patient safety is at risk.
- One member commented that he doesn't "think extravasation is a frequent occurrence in nuclear medicine. Otherwise, you would have patients being repeated beaucoup times, and it is a very uncommon occurrence." This member does not see extravasated procedures repeated

because centers often use compromised images to guide patient care. This can lead to under-staging or over-staging of the disease and unnecessary invasive procedures to assess false positives.

ACMUI 2009 meeting transcript

- One of the members stated: “I'm not aware of the vehicle for a radioactive treatment having the capability of being responsible for tissue damage.” Unless the member’s use of the word “vehicle” is referring to the pharmaceutical, it is very concerning that one of the members of the ACMUI whose voice will be considered by NRC is not aware of how radioactive drugs could cause tissue damage. If the member is referring to the pharmaceutical, then they should be aware that some pharmaceuticals can play a role in the dose to tissue. MDP for example does not have the same biological clearance as FDG. As a result, a straight stick extravasation of Tc99m-MDP does not rapidly diffuse in the tissue. The contribution of the pharmaceutical will result in a smaller volume of affected tissue and a higher absorbed dose.
- One member thought that “something like this should be reported to FDA under their adverse event or severe adverse event reporting system.” Since hospitals do not monitor or report radiopharmaceutical extravasations, there would be little reason to believe the FDA will receive reports of extravasations. The FDA would only receive such reports if they were submitted by the manufacturers of radiopharmaceuticals. These would only be submitted if by chance the manufacturer was aware of an issue.
- One member, referring to a hypothetical case of a patient receiving up a dose equivalent to tissue of up to 5.0 Sv said: “Now if we consider this as a medical event if we go through all the procedures and identify whatever-3 or 4 or 5-- the patient will have to be informed; the physician have to be informed, blah blah blah, and the - you have to go into all the reporting mechanisms. And therefore I am thoroughly against this being reported as a medical event.” This statement is very informative. Members of ACMUI continued to be concerned about extra work related to reporting, just as they did during the previous meeting. They were not concerned about patients who are irradiated with high doses, and they were not concerned about misleading diagnosis. What seemed more important to the members is that they did not want to be bothered with reporting. Unfortunately, based on the submitted public comments regarding the current petition, this also appears to be the position of the nuclear medicine community. For them, additional reporting means more work. This excuse not to monitor injections contradict the principles of patient safety and healthcare transparency.

Also, during the discussion in 2008 and 2009 members noted that extravasations happen routinely and can meet reporting criteria, but they still recommended not to change the policy. It is very obvious that during these meetings, the members are expressing their personal beliefs and attitudes rather than following scientific evidence.

ACMUI 2019 Recommendation

The 2019 ACMUI was presented with the scientific evidence regarding extravasations. The committee was on notice of the adverse effects, and on quality improvement projects that allowed centers to solve the extravasation problem. Still, the Committee made the following statements:

- "There is no evidence at this time for this subcommittee to recommend a reclassification of extravasation at the injection site for radiopharmaceuticals to be considered a medical event." This statement is inaccurate because there is clear, peer-reviewed evidence, that was provided to the subcommittee but it seems they simply ignored this evidence when making this recommendation.
- "Members are unaware of any cases of documented patient harm due to extravasations". 55 cases of documented patient harm are shown in the FDA adverse event and European vigilance reporting databases. Also, there are more than 50 peer-reviewed papers that indicate how patients have been or can be harmed by extravasations.
- "The NRC should classify extravasations as patient intervention". Extravasations should not be classified as a patient intervention issue: patients are not responsible for the improper administration of a radiopharmaceutical. Suggesting that passive patient intervention is the cause of extravasations is an ACMUI attempt to deflect responsibility. There is clear evidence that changes in tools, techniques, and training can quickly and dramatically reduce the extravasation rate. Also, this statement directly contradicts previous comments made by the ACMUI members in 2008 and 2009. In these meetings members addressed the causes of extravasations and suggested inexperienced technologists, lack of training, venous access tool selection, technique, etc., were the cause of extravasations. During the previous meetings, there was no mention that patients were a cause of extravasations. It appears that the ACMUI members (with the exception of the Patient Advocate, Ms. Laura Weil) have taken their passive patient intervention position to continue their efforts to avoid reporting.
- The subcommittee also suggested that extravasations should not be regulated by the NRC. But according to the NRC's Office of Public Affairs, NRC regulations aim to assure radioactive materials are used properly during medical diagnostics and treatments. So, there is a conflict with the NRC, because problems in the delivery of radiopharmaceuticals that result in tissue dose exceeding NRC reporting limits are within the NRC jurisdiction.

It is obvious that the 2019, the subcommittee (except Ms. Weil) and the remaining ACMUI continued sharing inaccurate or incomplete information with the NRC and maked their recommendations on personal beliefs/interests rather than scientific evidence.

ACMUI NRC Commissioner Meeting - November 2020

Recently, the ACMUI met with NRC Commissioners. Some of the discussion focused on the topic of extravasations. I am highlighting a few comments from the ACMUI, but am also attaching a transcript of the comments and an analysis of the ACMUI answers to Commissioners' questions.

- "In diagnostic administrations, the percentage of extravasations was approximately 0.1% and for therapeutic it was about 0.2%, so it's not a common occurrence." The 0.1% is the number of **reported cases of diagnostic extravasations in the literature** where **dosimetry** and patient **follow-up occurred** as compared to the **total number of reported cases of diagnostic extravasations in the literature**. This is widly inaccurate read of the referenced paper. The NRC have been shown peer-reviewed evidence that diagnostic extravasations occur approximately 15.5% fo the time.
- "The physicist really would not have the information needed to do an accurate calculation of the dose." All the information that a health physicist needs to perform dosimetry is available in 2020. There is no excuse to not perform dosimetry and assess if the dose exceeds the reporting

limit. The dose calculation should not be complicated for health physicists: technology exists now to capture the biological clearance, and cameras are not needed to do that.

- One of the members stated “I have been radiation safety officer now at 5 major medical centers for about the past 25 years. I have never been at one of these procedures when the AU was not there to administer the radiative material. It is their soup. It is their responsibility.” While authorized users indeed may be present for therapy administration they are rarely present during diagnostic administrations.
- Answering the question of how would a medical professional know that extravasation happened, one of the members stated that “it's visual”. In fact, most clinicians will not know extravasation has occurred, because extravasations do not cause an immediate change in the patient’s skin, and patients usually don’t experience any discomfort, unlike from CT or chemotherapy extravasations, where patients complain of burning sensations.
- “Just because it happened on patient 1, you are not going to prevent it from happening on patient 2 if you happen to have two patients with problem veins.” This argument indicates that the ACMUI member has not read any literature on quality improvements in the delivery of radiopharmaceuticals. ACMUI is very consistent in ignoring all the latest data regarding extravasations and do noy appear to make any efforts to educate themselves on the topic.

Summary

During the meetings in 2008, 2009, 2019, and 2020 the ACMUI presented misleading and inaccurate arguments, that are unsupported by scientific evidence and also inconsistent with the NRC’s mission “to ensure protection of people and the environment.” Additionally, the ACMUI changes its position regarding the frequency of extravasations, the potential harm, the cause, and the responsibility whenever it helps them to make a point. It appears that the ACMUI members have not studied any evidence presented to them, and are more interested in minimizing the reporting requirements of their own industry. This apparent conflict of interest should be considered when reviewing the ACMUI position on extravasations.

I urge NRC to follow your mission and protect the safety of patients.

Thank you for the opportunity to add to the public comment.

Sincerely,
Iryna Barvi.

NRC Commissioners – ACMUI Meeting November 18, 2020
Lucerno transcribed Q&A dialogue related to extravasations only, with analysis

Commissioner Comment	ACMUI Comment	Analysis
Baran: What is the current understanding of how frequently extravasations occur, and is there reliable data around that?	Martin: Thank you for the opportunity to respond. One study we looked at, actually Dr Jadvar provided some of this data. In diagnostic administrations, the percentage of extravasations was approximately 0.1% and for therapeutic it was about 0.2%, so it's not a common occurrence. It does happen. Since 1980, patient's veins have not changed, so the problem of having an extravasation due to a patient having a problem with the condition of their veins particularly if they are a chemotherapy patient really hasn't changed. I don't think anyone would say extravasations are common. They do happen, they happen routinely, whether it is with radio pharmaceuticals, with chemotherapy drugs, with any other type of drugs administered by IV. So, we do have extravasations. Every facility and every practitioner goes through training to try to avoid this. We have not seen a significant a difference between the percent of extravasations whether that occur whether a nuclear medicine technologist or authorized user are administering radio pharmaceuticals or anyone administering chemotherapy drugs or administering other IVs. So, it is not unique to radiopharmaceuticals that extravasations occur. I would certainly turn the floor over to our physicians to see if they have anything to add to these comments.	Diagnostic extravasations occur approximately 15.5% of the time. That data is supported by peer-reviewed evidence and by published comments from the four leading nuclear medicine societies. Ms. Martin is incorrect. The "study" Ms. Martin refers to is a literature review regarding reports of extravasation. This literature review did not have any findings regarding the frequency of extravasations. Instead the authors reported on the number of cases documented in the literature. Note, that the authors commented that the low number of reported cases is likely the result of a conservative attitude of the community to publish information about extravasations and also because extravasations are not always required to be reported. The 0.1% Ms. Martin is referring to is the number of reported diagnostic extravasations where dosimetry and patient follow-up occurred as compared to the total number of reported diagnostic extravasations. This absence of dosimetry and follow-up for extravasated patients should be alarming in itself. In the 3,016 reported cases of diagnostic extravasations discovered during this literature review, only three patients had dosimetry performed and were followed for evidence of adverse tissue reactions. All three exceeded medical event reporting limits. All three experienced adverse tissue reactions. One at 20 weeks, one at 2 years, and one at 3 years. The remaining 3,013 diagnostic extravasations did not report dosimetry or patient follow-up. This lack of dosimetry and follow-up is typical for diagnostic extravasations and many therapeutic cases, too. It is difficult to comment on the mixed messages that Ms. Martin offered when she mentioned patient veins not changing since 1980, that no one is saying extravasations are common and then saying they do happen routinely. However, she is completely incorrect in saying that there is not a significant difference in extravasation rates between nuclear medicine and chemotherapy. The petition includes clear evidence from 12 centers that have published or presented 8 studies of 3,254 patients since 2003. These retrospective reviews of images found an average nuclear medicine extravasation rate of 15.5%. Chemotherapy extravasation rates of similar administration techniques (IV) are 0.18%. Contrast CT rates are 0.24%. These are published national benchmarking studies. Please also note that Ms. Martin's comments are in direct conflict with the slide she presented and with comments made by previous ACMUI members (refer to the ACMUI transcripts from December 2008 and May 2009).

	Jadvar: I second what Ms. Martin just mentioned. She was referring to a study published in the European Journal of Nuclear Medicine and Molecular Imaging in 2017. It was basically a systematic review of publications on this particular topic of extravasations. These authors found 37 publications that were relevant, and in these 37 publications there were 3,016 cases of extravasations that were reported. These were all diagnostic in this group of publications. Ms. Martin has already mentioned that the incidence of extravasations was very small, 0.1% and only 3 patients were reported to have some mild itching [..] or redness at the site of the extravasation. With regard to therapeutic, which potentially are more problematic, there were 8 publications that we looked at, and in those 8 publications, the incidence was very low, and none of them had to permanent functional damage with regard to the patient which end of up having some extravasation of the radio therapeutic drug. But also I reemphasize that. As Ms. Martin mentioned, extravasation is not just for radio isotopes. It can happen with chemotherapy, so there is nothing particular to radio isotopes. Therapies are also an irritant, so if they are deposited, they can cause local issues. But again, there is evidence published out there that this is not a huge or major problem.	Dr. Jadvar makes the same mistake that Ms. Martin made referring to the article by van der Pol et al. The Commissioners need to be aware that the nuclear medicine profession frequently misquotes this reference. The article states the following regarding the three followed diagnostic cases: two cases of radiation ulcers were reported. One at two years and one at three years post extravasation. The third patient experienced a pruritic and erythematous patch at 20 days. There was no long term follow up of this patient. Since the radiation injury caused by extravasation is primarily from non-gamma energy that travels from 1-10 mm in the body, not all extravasations will result in a high radiation dose to the skin. The fact this one patient developed symptoms in just 20 days is indicative that this was a serious extravasation and the patient likely developed longer term tissue damage two to three years later. The ACMUI is concluding that not many patients are harmed, and they cannot reach that conclusion if 3,013 other extravasated patients were not followed. In discussing therapeutic extravasations, Dr. Jadvar emphasizes there was no permanent functional damage as if this is relevant. Medical events that result in a dose to tissue >0.5 Sv due to administration through the wrong route require reporting. Reporting is intended to help ensure that lessons learned are generated and communicated across licensees. No patient should have to suffer from adverse tissue reactions caused by an extravasation when they can be identified and mitigated at time of occurrence. Dr. Jadvar's statement that there is evidence that nuclear medicine extravasations are not a huge problem is incorrect. Over 50 peer-reviewed articles indicating how diagnostic extravasations compromise image quality and quantification have been submitted to the NRC. Furthermore, 36 examples of cases exceeding 0.5 Sv have been shared with the NRC. Extravasation frequency is high and significant extravasations are also frequent. They need not be.

Baran: Thank you, that is very helpful. And one of the other questions that the NRC staff is trying to determine is whether the dose consequences of extravasations are significant. You touched on this a little bit. Is there anything else you would want to add on the current state of knowledge on the dose consequences?	Martin: Yes, this is Melissa Martin responding from the physicist perspective. The actual dose calculations are fairly complicated to do an accurate dose assessment for an extravasation. Thankfully, the body has a lot of physiological functions going on to clear out the extravasation, so you have a physiological component to the calculations. The other problem we've run into is that to try to get an estimate of the actual amount of dosage that has been extravasated, many of the gamma cameras that are used today are of a vintage that do not give accurate uptakes. They can localize the extravasation, they can show what it is, but they don't give you the uptake values. And to replace that equipment, you're talking a very significant amount of money to replace a camera that is perfectly functional except for the fact that it doesn't give a quantitative information on doing dose calculations. So the physicist really would not have the information needed to do an accurate calculation of the dose.	Ms. Martin is not correct. The dose calculations may be complicated to the layman, but should not be for health physicists. Software and methods exist that can estimate the dose within minutes. Biological clearance is a factor in the dose. The faster the clearance the lower the dose. Capturing the clearance is very important, as the FDA extravasation expert pointed in recent FDA/NRC joint webinar. Technology exists now to capture clearance. This improves the dose estimate. Cameras are NOT needed anymore for this function. Additionally, medical guidelines urge clinicians to image the injection site of suspected extravasation patients and to characterize the extravasation to understand how the misadministration negatively affects the image. This information is helpful in the dosimetry. All the information that a health physicist needs to perform dosimetry is available in 2020. There is no excuse to not perform dosimetry and assess if the dose exceeds the reporting limit. Patients and their treating physicians would also want to know.
Baran: So that's interesting. Part of what your saying there is if we were to change the policy and the medical event dose criterion would apply, for example, a dose to an organ or tissue that exceeds the prescribed amount by more than 50 rem. There may be a challenge in ascertaining whether that's occurred in any particular instance.	Martin: And the fact that basically that organ would be the skin. That's what we are looking at, a dose to the skin that would be from an extravasation. And yes, we don't have the data right now. For every facility that performs these examinations does not have the ability to provide the information that would be required for a nuclear medicine physicist to do a dose calculation. We could do an estimate, but its very much of a raw estimate. It is not going to be accurate due to the limitations of the equipment that is out there.	There appears to be a misunderstanding about medical event reporting. Subpart M requires reporting if the tissue receives a dose equivalent of 0.5 Sv or if the skin receives a shallow dose equivalent of 0.5 Sv. It is not a requirement that the dose to the tissue exceeds the prescribed amount by 50 rem, because there is not a prescribed dose to the tissue or the skin. Licensees are required to report medical events. If they are able to report other medical events that require dosimetry, why would the NRC not expect them to be able to report extravasations? Again, technology, methods, and software are available to characterize extravasations. The offered excuses are just that, excuses.
Baran: So, at this stage, would you say we have a sense or really not about whether the 50 rem dose criterion would be met pretty frequently?	Martin: It would be hard to reach the 50 dose limit unless you had an extravasation of a very small area with a very high uptake. The larger the area, the does spreads out, so the actual skin dose in any one area is diminished. So the 50 rem – it is possible to reach that, particularly with a therapeutic administration. Again, it depends on how large an area that the radio pharmaceutical is infused into.	The dose to tissue depends on the amount of radiation absorbed and the volume of the tissue. Ms. Martin is incorrect in stating it would be hard to reach a 0.5 Sv dose. That comment is likely the result of not performing dosimetry on extravasations. The Commissioners should note that in 2008, when the Boston VA performed dosimetry on a diagnostic extravasation, the estimated dose exceeded the reporting limit. Additional clinical examples of diagnostic extravasations in 5 cc of tissue have been shared with the NRC. Several of these cases also show that 10 cm^2 of skin overlaying the extravasated tissue also receive a reportable dose. Many ACMUI members may be unaware that the positron energy in PET diagnostics (that would be deposited locally during an extravasation) represents the same energy being deposited by beta emitting therapeutics. Furthermore, many also seem unaware that the most frequently used diagnostic isotope, Tc^{99m}, deposits a substantial amount of conversion electron, Auger electron, and photon energy in tissue during an extravasation.

Baran: Recognizing the challenges you have been discussing about making a determination on the dose, one of the things I am trying to figure out is whether the medical event reporting exclusion for extravasations is actually impacting the amount of reporting. If we applied the medical event reporting criteria to extravasations, as ACMUI prior patient advocate member suggested, would that actually result in many extravasation-related medical events being reported, if in fact it would be pretty rare for the 50 rem threshold would be met?	Martin: In our opinion, it would still be a rare event. I think Mr Sheetz might have more information on that to help fill in that information, but we did not feel it would be a routine occurrence.	These are not rare events. Thousands of diagnostic nuclear medicine patients are currently extravasated every day. Many of these are significant extravasations that would exceed reporting limits.
	Sheetz: The challenge is, as Ms. Martin alluded to, is trying to do the dosimetry calculation because of all the variables on the clearance rate of the radio pharmaceutical from the extravasated tissue, the volume and shape of the extravasated tissue, and so this becomes very complex. And if you consider all that, it probably clears out and would not exceed the 50 rem tissue dose. But if one assume a very simple model where you assume a 1 cc cylinder of tissue and the activity stays there until physical decay, it would only take 150 micro curies of technetium 99m or 30 micro curies of F18 to reach the 50 rem dose. So, if you do a very simplistic model, a conservative model, you will have a lot of reported medical events from this. If you take the time to look at the clearance rate, then most likely the tissue dose would not exceed the 50 rem, so it really would create a large burden for this rule to address extravasation as a medical event. It would require every administration to be evaluated whether an extravasation so that would require either an image over the site or some radiation detection system to monitor the injection site. And then once you detected or monitored or identified any extravasation, you would have to do those calculations, which again are very complex, very time consuming, and so yes, it would result in probably a significant number of medical event reports just because of trying to do it simplistically and not spending a lot of time on it.	Mr. Sheetz overstates the complexity of the calculations and oversimplifies the assumptions about the clearance rate. Standardizing the dosimetry calculations for a reference volume (like skin dosimetry for an area of $10cm^2$) would simplify dosimetry and provide comparative values across extravasations. For a paper currently in press with *Health Physics Journal*, the authors used a substantial amount of tissue (5 cc) as a reference volume. Mr. Sheetz makes several assumptions to make his point; however, clearance rate does not need to be an assumption anymore. Non-imaging technology can be used today to provide insight into biological clearance. As a result, patient-specific clearance can be used to calculate dose. Mr. Sheetz also assumes that the monitoring process can be very time consuming. One center has reported on their monitoring experience: after reducing the extravasation rate through improved technique, they estimate that they have prevented hundreds of significant extravasations. Since January 1, 2020 they have performed dosimetry on five patients, one of which has exceeded the reporting limit. This patient has been added to their fluoroscopy guided intervention monitoring process for long-term follow-up. Monitoring the quality of each injection adds 20 seconds to the patient experience and 1 minute to the technologist workload. Dosimetry on 5 patients have require a total of 50 minutes to date. Adding the one patient to the follow-up process involved a five-minute discussion at the Radiation Safety meeting. If centers are routinely extravasating, their reporting workload would be higher. Once they improve their quality, they should expect a lower reporting burden and improved administration quality.
Baran: This is very helpful, thank you so much for your perspectives on this, and I am looking forward to reviewing what the staff finds and recommends this spring.		
Caputo non-extravasation related questions		

Caputo: The subcommittee more or less confirmed that the committee does not consider extravasations to be a medical event, that its virtually impossible to avoid, and that the subcommittee is unaware of any cases of documented patient harm. As a practice of medicine issue, the NRC need not regulate it. However, the subcommittee recommended that extravasations that lead to "unintended permanent functional damage" should be reported as medical events. If the subcommittee members are unaware of any cases of documented potential patient harm, what scenarios do you envision or have the members postulated that could cause permanent functional damage, thereby requiring reporting of medical events?	Martin: We put that in there basically to cover the potential in the future of these new drugs that are being developed. We just don't know what would happen in the future, but if there is a possibility of one of these therapeutic agents causing a permanent damage, we're agreeable that that would be reported as medical event. The worst reactions we have seen to date is, I think there is a few documented cases of ulceration that have occurred, and those have been cured, they have not been permanent, but if there is something in the future, we just wanted to make sure. We agree that if it is permanent damage, that is should be considered a medical event. Michael Sheetz has a comment.	The ACMUI has been consistent in their attempts to minimize reporting of extravasations, even to go as far as saying extravasations are the result of passive patient intervention – even though the evidence is clear that changes in tools, technique and training can quickly and dramatically reduce extravasation rate. The ACMUI fails to acknowledge that the medical event reporting requirement does not include patient harm as a criterion. When tissue receives a dose of 0.5 Sv or 500 millisieverts, that indicates that the tissue has received ~500x the dose it would have received during a proper administration. If centers are routinely extravasating patients to a dose that exceeds reporting limits, that indicates that the center is not handling medical isotopes properly and the NRC and patients should be made aware.
	Sheetz: If we consider extravasation a type of patient intervention, then it is consistent with the Part 35 regulation that even those events caused by patient intervention, if they caused permanent functional damage, they would be reportable as a medical event. So, it is consistent with extravasation being considered a type of patient intervention.	There is no logical argument that supports sweeping all extravasations into the fanciful explanation of passive patient intervention. This seems nothing more than the ACMUI's effort to deflect responsibilities for this serious quality and safety issue away from the licensee.
Wright non-extravasation related questions		
Wright: [Regarding the minority opinion on changing the T&E framework] At the OAS meeting…NRC received feedback that the NRC needs to shift focus from the physicians to those actually handling and administering the materials. What are your thoughts on such a shift?	Simon: That was a minority opinion. The subcommittee thought that any sort of co-working, team approach to administering radio pharmaceuticals requiring a written directive would still require an authorized user understanding all the radiation safety issues and being able to address them, particularly in the case of infusions, infusion errors, extravasated patients, patient events that might require complex dosimetry and so forth, and that relegating that to others would not necessarily promote safety.	For clarity, our experience indicates that technologists usually administer diagnostic radiopharmaceuticals without any authorized user supervision.
Wright: Does the medical event reporting data support the assertion that AU are often not present or supervising at the time of these events?	Martin: I have been radiation safety officer now at 5 major medical centers for about the past 25 years. I have never been at one of these procedures when the AU was not there to administer the radiative material. It is their soup. It is their responsibility.	Authorized users may often be present for therapy administration but are rarely present for diagnostic administrations.

Wright: Thank you for the presentations today. Extravasations and patient interventions. A lot of this, especially the extravasations part, has gotten a lot of external attention, and we keep circling back to where do we draw the line between radiation safety and the practice of medicine. Along those lines, a couple of questions. So with the current practice and standards of care, how would a medical professional know that an extravasation happened for a diagnostic dose, and how, if at all, would that be different for a therapeutic dose?	Martin: Well, obviously you can doc…its visual. You can also image the injection site with the camera if it was a large enough extravasation that you think it is going to affect the study that the patient is having done. You can image it, you can document that it happened, but its basically a visual perception.	Medical professionals cannot always know when a diagnostic extravasation has occurred. The small volume of radiopharmaceutical that is injected (~1-2 cc) will not be enough to cause a change in the patient's skin, unlike the injection of 500 cc of contrast, which will cause a golf ball-sized swelling of the patient's skin. Nor does the patient usually experience any discomfort since most radiopharmaceuticals do not burn. Furthermore, the injection site is not always in the imaging field of view. In fact, it is rarely in the field of view across all nuclear medicine scans. Therefore, most clinicians will not know an extravasation has occurred. Therapeutic doses are often infused, not injected, so there is a greater chance that there may be a visual sign of swelling near the injection site. However, it is not a common procedure to image the patient after a therapy delivery, so if the extravasation is missed by visually inspecting the patient skin for swelling, the patient will go home without anyone knowing of the extravasation. Rather than guessing if a dose has been extravasated, it is possible to monitor administrations prospectively.
Wright: OK, so that means proposing that extravasations being treated as a passive patient intervention, and given current therapeutic and diagnostic doses, could you have an extravasation that met the threshold for reporting as a patient intervention and resulted in permanent functional damage to an organ or a physiological system?	Martin: You can certainly reach the point of 50 rem, but what you don't reach is level to cause permanent functional damage. That is a discrepancy. 50 rem does not cause permanent functional damage. If you have gone through radiation oncology, you were probably given 180 to 200 rem, uh rads, on a daily basis. That does not cause permanent functional damage. So just because you reach that 50-rem dose it's not going to cause you permanent functional damage. I think we need to disassociate the two—that result from the 50-rem dose.	We agree with Ms. Martin that for reporting, the NRC should focus on the 50-rem dose threshold. Medical event reporting does not require permanent functional damage. An extravasation of a diagnostic or therapeutic can easily exceed 50 rem to the tissue and that is all that is required to be reportable.

Wright: Let's stay with 50 rem, or less than 80% of the prescribed dose being delivered to the patient being reported as a medical event. Can you discuss with me, maybe expand a little bit more how a licensee would go about making that determination for an extravasation?	Martin: That's why right now that's only referred to pretty much on the PET isotopes, because the SUV values would be affected. What happens most of the time is that the study is repeated within a day or so and then you start from scratch, the numbers are fine. That number is picked up pretty much for the PET isotopes at this point. I am not the physician, so if Dr Jadvar or Mike has other information on this, I would be glad for them to add information to that.	Ms. Martin did not answer the question. If the extravasation reporting exemption were removed, here are the steps that could be used to assess if an extravasation exceeded the dose to tissue reporting limit. 1. Monitor the administration. If an extravasation is suspected, take steps to mitigate the dose to tissue and ensure the injection site is included in the imaging field of view. 2. Assess how much activity remained at the injection site at time of imaging. If quantitation is not possible, estimates can be made of the dose left in the tissue. The accuracy of these estimates can vary based on the capabilities of the licensee. 3. Use serial measurements of the patient-specific biological clearance (including clearance and half-life) to estimate the initial extravasation activity. 4. Use dosimetry software to compute dose to the estimated tissue volume and to a 5cc reference tissue volume. Imaging of the injection site and assessment of the activity at imaging time is a process that medical guidelines currently suggest should happen if extravasations are suspected. The remaining activities can take ~3-5 minutes per case or less if there is evidence that the residual activity at the site and biological clearance indicates that the dose will not exceed 0.5 Sv.

	Jadvar: All I can say as a physician is extravasation can occur, and as Ms Martin already mentioned, usually visually you can see that there is a little bump or swelling even forming, and when you do the image on the PET camera you see that that area is hot on the image and sometimes if we know for a fact that some of the tracer has been extravasated, you may want to exclude that area from the image so that it does not damage the image processing of the rest of the scan, because it can do that. But you know it is common that you warm the area, using hyperthermia to make sure that the clearance is made more rapidly. We have the patient's arm elevated. There are interventions that we do like massaging the area just to make sure that the clearance is improved. And then of course we ask the patient if they have any symptoms of any sort in relation to that. It has not been, to my experience, a major problem, even the images are not that bad. They are of diagnostic quality, and we can make our determination of what is going on with the patient. But if there is a large amount for some reason that get extravasated, some of these patients have received many many chemo therapies, their veins are fragile, that can happen. And it turns out is may be a difficult redo of the procedure, we actually have in our hospital, and I'm sure in many other places, nurse practitioners or other folks, typically from oncology, in our case from our cancer center, who are very good at accessing the veins even in these difficult cases. So we can do that, or if nothing works, some of these patients have PICC lines or central lines, so we don't even have to worry about injecting the tracer through our own access but the access has been provided to us and we use that access for delivering the radiotracer.	Dr. Jadvar assumes the extravasation can be visually identified. This is rarely the case, as previously noted. His suggestions to mitigate the damage have been described in the literature. While there are no clinical studies that provide scientific evidence to suggest why these steps might be beneficial, these steps, combined with flushing the site with saline, seem appropriate. As noted earlier, patients rarely feel symptoms from radiopharmaceutical extravasations, unlike contrast CT or chemotherapy, where patients complain of burning sensations. Dr. Jadvar also mentions that physicians sometime try to "read through" the extravasation if the diagnostic quality of the image is not too bad. For any quantitative procedure, a physician cannot read through an extravasation. As the co-inventor of the PET/CT scanner has attested, an extravasation invalidates quantification. Additionally, if a lesion is not visible in the image as a result of an extravasation, it is inappropriate to suggest that a physician can see what can't be seen. The nuclear medicine communities' consistent messaging that bad veins cause extravasations is misleading. Many of these same patients with bad veins are chemotherapy patients and receive infusions in peripheral IVs. Yet, chemotherapy peripheral IV extravasation rates are 0.18%. Dr. Jadvar also mentions that some nuclear medicine patients have their injections administered through PICC or central lines. These administrative routes are usually contraindicated for nuclear medicine administrations, since the lines retain the injected radiopharmaceuticals and can compromise the image.

Wright: One last quick question, because you were hitting right where I wanted to go. As a patient myself, I had a port. What is the percentage of ports for the patients that are getting the real wicked stuff, versus PET scans or MRIs or CT scans or whatever, how many are going through veins versus a port? I would think, intuitively, if someone has been sick for a while, it would go through a PICC line or a port. Can you give me some idea of the percentage is there?	Jadvar: I can't tell you the percentage, but generally we don't use, at least in our place, we generally don't use the port because that's an area that is used for delivery of chemo therapeutic drugs, and typically we don't want to interfere with the function of that port. But PICC lines have been used, I can't tell you the percentage for PICC lines, and again, with patients with ports and PICC lines, well not PICC lines, if PICC lines we use it, but if there is a port, most of the time there is a way to access the peripheral vein, and that is not a problem. We try not to use the ports, and sometimes they tell us not to use the port, you know, the oncologists.	In over 20,000 cases monitored by Lucerno technology, less than 1% of cases involve the use of a port or PICC line. Again, these are contraindicated for administration of radiopharmaceuticals, since the materials used in these access devices can retain radiopharmaceuticals even after multiple saline flushes.
Hanson asked only extravasation questions		
Hanson: The subcommittee recommends that extravasations should be considered a type of passive patient intervention. Is that always a type of passive patient intervention, so it is never a misadministration, for example?	Martin: As far as I am aware, and as far as this committee is aware, I would certainly say that is it. I don't think anyone in the medical field is going to purposely misadminister or cause an extravasation. As far as I am aware, that is a patient intervention from a problem with the patient's physiological status.	Ms. Martin is incorrect. Passive patient intervention is not the cause of extravasations. The evidence is clear that through improved tools, training, and technique, extravasations can be reduced. Certainly, some patients are more difficult to inject than others. Perhaps the Commissioners can reach out to the Association of Vascular Access to solicit their opinions on the topic of "passive patient intervention." Ms. Martin's suggestion that no one is going to purposely misadminister is irrelevant—that would likely be a criminal act. It is assumed that all misadministrations are accidental. This should not exempt them from being reported.
Hanson: So, there is never a medical error? Of course, not intentionally.	Martin: I am not aware of a medical error when it comes to extravasations. I'm sure. Like I said, I don't know of anyone that would certainly do it on purpose. All extravasations…when you are trying to make those injections, will depend on whether you say…there are some people that are just hard to hit the vein correctly would be how you would define that. But I don't think it is a purposely caused medical error.	Ms. Martin has either not read the literature regarding factors associated with extravasations or is deliberately evading the question.

Hanson: Right, no, not purposely caused or intentional. I am not trying to ascribe intention. And yet, errors happen. Sometimes you don't sink the putt or hit the ball or score the touchdown. Sometimes you fumble or there's an interception that happens. I have similar question on page 75…	Sheetz: May I comment on that? I think the performance of injection is a combination of technical skill and navigating the patient anatomy. Prior to going into radiation safety and health physics, I was a practicing nuclear medicine technologist a number of years ago. I performed thousands of intravenous injections. Some of those resulted in extravasations. Sometimes I realized it, other times I didn't and it appeared on the image. It is very difficult to tease out whether it was an error on the part of the person performing the injection or the patient's anatomy was such that it was very challenging or difficult to get the needle into the vein, or the vein tore, or when removing the needle, there was some leakage out. There are so many different variables and factors I think it would be very difficult or, again, that is why we keep going back to this is a practice of medicine issue and it really should not arise to a medical event reporting unless it results in permanent functional damage. Thank you.	Mr. Sheetz accurately assigns technical skill as a cause of extravasations. While some technologists may have trouble with certain patient anatomy, other technologists may have less difficulty. Mr. Sheetz also accurately describes how technologists may not always know they have extravasated. The administration of a radiopharmaceutical is certainly a practice of medicine. However, when that administration results in an extravasation that exceeds 0.5 Sv dose to tissue, then it becomes a medical event. By reporting these significant extravasations and by performing a root cause analysis, authorized users can determine which of the many different variables lead to extravasations at their centers and can improve their administration quality. This is basic quality improvement technique that has been proven in many other fields outside of nuclear medicine.
Hanson: Thank you, Mr Sheetz, that is a really interesting point and I want to drill down on that a little further. We have similar language on page 75 where exceeding the medical event dose threshold doesn't indicate error or harm. Does it not? Is that a never statement or a not necessarily statement?	Martin: I'll take a first answer at this. I think it is not a never because, particularly with some of these more potent therapeutic agents in a very small area, you can get the dose up to a level that you could potentially cause ulceration or something. But most of the time that is a not necessarily comment. In other words, exceeding the 50 rem does not necessarily mean permanent function damage.	Commissioner Hanson is correct. The NRC states that this 50-rem limit does not necessarily translate into patient harm. However, the nuclear medicine community has stated that 100 rem is the threshold where one could expect adverse tissue reactions (patient harm). But exceeding 50 rem (500 millisievert) dose to tissue does indicate that a licensee may have an issue with the proper handling of radioactive material. A properly administered diagnostic radiopharmaceutical will result in a dose to tissue of ~1 millisievert. A dose of 500 millisieverts indicates that the administration did not go as planned.
	Sheetz: Exceeding 50 rem, or at 50 rem, it will not cause any tissue damage no matter where it is. So you can exceed the dose threshold for reporting a medical event and there will be no harm to the patient. There will be harm if the dose gets great enough, and I would say that would almost be exclusive to therapeutic radio pharmaceuticals and would be very, very rare for a diagnostic radiopharmaceutical to reach the level of patient harm or tissue damage. Thank you.	Here Mr. Sheetz makes an important point. While there is disagreement if 50 rem harms a patient, there is consensus from the medical community on what dose does cause harm. The information is on the NRC website. The societies agree that 100 rem is limit where tissue starts to experience adverse effects. And the higher the dose the greater the likelihood of stochastic effects. Clinicians must characterize the extravasation in order to know if an extravasation exceeds the medical event limit or the limit the profession states will lead to adverse tissue reactions. This characterization is also required in order to inform the patient and their physician of the extent of the extravasation. Furthermore, tissue dose is reported in sieverts. Therefore, it does not matter if the extravasated radiopharmaceutical is diagnostic or therapeutic as long as the dose exceeds the reporting limit. Clearly some radiopharmaceuticals would be more likely to exceed the limit than others, but reporting is correctly based on dose to tissue or skin.

Hanson: Thank you both very much. I want to follow up on that, because some of the language that we are talking about is the language of medical liability and I think that is bleeding into regulatory and practice of medicine type language, and I think that, at least for me, part of what is confusing and difficult to tease out in this issue. Whenever we talk about errors, there is talk about who made the error, who's fault is it, was there any damage, and so forth. I am concerned that, for instance, by not reporting…there is a categorical statement on page 77 about…that medical events resulting from patient intervention, which is the bucket that all of these things are falling into, would not improve the practice of medicine. And I'm finding that…and would not…it would potentially infringe and would not help prevent the occurrence of these events in the future. That seems confusing to me. If we had information about how these events are occurring, either on the patient side or the administration side, whether they rise specifically to the level of medical events or not, how could that not improve the practice of medicine and not prevent them from occurring in the future, at least in some way, even on the margins?	Sheetz: I can respond to that. Again, the causes for extravasation are varied. And again, depending on technical abilities and patient anatomy. I'm not sure you would get in the medical event report the actual root cause analysis of what the reason was. You would just get that it extravasated and exceeded the dose threshold. So, I don't see that information coming back to the licensees and providing any benefit.	Commissioner Hanson is absolutely correct. While Mr. Sheetz may be correct about causes of an individual extravasation, understanding what factors are associated with a series of extravasations should lead to improvement programs that will reduce their rate in the future. This quality improvement approach has been successful in many industries and nuclear medicine is no exception. If a licensee routinely extravasates patients with very high doses and does nothing to evaluate root cause or to improve, the licensee should not be allowed to continue to practice. Patients need to know which licensees have high-quality injections. Payers need to know this information. Regulators need to know. Mr. Sheetz has completely missed the point of monitoring, tracking, and reporting.
	Martin: I would support that answer too. You can say you had an extravasation, but that is not necessarily going to cause…there is not a transference from one patient to the other. So in other words, just because it happened on patient 1, you are not going to prevent it from happening on patient 2 if you happen to have two patients with problem veins.	Ms. Martin's response indicates that she has not read the literature on quality improvements in the delivery of pharmaceuticals and radiopharmaceuticals. Information can be gleaned from cases that can be used to help licensees and individual technologists get better…if they choose to improve. Wake Forest Baptist Hospital presented a poster at the SNMMI/ASNC 2019 mid-winter meeting that captures this point perfectly. They performed a quality improvement project on PET/CT injections because they were extravasating frequently. One lesson they implemented was the need for their technologists to replace use of butterflies for venous access with IVs. One technologist's extravasation rate dropped from 16% to 0% immediately. When the technologist believed the project was over, they returned to using butterflies for access because it was their preferred method. Their extravasation rate immediately jumped to 13%. If reporting of extravasations were mandated, it is doubtful that licensees would allow known bad practices to persist. This is how the NRC could positively affect patient safety and quality of care.

Hanson: Hmm. Ok, well let me take a different angle on that slightly. In the 2019 report on the subcommittee on extravasations, it said the prevention of extravasations is a medical training issue. So, if it's a medical training issue, why do we call it passive patient intervention?	Martin: Well, Mike is actually the one who has been through the training. I've been on the teaching end of it but not doing the actual needle training. My understanding is whether you are a nursing student or whether you are a nuclear medicine technologist, they all go through the basic training on how to do injections. Mike probably has more information than I do on that.	Our conversations with the teaching programs indicate that every program is different and few, if any, actually teach hands-on phlebotomy skills. Technologists get much of their injection training while on site at affiliated hospitals or once they are on the job.
Hanson: Presumably, even on people with bad veins, right? Different approaches and techniques, and so forth?	Martin: Correct. I happen to have a niece that's an RN and we've gotten into this discussion fairly often and that was when I learned about what all training they went through. And I know the nuclear medicine technologists in the programs I have been involved with do basically the same training. In fact, they are trained on patients with difficult veins, because they know that many of their patients are going to have the difficult veins. Mike, as nuclear medicine tech, do you have anything to add to that?	
	Sheetz: There is a training component. Certainly, you have to learn how to perform injections, and the skill level increases with the more you perform and the more different types of challenging veins you encounter. Again, I caution, this is not something to try to regulate. Regulating the person's skill level. Certainly, there should be the basic instruction and training on how to perform injections. All nuclear medicine technologists receive that, physicians receive that. And then you acquire more skills the more administrations you do.	Mr. Sheetz confirms that technologist training continues on the job as their experience grows. Mr. Sheetz confuses medical event reporting with regulation of a person's skill level. It remains the prerogative of the licensee to ensure their technologists are adequately trained. However, if technologists without the proper training and/or skills continue to extravasate patients with doses that exceed medical event reporting limits, this indicates that the licensee is not handling radioactive materials appropriately. This is the exact scenario through which medical event reporting can help protect patients and ensure the accurate and safe delivery of radiopharmaceuticals.
Svinicki closing comments		

Svinincki: Things that we have been talking about today that fall within the domain of radiation safety around occupational things for medical workers. Looking at that, we do get into the area of medical event reporting. Ironically, I am sure to many, medical event reporting is not necessarily linked to patient harm or overall negative patient outcomes…what we are trying to do is bring to light things that are systematically, programmatically may be deficient, and therefore our regulations are meant to bring those forward or identify if its occurring, either with individual practitioners or within the program of a large medical facility. Our regulations would, once bring those out in to the daylight, hopefully get the examination so that corrective actions or training could be taken. A lot of the focus in this particular meeting with the ACMUI has been on things that get very, very close to patient care.		Chairman Svinicki is absolutely correct. Eliminating the reporting exemption will shed light on an issue that is leading to a large number of significant extravasations every day in the US. These are almost completely avoidable. However, the ACMUI and the community continues to find excuses and illogical reasons to retain this exemption. There is an abundance of evidence indicating extravasations are NOT virtually impossible to avoid. Many extravasations exceed the medical event reporting limit and thus become a regulatory issue. Some cause radiation harm to patients. Some negatively affect images used to guide care. All are undesirable. Action needs to be taken immediately to address this issue. Patients will benefit. Healthcare costs will decrease. Nuclear medicine administration quality will improve. This is essential as the nuclear medicine profession enters the new and exciting age of radiotherapies.