LUCERNO DYNAMICS, LLC
140 Towerview Court
Cary, NC 27513
919-371-6800

May 13, 2021

Kevin Williams
Director, Division of Materials Safety, Security, State, and Tribal Programs
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Delivered via email

Dear Mr. Williams,

During the March 16, 2021 ACMUI meeting, the NRC hosted Dr. van der Pol, author of a 2017 literature review published in the European Journal of Nuclear Medicine and Molecular Imaging. Dr. van der Pol addressed several topics pertinent to the extravasation issue and petition (Docket: NRC-2020-0141).

As outlined in the petition, the current NRC policy that exempts extravasations from medical event reporting is based on the incorrect premise that extravasations are "virtually impossible to avoid." Dr. van der Pol suggested extravasations are **not** virtually impossible to avoid; in the recently published transcripts from this meeting, he stated:

> "But, I think, if we do the right – if you have the right precautions then extravasations is [sic] definitely something that can be – yes, that can be – I'm looking for the right word, sorry. Something that doesn't – it's something that doesn't have to happen."

Throughout his presentation, and during the question-and-answer session, Dr. van der Pol never once mentioned that an extravasation is caused by the patient or passive patient intervention. Rather, while discussing clinicians administering radiopharmaceuticals, Dr. van der Pol stated:

> "The way you perform your trace injections – it's very important, of course. And I know from my older colleagues who already retired a few years ago that – not so long, for instance, they used straight needle injections and they saw a lot of extravasations…"

Dr. van der Pol's comments suggested that the frequency of extravasations can be reduced by training technologists and by choosing the proper tools to access and administer radiopharmaceuticals. His comments are consistent with what the extravasations experts in the Association for Vascular Access stated in their November 2020 public comment. Extravasations are the result of lack of training, poor technique, and improper tools.

Dr. van der Pol also shared with the ACMUI a graph that showed even low levels of extravasated activity from routinely used therapeutic and diagnostic isotopes can easily exceed regulatory reporting limits. These comments supported other evidence provided to the NRC that significant extravasations can exceed reporting limits, including:

- several examples provided in the recently published method of performing dosimetry for extravasations using patient-specific biological clearance,
- dosimetry cases submitted to the NRC as part of the petition,
- and independent research supported by the North Carolina Policy Collaboratory that was also provided to the NRC.

Dr. van der Pol's presentation was followed by a question-and-answer session reserved for members of the ACMUI. Comments and questions by ACMUI members from this session, along with comments from leading nuclear medicine society members and ACMUI members in other venues (December 2008 meeting, May 2009 meeting, Fall 2019 extravasation position paper, Fall 2020 conversation with the NRC commissioners, and the 12/8/2020 public comment meeting) continue to reveal contradictory, circular, and untenable positions in an attempt to avoid regulations.

- They claim extravasations frequently occur, then they claim extravasation only occur 0.1% of the time. Often, the members perform incorrect arithmetic or completely misinterpret rates.
- They say that diagnostic extravasations cannot result in a dose that exceeds reporting limits and only therapeutic extravasations might matter. But when shown evidence to the contrary, they then state that the dosimetry is really hard to perform and time consuming. Ignoring the dose to tissue, they state that any patient with a significant diagnostic extravasation is reimaged.
- When shown that extravasations can be characterized accurately and quickly and very few patients are reimaged when experiencing a significant extravasation, they then claim that extravasations are a practice of medicine issue.
- When reminded that extravasations can routinely exceed 0.5 Sv to patient tissue, they disregard this risk-informed regulatory limit that suggests possible mishandling of isotopes and they suggest that the reporting limit should be ignored since it is unlikely a patient can be harmed by 0.5 Sv to tissue.
- When reminded that high absorbed doses can lead to adverse tissue reactions, they ignore their own stated threshold of 1.0 Sv and claim they never see patient harm.
- When shown evidence that radiation symptoms can take weeks, months, or even years to manifest and would not be visible to the community, they claim that if harm was happening it would be reported.
- When shown evidence that dosimetry and patient follow-up is not performed on diagnostic extravasations and, since there are no requirements, are not reported, they state that is because diagnostic extravasations do not cause harm.
- When confronted with evidence that extravasations are caused by lack of training, poor technique, and improper tools, they claim that the patient is to blame.
- When shown evidence that these same nuclear medicine patients are also contrast CT and chemotherapy patients and experience extravasations in these areas of medicine only a fraction of 1 percent of the time, they state that nuclear medicine technologists use best practices to administer radiopharmaceuticals and again, the patient is to blame.
- When shown evidence that technologists are not using best practices, they claim that there is no intent by technologists to extravasate.
- When pressed to do something about the extravasation issue, they released a patient education leaflet that suggests some technologists are better than others, sometimes things happen, and it may be best to ice the injection site when an extravasation occurs, which is the exact opposite of the proper mitigation step – applying a warm compress.

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Many of these attempts to deflect regulation and accidental arithmetic errors were evident in the March 16, Dr. van der Pol question-and-answer session (unfortunately, the public could not participate). A detailed analysis of the meeting transcript is attached for your consideration. One ACMUI member suggested that five significant extravasation out of 400 administrations that required reimaging represented 0.01%. The correct rate is 1.25%. Our experience suggests that ~2.5% of radiopharmaceutical extravasations are significant. However, if the correct rate for extravasations so significant that they require patients to undergo another imaging procedure is 1.25%, then over 375,000 patients are experiencing significant extravasations in the US every year. This needs to be addressed now.

Lucerno approached the NRC in December of 2018 and shared evidence that extravasations are not virtually impossible to avoid. For the past 30 months we have shared evidence that the 1980 exemption policy for radiopharmaceutical extravasation is based on incorrect assumptions and that significant extravasations can exceed existing medical event reporting limits. Evidence-based policymaking principles require the NRC incorporate the implications of these findings in its regulations and acknowledge that extravasations are avoidable and warrant NRC oversight. During this same time, the community and ACMUI (except for the patient advocate) have responded with the previously listed circular responses. Moreover, several medical societies have submitted public statements that are full of errors, misrepresentations of the facts, and without scientific support. These society issues were highlighted by a group of experts in an email from Dr. Daniel Fass to you on March 16, 2020. During the 30-month period, we estimate that over 1 million patients have received a significant radiopharmaceutical extravasation. We believe it is time to approve the petition and move into rulemaking so that the community will begin the process to reduce the rate of radiopharmaceutical extravasations.

Sincerely,

Ronald K. Lattanze

Digitally signed by Ronald K. Lattanze
DN: cn=Ronald K. Lattanze, o=Lucerno Dynamics, LLC, ou, email=rlattanze@lucernodynamics.com, c=US
Date: 2021.05.13 23:58:15 -04'00'

Ronald Lattanze
Chief Executive Officer

Attachments:

1. Analysis of March 2016 ACMUI Dr. van der Pol presentation

Cc: Chris Einberg
Lisa Dimmick
David Crowley

ACMUI March 16, 2021 Meeting Transcript

ACMUI Transcript, related to extravasations	Comments
DR. VAN DER POL: Okay. So -- let me just share these slides. Oh, here it is. So well there's not a lot of further introduction needed, I suppose. But I -- I made these slides anyway. So I'll share with you it -- it also shows where Maastricht is in the Netherlands in relation to Amsterdam. But let's just start with the main part of the presentation because you asked me to tell you something about extravasation, which I did a literature study, as Mr. Sheetz already told. So the -- actually came following a discussion on an extravasation case during my -- the other part of my training to become a nuclear medicine physician. And there was no protocol -- no local protocol on how to act in case of extravasation. So we had a lot of questions on that. So, like, can -- can extravasation actually cause deterministic effects such as skin burn or other symptoms? Should you apply any kind of therapy, like cooling or should it be warming? And should you perform dosimetry and how should that be done? And a lot of other questions. So we started looking in -- in guidelines from all kinds of association -- the Dutch Association, of course. But also the European Association. The SNMMI and also the German Association of Nuclear Medicine. But none of those had guidelines on extravasation. So we -- we -- the only thing we could do was try to -- to search in the literature for ourselves. So we did quite an extensive literature search. And after all the work we said we should share this information. So why not publish this -- this data? And this actually led to a publication in the European Journal of Nuclear Medicine and Molecular Imaging in 2017.	In his opening comments, Dr. van der Pol points out that there is a lack of information in the medical community regarding how to address extravasations. He makes this same point in his paper. This highlights the issue that, in general, the nuclear medicine community does not understand radiopharmaceutical extravasations. This has been reflected in the many public comments by the community.
So we did this extensive search on Pubmed and Embase with the following search strings. It was a combination of extravasation and several synonyms, like infiltration, misadministration -- combined with a variety of isotopes which are used in nuclear medicine -- also spelled in different ways to -- to make sure everything was included. And it combined with radiopharmaceuticals. So radio isotopes. And it yielded 2,153 results in Pubmed and 3,493 in Embase. And of course were a lot of doubles. So we -- we merged all the results of Embase and Pubmed and of course excluded all the doubles. And we screened all those abstracts -- myself and another person. And if the abstract mentioned human radioactive tracer extravasation, then the publication was marked for further analysis which were subsequently retrieved from online sources from different university libraries, or by just tracking down the authors' email addresses and just ask for the publication. And afterwards, bibliographies were screened to compliment the search. So when we have collection, these data were extracted -- a number of cases -- to tracer involved injection place, estimated extravasation following an activity, estimated tissue dose, follow-up duration and method, applied medical interventions, and if these were advised or discouraged by the authors.	

So we had 4,523 abstracts and a lot of those were rejected because there were animal studies -- and I think I should add that only a few animal studies were actually the subject of extravasation of a radiopharmaceutical dosimetry study. A lot of excluded abstracts were because they reported about extravasation or infiltration of a substance other than a radiopharmaceutical. Also, excluded when extravasation was mentioned as a technological finding which was actually not associated with the injection of radiopharmaceutical. And 603 abstracts were excluded because radionuclides were used for other purposes than medical imaging assays. And so we eventually retrieved the full text of 81 included publications. So we were actually able to retrieve all the full-text PDFs, or -- or printed versions of those publications. And we added 27 publications to a total of 108 publications. And 44 of those actually reported on extravasation of radiopharmaceuticals. So actual cases. And 37 of those reported diagnostic and 8 therapeutic. That makes for a total of 45, but one did both diagnostic and therapeutics. Ten expert opinion manuscripts were also included based on publications, but they did not report a case of extravasation.	
So this table summarizes the results of the diagnostic traits for extravasations. And -- and you see the -- the largest number we're seeing in FDG as well as Tc bone tracers. And to be honest, that number is an overestimation because in one article there were actually a lot less extravasations reported then. And we reported in our article, that's actually something Mr. Sheetz found out. So we made a mistake. But still a decent number of reported extravasation. And so I'll give you some examples -- of course, I cannot give you all those publications in -- in just 30 minutes. But I'll give you some examples to show you what kind of publications these are. So starting by this publication by Wagner, et al. from 2011. And actually a lot of -- lot of cases we included were case reports in which axillary lymph nodes was visualized after a extravasation. So see in the right, lower quadrant, in the MIP image that there is an extravasation at the right arm. And you see a lot of intensity over there. And you also see this lymph node, which accumulates a lot of tracer. And they reported this case because they had a petechiae [PET/CT] from before the lymphoma treatment. And that actually didn't show any activity and they didn't see any anatomical evidence for a pathological lymph node. It should be a more mass-like nodule without hilum. So based on the CT image and based that there was no morphological change, they concluded that this was actually benign lymph nodes and probably the cause of the tracer extravasation.	
The other similar example by Alibazoglu -- they are from 1998. And we see a lymph node pointed out, over here, with a tracer extravasation over here. And, you know, repeat study. Which is displayed in C and D. You don't see that lymph node anymore on this repeat study was done a few days after the first PET.	The nuclear medicine community suggests that they understand that an extravasation can result in a positive lymph node, but what they fail to share with the NRC is that if the injection site is not in the imaging field of view and if

So that -- that's -- because an important finding because you have to be aware that extravasation can cause a false positive lymph node in oncology studies, which could lead to over staging of disease. And this is an example of by Hall et al. from 2006. And that's another type of studies. So these are more patients series in which they also measure the amount of activity at the injection site. In this case there were 190 FDG PETs evaluated and 39 of those, which is a fraction of 21 percent, had a visible focus at the injection site.	they see a positive lymph node, they cannot, and do not know for sure, if the positive lymph node is a true clinical issue or if the lymph node is positive because of an extravasation. In this situation the patient suffers. One of three things is likely to happen: • the finding is documented, and nothing is done, • the study is repeated and if there is no extravasation and the lymph node is not positive, then the interpreting physician can deduce that the first image must have been extravasated. In this case, the patient underwent another imaging procedure and exposure to radiation because of an extravasation, or • an invasive additional procedure is ordered for the patient to determine if the lymph node is positive for a clinical reason. In all of these cases, the patient is receiving compromised care and, in some cases, additional radiation.
And 36 of those only had less than 1-percent injected dose. And three of those had more than 1 percent. And in those three, the -- as the SUVmax actually ranged from -- the change in SUVmax actually ranged from zero to 21 percent. So that's, I think, another important lesson that significant tracer extravasation can actually give you a variation in SUVmax which is also something you have to be aware of when you're reading a nuclear medicine scan and have to choose PET scan, or another PET scan.	Note that these estimates of activity were from imaging time. They do not consider that there may have been substantially more activity during the uptake period which was biologically cleared. When you consider the amount of radioactivity that was not in circulation during the entire uptake period, many extravasations that appear to be minor when looking at a static image taken over an hour after injection can in fact, be much larger extravasations earlier in the uptake period. This is important to the absorbed dose as well as to the quality and quantification of the image. There was nothing in this paper that suggests that the patients were reimaged and completed a test-retest analysis.

So this is a similar study with 400 FDG PET scans evaluated and also in about ten -- 10, 25 [sic] percent there was no visible extravasation. And five studies had repeat studies, so they gave numbers about these five patients with two FDG PETs -- one with extravasation and one without. So they saw a change of about 10 percent in -- with Mediastinal SUV and Hepatic SUV. So this -- it's a minor change in SUVmax in those studies.	We believe the transcript should read 2.5% (10/400) not 25%. One should not use reference organs to predict the change in the SUVs. They are inadequate and there is no clinical evidence to support that a change in mediastinal or liver SUV is an indicator of change in the SUV of a tumor. **Note, that 5 of the 400 cases were reimaged. That's 1.25%.**
So now let's proceed to the technetium tracers, or the bone tracers -- example of a similar (audio interference) reports I showed you. So it's something you can't see in a severe extravasation case that there is lymph node drainage of the tracer and as a result, the lymph node will -- can't really be seen as a focal spot of activity in this patient. So a lot of those other technetium tracers shows similar case reports of focal activity in a lymph node -- or just a painful experience for the patient. So let's proceed to the three cases which showed actually clinical symptoms, because all those cases -- they did not -- did only say there are extravasation. Of course they didn't report any follow up. So that's something you should know -- there isn't really much known about a follow up of basic tracer extravasation. Of course, if there would be severe consequences, you would expect with the high number of -- of nuclear medicine students all over the world every day, you should expect that someone should have published more severe symptoms, if there were any.	Regarding 99m-Tc tracers. Dr. van der Pol has not reached his conclusions based on evidence. Today there is evidence that Tc based radiopharmaceuticals can result in very high absorbed doses. Patients may or may not experience initial discomfort, but may experience adverse tissue reactions much later in time than what the community thinks is appropriate follow-up. No 99m-Tc extravasation cases were followed in the literature review. One should not reach a conclusion that patients were not impacted when there is NO patient follow-up. And one should not believe the statement that we would expect to see cases in the literature. In our data set, we have observed hundreds of significant extravasation cases. Only one has been submitted for publication.
Now let's proceed to the patients with symptomatic extravasation. So one actually is from a case with iodocholesterol, which is used in an adrenal gland study. So after 13 days this patient developed an erythematous puritic patch, as you can see in the photo. And they measure it -- almost complete tracer retention. So this tracer had the property that it really adhered in that injection place and didn't go away -- and actually deposited all the radiation in that place. And gave the symptoms. This is the second tracer with the reported symptoms, which is Thallium-201. And in this case, almost after two years of the injection of the extravasation of the patient also referred to -- also with an ulceration. So that -- these are the cases with diagnostic tracers. And these are the cases from therapeutic tracer extravasation. So in seven publications -- sorry, eight publications,	Of the 3,016 diagnostic tracer extravasations reported in the literature, only three cases were followed and all three resulted in adverse tissue reactions. **NONE OF THE OTHER 3,013 cases were followed.**

ten cases were actually published in literature, which also generally showed more severe symptoms like this very early publications from Dr. Patton in 1950 with skin ulceration from hydroxycitrate complex, 90-Y, hydroxycitrate complex. And this one by Williams in 2006, which showed these combination -- this combination after Yttrium-90.	
So the conclusions of our literature study were that extravasation of tracers is common. But I also think it depends on your definition of extravasation because if you only count a spot at the injection site, that's actually very common. But if you look at the -- at the -- at the PET studies, you see that the tracer extravasation cases with more than 1 percent are actually just a few. So it really depends on what you define to be a extravasation or a clinically significant extravasation.	Dr. van der Pol, concluded extravasations are common. But he also mistakenly concludes that there are just a few cases with extravasations greater than 1% of the administered dose. Again, he is not aware of how much activity was initially extravasated and was cleared during the uptake period before imaging. Therefore, one cannot reach the conclusion he reached, since **diagnostic extravasations are not characterized.** In our data set of over 22,000 monitored radiopharmaceutical administrations, it appears that approximately one in four or one in five extravasations are quite serious and can cause significant changes to SUV and other quantification measures. This roughly equates to 2.5-3% of radiopharmaceutical administrations. Minor extravasations are defined by RSNA QIBA as less than 5% of the injected activity.
I think the most important for us that -- us looking at is as physicians -- that there were no adverse effects of 18F, 99mTc, 123 Iodine, Gallium-68. And I think we should also add Indium-111. Now reported in literatures, which is good news because you don't even -- you don't have to expect any symptoms -- radiation symptoms in those tracers whenever there is an extravasation. Sporadic reports of other diagnostic tracers, like Gallium, have described soft tissue lesions. And multiple reports of severe events following therapeutic tracer extravasation were reported. So like Mr. Sheetz -- so then as introduction you had a number of questions for me to give our perspective on.	This is an assumption, and it is not based on clinical evidence. None of these patients had dosimetry performed. None had follow-up.
So the first of these is, what is the frequency of extravasation in nuclear medicine, and what criteria should be used for identifying an extravasation? So first of all, the frequency is -- is of course not very known. The only thing -- it's a few case series which -- from which I presented a few studies. So ranging up to 20, 25 percent in some studies. But depending on the definition, I looked at our report of radionuclide extravasations in our hospital. And in the period from	Dr. van der Pol suggests that the true extravasation rate is not known, because it is not measured and there is not a definition of what percent of the dose left at the injection site would qualify as an extravasation.

2007 to 2018. And actually, only three extravasations were reported well. I -- that must be some underestimation, but we only reported the extravasation case in which there was a clear clinical substrate. So when a patient's had pain and -- and you know, that's -- that's -- even that is quite rare in our clinic with the precautions we take. And to put it in perspective, we do around 6,000 nuclear medicine studies per year. And another perspective is that the report of contrast extravasation in -- in radiology in our -- radiology department in MUMC is 91 in the same period, between 2007 and 2018. And we estimate it to be about 50,000 procedures per year. So of course, there must be some under-reporting. But I think, if we do the right -- if you have the right precautions then extravasations is definitely something that can be -- yes, that can be -- I'm looking for the right word, sorry. Something that doesn't -- it's something that doesn't have to happen. So there's no national registration which -- from which I was able to -- again, get the numbers on a national level. So the second part of the question, what criteria should be used for identifying extravasation? Visualization, fraction of the injected dose -- well, I think there should be multiple criteria, of course.	However, he then uses his center as an example. His center may be very good at administering radiopharmaceuticals, since they care enough to monitor for extravasations, but his center is not representative of the rest of the nuclear medicine community, which does not monitor or track extravasations. While Dr. van der Pol only noted three extravasations had been reported at his center over an extensive period of time, his center has been focused on improving radiopharmaceutical administrations. Additionally, his center ignores certain extravasations that likely should have been reported and only considers images of the injection site, not the uptake period when evaluating the extent of an extravasation These conditions will result in an underreporting of radiopharmaceutical extravasations. **Dr. van der Pol makes his most important point here – extravasations are something that do not have to happen.** This clearly supports the position that extravasations are NOT virtually impossible to avoid. He also points out that no one is tracking these extravasations nationally. And there should be criteria. **To know which ones to track, one must characterize the extravasation.**
First of all, the clinical criteria -- is there a painful injection? Is there swelling? Is there a redness or pallor? A visual and -- with visual, I mean, on the skin itself directly? So can you see injection sites in relation -- or do you see -- skin quality? Of course, skin quality that can be -- can possibly be attributed to extravasation. And the injected dose, of course, quality -- in my opinion, is a parameter in nuclear medicine physicians who monitor. So I don't think, if you have a fraction of the injected dose, that there is actually a possible threshold under -- over which you say that you should repeat the study. I think that something in which -- do if you -- if you judge that your quality is too low, then you should always consider a repeat study.	These comments reflect the consistent misunderstandings in nuclear medicine about extravasations. • Most radiopharmaceuticals do not cause discomfort, • most radiopharmaceuticals have a very small injection volume – they will not cause swelling, and • there will be NO change in skin for hours or days after a significant irradiation. Again, van der Pol suggests characterizing the amount of activity

	that was extravasated so that clinicians can decide if the imaging study must be repeated. This is an essential step that providers must take to understand the regulatory implications as well as whether the patient should be followed. Ignoring the need to characterize extravasations should not continue.
Also, if the quality is degraded by other costs. One caveat to this -- the studies with the FDG PETs do show that there is a possible effect from SUVmax, so I can imagine that percentage, or a fraction of the injected dose actually -- can actually be helpful in estimating the difference in SUVmax if you have more data available on what the influence is on your SUVmax, and even better if your scanner actually provides a correction on the SUVmax based on the percentage of injected dose in your injection spot. I think that could be a future -- a future that would be very interesting for a future as you use PET scanners and software. In case of a therapeutic extravasation, any extravasation noted at any time point should be adequately treated and registered, irrespective of the dose. But what we do is we -- we register it locally. And we don't necessarily register in any national or -- register, or in -- to the authorities. I will come back to us in one of the later slides. So what of the appropriateness of reporting extravasation that we saw in a certain dose threshold as a medical event? Well, if you ask me that question then I am really curious about the method you use -- dose will be calculated because there is a huge variety in calculated dose based on the variation -- on the small variation of different parameters. I will come to that shortly.	It is important to characterize the dose and activity. **But you cannot use it to correct the SUV.** Clinicians have NO idea what happened during the uptake period. You can only estimate what is the amount you are SURE did not get into circulation. Please reach out to Dr. David Townsend, the leading expert on reconstruction algorithms if you have any questions about this particular issue. Future technology will be available in the next couple of years that will quantify the activity every second in the uptake period. This will help ensure clinicians know that the radioactivity was not present in circulation. However, no one knows the amount of activity that has cleared from the injection site via the lymphatic system and not yet entered the vascular system as intended. A therapeutic extravasation should also be characterized, just like a diagnostic. If the absorbed dose is greater than the reporting limit, the patient, their physician, and the State and Federal regulatory bodies should be notified.
If you want the threshold -- and I don't personally see any use in 0.5 Sieverts. You could use the erythema threshold of 2.5 Sieverts, but then again, if you don't have adequate method of very accurately measuring the -- the effective dose, then I don't think it's -- it's really useful to have a threshold in place, as a rule.	Dr. van der Pol does not understand the NRC already has a regulatory threshold that has been in place since 2002, which indicates that a center may have a problem handling isotopes. The threshold is not necessarily an indicator of patient harm. Dr. van der Pol's statement about not measuring the dose if there is not an adequate measure is consistent with a commonly held position. Dosimetry

	measurement methods do exist; while they may not be perfect measures, that is not a reason to ignore characterizing an extravasation. Published methods exist for characterizing extravasations. These methods should be used and if the value exceeds the reporting thresholds, the extravasations should be treated as any other reportable medical event.
So how has the -- the European community address reporting of extravasations? There is no European legislation on healthcare. That's something the EU let's -- let's the nations -- the member states decide for themselves. So every member state has a -- state has its own legislation on healthcare. So I can give you the Dutch perspective on that. There is no definition or mentioning of extravasation, let alone where your pharmaceutical extravasation. So our laws are quite -- yes -- have a broad interpretation on what -- what is an adverse event. There are two different definitions we use, which is a complication -- an incident, or a calamity. So a complication is an unintentional and undesired outcome during or following the actions of a medical care provider which demands adaptation of the medical procedure, or causes irreparable damage. So in this case, a medical care provider worked according to the medical standards and there was an unintended outcome -- undesired of course -- but which can actually be expected. It's a known complication. So we call that complication and (audio interference) in general to be a complication. So we also have incidents, and calamities and incidents is an unintentional or unexpected event that is related to the quality of healthcare. And that could have led to the death of a patient, or serious harmful consequences. And calamity -- which has a very similar definition but in this case the -- the event actually has led to the death of the patient, or serious harmful consequences for the patient. So we only report calamities to healthcare authorities, and incidents of complications are reported and registered locally as advised by healthcare professional societies. Unless one nature is not clear, and calamity is not ruled out, then we should let the authorities advise on the type of event. So next question. If -- what are the issues and challenges in determining the tissue dose for an extravasation. So first of all -- geometry. So you see that in -- in some case reports they actually try to do a dose calculation and most of the time they use a sphere model, or a disc-shaped model. So of course it's most easy to work with a point source, but it's not realistic when the source is within the patient. So you have -- you have to work with other types of shapes. But -- especially the disc-shaped source is already giving you very complex mathematics.	Dr. van der Pol is confusing the clinical term adverse event with regulatory reporting. The European clinical guidelines for nuclear medicine are clear. Procedure guideline for FDG PET (Boellaard et al, 2015) states that any problems with FDG administration must be reported, and if extravasation is suspected, then the injection area should be imaged. Dr. van der Pol admits that in his center, FDG and Tc are not characterized. If centers characterized radiopharmaceuticals, they would have an idea of the absorbed dose to tissue and would follow patients. Once they followed patients, the development of adverse tissue effects could trigger adverse event reporting. Dr. van der Pol also suggests, unfortunately, that an extravasation is a known complication, when previously he stated that they do not have to happen. The challenges that Dr. van der Pol suggests are part of dosimetry for extravasations have been addressed in the recent Health Physics Journal article that describes a method for characterizing extravasations. In that article, three different tissue geometries are modeled to address the point source issue.

And totally a very coarse model of the reality. Furthermore, which associated with geometry is that activity concentration is a very great factor in those calculations. And actually I have calculated some tracers in a sphere volume model. So you see on the x-axis, different sphere volumes ranging from zero to 100 cubic centimeters. On the y-axis, you see the amount of tissue dose, which actually should be effective dose in millisieverts but it's -- I made a mistake there. It's milligray on this slide, but it's -- it is millisieverts. For four kinds -- for four -- excuse me. For four different amounts of activity, one, ten, 100 and 1,000 megabecquerels and a variety of tracers.	The "complex" mathematics of the disc-shaped source are not complex, as described in the publication.
So you see that, of course in all those amounts of extravasation sheet, that of course these therapeutic tracers, the Alpha emitters, and the beta emitters are on top. And then the PET tracers, which are also beta emitters, follow and after that, technetium -- the pink line -- it's the lowest line. So I also plotted two horizontal lines, one dotted line, and one solid line. And the solid line represents 0.5 millisieverts and the dotted line -- so the solid line is 0.5, the dotted line is 2.5 millisieverts. So you already see in only one megabecquerel that if the volume is small enough -- which is actually quite realistic for the amount of volume used in tracer studies -- then in these theoretical cases, you already are well beyond these dotted line -- especially if you look at the gross for a more realistic amounts of tracers. Which shows that the activity concentration is -- is fairly important in calculating radiation dose. And it's fairly sensitive for small changes in volume, especially for the volume we use for tracer studies. You -- and of course, if it's, in a way, a worst-case scenario and an unrealistic geometry. But the point is that the activity concentration is a great factor. So what about cystic distribution with -- which mean that the tracer can actually be in between layers, for a large part, and then actually there is quite a -- an amount of self radiation of the tracer fluid. So I mean, this fluid is in a sense between different layers of tissue. And the energy is the deposited within the fluid itself. Another point is the homogeneity of the distribution, which can be fairly -- and in the real world, of course, you also have very complex geometry, which if the saying on time point one asked -- in time implies ten minutes or one hour or three days. It's any -- it evolves. It's not a simple disc shape, which remains the same during -- I mean, all the time. So it evolves.	Dr. van der Pol provides the NRC yet another example of how routinely used diagnostic isotopes (18F – FDG and 99m – Tc) along with beta-emitting and alpha-emitting isotopes can easily exceed reporting limits if a certain amount (in this case one Megabecquerel and higher) is extravasated. Please note that Dr. van der Pol states that PET tracers are also beta emitters. This is an important fact the nuclear medicine community routinely overlooks. Positrons are positively charged beta particles, often with higher keV values than the negatively charged betas used in therapies. For the community to state that a diagnostic cannot result in an absorbed dose that exceeds the reporting limit is incredulous. This information, along with the examples provided to the NRC in the petition, the publication of the Health Physics Journal article, and the independent research supported by the North Carolina Policy Collaboratory all show how significant extravasations can result in absorbed doses that should be reported to the patient, their physician, and the NRC according to Subpart M. Dr. van der Pol suggests his analysis uses worst-case scenarios and unrealistic geometries. However, the other examples provided in the HP Journal article, in the petition to the NRC, and in

	the independent research sponsored by the NC Policy Collaboratory use very realistic reference volumes of 5 cm^3, routinely extravasated activity levels, and several representative tissue geometries. In all cases, significant extravasations result in absorbed doses to tissue that should be reportable, if not for the outdated extravasation exemption policy. Because of the distance that energy emissions will travel in tissue as a result of an extravasation, Dr. van der Pol is correct in discussing self-radiation, but not in the idea that there are cysts of fluid in between cells that only irradiate the cystic radiopharmaceutical, itself. These emissions will travel millimeters in distance and there is no evidence that "pockets of activity that are millimeters in diameter" exist between layers. In the previously described examples that demonstrate how extravasations can result in high doses, the vast majority of the dose is the result of a self-dose being absorbed by the tissue in the immediate vicinity of the radioactive decays. In an article that studied how infiltrated activity dispersed in arm tissue, the authors did not find cysts several mm in diameter between individual tissue layers. Rather they found that the infiltrated substance "appeared to have spread in an oval pattern, but the site borders were more difficult to determine and measure…" and "as time after extravasation progressed, it became increasingly difficult to accurately palpate and measure the borders of induration." Yucha CB, Hastings-Tolsma M, Szeverenyi NM. Differences among intravenous extravasations using four common solutions. J Intraven Nurs. 1993;16:277-281

	Furthermore, Dr. van der Pol describes the evolution of the distribution of radioactivity during an extravasation. This biological clearance (dispersion and removal by the lymphatic system) is actually modelled in the Health Physics Journal article dosimetry method as well as in the independent research from the NC Policy Collaboratory. This biological clearance is patient- and radiopharmaceutical-specific, which builds the case for monitoring the uptake process to capture patient-specific biological clearance.
Biological half-life -- that's -- that's also a very important tracers. Very important factor. It's probably somewhat less relevant for short half-life PET tracers. But still, very important. But it's more relevant for tracers with longer half-life. So if -- if you want to do a good -- go calculation, then you should know a lot about the dynamic behavior of the tracer about the biological half-life. And the unique -- like I said in the last slide, you should also know the difference in -- in the shape of the extravasation during that time. So what personnel training qualifications and quality assurance should be placed and monitored to prevent extravasation in medicine. Excuse me.	Dr. van der Pol describes the evolving nature of the extravasation as biological clearance in this statement. He urges that this information is very important. He then notes that in order to provide a good calculation, one needs to know the dynamic behavior of the extravasation. **This is exactly what the Lara System provides clinicians.** This information is included in the Health Physics Journal article.
So a technician should be appropriately trained for obtaining -- obtaining the IV access and that should be something only a nurse or a doctor can do. But we have this special exception. So technicians can also do that. They should be trained how to do that and how to check if the patient is -- is okay. See if there's any obstruction, or see if -- if there -- if you can draw some blood. And you use a cannula instead of just a straight needle injection. For a nuclear medicine physician and radiologist, you should always check the image quality, which is also something that the technician should be looking -- as well, of course. And if they're not adequate, regardless of the result, you should repeat the study. And always look for signs of significant tracer accumulation near the injection site. And the radiation safety officer should keep a local registration of extravasation cases. And the only goal of that is to improve the quality and to train technicians, or any physician for the bad track records. And of course also to assist in cases where there's actually a -- a symptomatic tracer extravasation in -- for instance, therapeutic tracer extravasation. So that's it. I think we can move on to the discussion now.	Dr. van der Pol points out that training is critical for successful administrations. He notes that certain techniques and tools should be avoided. This is consistent with what causes extravasations. Dr. van der Pol clearly disagrees with the ACMUI and the SNMMI when they claim that patients are the cause of extravasations. They are not! Dr. van der Pol suggests that if image quality is not good one must check the injection site. This is not done in the US, because in the vast majority of radiopharmaceutical administrations, the injection site is NOT in the imaging field of view. As a result, poor quality imaging is used to diagnose and assess treatments. Additionally, Dr. van der Pol suggests the Radiation Safety Officer should have a register of those patients with doses exceeding a certain limit. We suggest that patients who exceed 0.5 Sv should

	be followed. They can be added to the Fluoroscopy-Guided Intervention registry (or some similar registry) of patients receiving high levels of radiation during interventional cases. He suggests **keeping track of these high dose cases so that lessons can be learned, and information shared to improve quality and training of clinicians with bad track records. This is the purpose of medical event reporting.**
CHAIR METTER: Thank you, Dr. Van Der Pol. I -- that was a very interesting presentation. And very thorough. Thank you for answering our questions that we -- Mr. Sheetz posed to you and in a very nice fashion. Are there any members on the ACMUI Committee that has a question for Dr. Van Der Pol? MR. SHEETZ: Hello, this is Mike Sheetz: CHAIR METTER: Yes, go ahead.	
MR. SHEETZ: Thank you very much, Dr. Van der Pol, for the excellent presentation. I appreciated the issues and complexity in calculating the dose that you brought up. And I actually appreciated the cystic model that you mentioned and I -- my opinion is that's probably the more realistic model to follow in trying to calculate tissue dose from extravasation will be contained within layers of tissue. And the tissue will not be uniformly mixed throughout the extravasation. And so, by sending it to via sphere or even a disc in calculating the dose within that sphere disc, there is a gross overestimate of the dose. And in the tables you showed how it exceeds millisieverts very early on from a small amount of activity. And an actual dose to -- to the tissue, or to the skin -- wouldn't be reaching that level, I think. I'm going to ask your opinion, we haven't been seeing these tissue reports occurring. But the fact that we do not see these occurring routinely means -- that little dose is really just not being achieved to the determined tissue or skin. Thank you.	This is another example of the ACMUI not considering peer-reviewed literature as evidence and fabricating theories. There is an abundance of evidence that infiltrated activity does not only reside in a cyst-like bubble in between tissue layers. If what Mr. Sheetz suggests is true, then infiltrated activity in the tissue would not be visible outside of the cystic bubble he is wishing exists. Instead, all the images show that the infiltrated radioactivity spreads among the tissue and surrounds tissue. Furthermore, there is a peer-reviewed article that describes this exact process in patients who were intentionally infiltrated with saline. Yucha CB, Hastings-Tolsma M, Szeverenyi NM. Differences among intravenous extravasations using four common solutions. J Intraven Nurs. 1993;16:277-281 As a result, and contrary to Mr. Sheetz' theory, the infiltrated activity is spread throughout layers of tissue and as a result the ionizing radiation is depositing energy in tissue cells and is not

	harmlessly irradiating other atoms of isotopes. The tables that Dr. van der Pol presented are correct. It does not take a large volume of radiopharmaceutical to result in a high dose to patients. And as proven in recent studies using a now-published method, actual diagnostic extravasations do reach very high levels of absorbed dose in patient tissue. Furthermore, the reason that Mr. Sheetz and Dr. van der Pol do not see adverse tissue reactions from these extravasations is because patients are not being followed for the appropriate amount of time during which the symptoms will develop.
DR. VAN DER POL: Yes, yes -- I definitely agree with that. And that's actually the basis of our conclusion of our publication four years ago. Since there is just no evidence literature of symptomatic radiation damage in these traits -- in a lot of traits that are used which I mentioned before, on the same basis. I find it very unlikely that these cause these levels of radiation needed to -- to give symptoms -- radiation symptoms.	One cannot reach this conclusion without performing dosimetry and following the patient. In fact, when patients are followed for the appropriate amount of time, as Dr. van der Pol described in his paper, the patients do develop adverse tissue reactions.
CHAIR METTER: Thank you, Michael. Are there any other questions from the ACMUI members -- from the subcommittee, or the ACMUI committee itself? (Simultaneous speaking.) CHAIR METTER: Go ahead. PARTICIPANT: Go ahead. MEMBER DILSIZIAN: Sorry, should I go first? PARTICIPANT: Yes.	
MEMBER DILSIZIAN: Thank you. Dr. Van der Pol, congratulations for putting together the meta-analysis. You know, these are not comments in anything to do with your publication. I just want to highlight some of the things you said, and summarize it, and maybe you can give your opinion about the four points that I'm going to make. One is clearly we should separate diagnostics and therapeutic extravasations. The criteria probably should be different and just something that, you may, want to give your opinion about. Second, in general, it's much more difficult to publish negative studies. So all the -- all the publications are biased. So it's those that potentially have something to say about extravasations, otherwise, no paper would be published. If I just present all of my experience from Mayo, for example, with only one repeat study that's over the last 20 years,	Dr. Dilsizian suggests it is important to separate diagnostic and therapeutic extravasations. And he suggests the criteria should be different. These suggestions indicate that Dr. Dilsizian may be unfamiliar with the medical event reporting criteria, the intent of reporting, and the energy emissions in routinely used diagnostic isotopes. The medical event criteria is appropriately agnostic to the type of radiopharmaceutical, since what matters is the absorbed dose to the patient tissue. Since diagnostic and

that would not be published. On the other hand, if you have a paper with 400 pieces where five of them were repeat studies, then it becomes interesting -- even though that number is 0.01 percent of repeating studies. So in my opinion, then, you know, the way you presented it -- there's extravasations and there's extravasations. The small ones -- they are inconsequential, even if you have an actual lymph node -- the couple of examples you gave -- we're all learned that and educated to know that. We can differentiate an extravasation inside a drainage from real malignancies. That's not confusing. So the ones that are important, in my opinion, are the ones that were repeated. So of the FDG PET studies that you presented, five of them were repeatable of 400. That's 0.01 percent. That's pretty low. But that's -- to me, the repeat ones are the most significant ones. And yet, those were very, very small. Obviously, if clinical symptoms -- symptomatic extravasations are important, then we should be -- you know, knowledgeable about it and report it. And regarding the SUV, we all know that the SUV counts per inject of dose per weight. I think that all of us who use SUVs are educated enough to understand not only does it depend on the injected dose -- and the extravasation, obviously, it would confuse an SUVmax -- but also it's based on weight. A lot of oncology patients that we follow are losing weight every year. So we are very familiar that the SUV values are not an absolute -- that it's all clinically based, and we don't rely on SUV completely when we interpret images. So it's nice to say that, but it's not as critical because we're all very well educated on knowing the changes of SUV max based on injected dose and weight. So in summary, I think in my opinion it seems to me that, just -- regular minor, extravasations is not clinically relevant. Those with -- who are repeated studies would be relevant, but except I think in this type -- these publications, only 0.01 percent. Clinically symptomatic extravasation should be paid attention to because obviously, it's rare but it's significant. And in my opinion, I think therapeutics, which is a new area, should be different from diagnostics. Maybe you can comment on all of those points.	therapeutic extravasations can exceed the absorbed dose and thus dose equivalent criteria, both should be reported. Furthermore, the energy emissions in certain diagnostic isotopes are no different from certain therapeutic isotope emissions. Dr. Dilsizian also claims that it is more difficult to publish a negative study. There is no evidence to support this statement. And if he is suggesting that there is a lack of published data indicating that extravasation rates are really not that high, then his suggestions run counter to over 40 years of literature, previous ACMUI meeting minutes, medical society statements, and comments from nearly every technologist who all state that extravasations are very common in nuclear medicine. Dr. Dilsizian also misrepresents arithmetic, when he suggests that 5 repeated studies out of 400 is 0.01% and thus pretty low. In fact, 5/400 is 1.25% and considering that most injection sites are outside the imaging field of view, a 1.25% repeat imaging rate likely suggests that 2.5-3% of images should be repeated. Furthermore, Dr. Dilsizian as a nuclear medicine physician and cardiologist has misunderstood the Standardized Uptake Value ratio and the role that patient weight plays in the SUV formula. His comments regarding this tumor metabolic comparison value used by oncologists suggest that he misunderstands how SUV is used in practice and how it is required by the ACR in certain patient imaging studies. He then states that minor extravasations are not clinically relevant, but he also suggests that significant extravasations are repeated. There is absolutely no evidence to support this statement. In

	fact, it is more likely that most significant extravasations are not visible in the imaging field of view, and when they are present, they are not repeated and not reported. Dr. Dilsizian then suggests that extravasations that result in adverse tissue reactions be paid attention to but does not seem to understand that if one does not characterize the absorbed dose and the then follow the patient for up to 2-3 years, one will not see adverse tissue reactions.
DR. VAN DER POL: I'll try. So I think your first point was -- should you only discriminate between a diagnostic and therapeutic? I think that would be most convenient. But the problem is that we found some diagnostic cases with actual symptoms. So that's why -- and -- and if you read the article, then you would see that we also devised a protocol in our hospital, which we published. We -- we basically say those four tracers I mentioned earlier -- in those cases you can just ignore possible effects of radiation -- or, not ignore. You don't have to expect any clinical symptoms. So in these cases, you don't -- yes, that's no -- no reason to assume that there -- be any clinical symptoms. But there might be some tracers. Like F-Fluoride which could possibly give you radiation burns. So in those cases, I think it's a different -- that's a different plane because I think actually, if you know there's a tracer extravasation, that would be worthwhile to just follow that patient and let him come after a few weeks and see if there are any symptoms. And if you do see symptoms and comes up with a -- plastic surgeon, for instance. So I would like to only discriminate between diagnostic and therapeutic tracers, but to discriminate between the tracers for which no evidence is found that they give radiation symptoms, and the other tracers -- only two, actually -- for which there was some publications for -- with symptoms of radiation burns. Do you agree on that? Or would you like me to --	Yes, it would be convenient to only look at therapeutic, but it would be inappropriate, since diagnostic extravasations can result in very high doses to patient tissue. Dr. van der Pol has suggested a protocol in his center, but it ignores extravasations from isotopes that can lead to a high dose. In his center, they do not consider FDG to be a problem. But, as we know from the recent (April 13) report of the case in North Dakota, it is possible to cause a very high absorbed dose using routinely-used diagnostics isotopes. 18F positrons are positively charged beta particles, so no different than many beta-based therapeutics. It is not appropriate to only follow extravasated patients for just a few weeks. In many cases you need to follow for months and years.
MEMBER DILSIZIAN: No, I agree obviously. I -- diagnostic -- as long as using symptomatic extravasation rather than diagnostic or therapeutics, I think it's important.	
DR. VAN DER POL: Yes, okay. So your next point was on the amount of evidence. Yes -- no, the evidence was very, very sparse. And that's also a conclusion of our study. And that's -- it would be very much -- it would be very worthwhile if we would have more studies. And most of those could be quite basic. If you only -- in case of bone scan with osteo patients -- and by telephone, if you could two weeks later and gather this data. You can also say -- you can already say some more about tracer extravasation. Or in case of the SUVmax, I think that's a good point. There are only a few cases in those studies filed	This two-week comment suggests that the community truly does not understand the latent effects of ionizing radiation on normal tissue. Patients need to be followed for many years. There are numerous studies that clearly show that the arithmetic of the formula is not violated by extravasations. Since the administered dose is part of the SUV

as a repeat study. So if you want to learn more about SUVmax then you should -- you should want more – more research done. So about negative results, yes that's true, there's always publication bias. I can't deny that. So the -- yes. That might be a reason for a lot of scientists not to undertake these kinds of studies. But I think since there are some tracer studies with FDG PET showing that there is some change in SUV max, you know, it's interesting to repeat that on a larger amount of repeat studies. And if you aggregate multiple hospitals and multiple studies, then you should be able to come up with some -- dozens of results. And -- which basically would be interesting to publish -- actually negative -- publication would be, but I think there might be an incentive still if you take the right angle. So your next point was --	formula, if you overestimate the administered dose, because you think it was all delivered as intended, then the SUV values will be artificially lower than they should be. This math has been supported in test-retest cases. The underestimation is completely dependent on the amount of extravasation.
MEMBER DILSIZIAN: No, I think -- no I think you covered them all. I appreciate -- I appreciate all of your responses. The bottom line I think is that the repeat studies, which is the most important part. Because the images will contour, not reliable -- even in a positively published paper, was only 0.01 percent.	Dr. Dilsiizan is confused about the rate. It is not 0.01 percent. It is 1.25%. If we assume that 1.25% of studies are repeated because of significant extravasations, that suggests that every year in the US over 375,000 patients are being significantly extravasated. It is likely higher.
DR. VAN DER POL: Yes, and I agree actually with your point of view on that SUV max is just something that can help you.	
MEMBER DILSIZIAN: -- we don't use it as a diagnostic end tool, right? We just -- it's an adjunct to our read. It's not a -- and we -- we are on the way about issues related to SUVmax.	Again, Dr. Dilsizian is not familiar with the role that quantitative nuclear medicine plays today in oncology.
DR. VAN DER POL: That's true but there are some -- some diseases like neurofibromatosis in which there are thresholds knowing about which there is --	
MEMBER DILSIZIAN: There's always an overlap, there's no such thing as a threshold --	Again, Dr. Dilsizian does not understand how quantification and thresholds are used today in Nuclear Medicine and interrupted Dr. van der Pol as he tried to provide Dr. Dilsizian with examples where thresholds are actually used.
DR. VAN DER POL: Yes. MEMBER DILSIZIAN: If -- if there's a -- there's an overlap -- of data. DR. VAN DER POL: Exactly, yes. MEMBER DILSIZIAN: Thank you. DR. VAN DER POL: You're very welcome. CHAIR METTER: And thank you, Vasken. There was another question, I believe, when I made a comment from the ACMUI?	
MEMBER OUHIB: Yes, this is Zoubir. First of all, thank you for this -- a great, great presentation. Valuable information. And more importantly, clarification -- the myth of extravasation. I was -- I have to admit I was -- I was very encouraged when you reported your own data over many years, which was very, very small percentage. Like it was -- like in one category it was 0.01 and in the other category was	Why does a member of the ACMUI to refer to a known complication in nuclear medicine, as a “myth”? Dr. Ouhib suggests that a registration is preferred to medical event reporting. There is no justification for why one

-- it might have been like, 0.6 -- 0.7 percent or something in that nature. I like the idea of -- I didn't -- I like the idea of registration versus medical event reporting. I think that's really valuable and we can already learn, perhaps, from that. Which leads me to another point is your -- in your very first slide was like -- there was a bullet point on how to act in the case of extravasation. But I think I was hoping -- which you actually covered in part -- regarding the how to prevent these types of situations. And so that leads me to, do you think there might be a need of some sort of a practice guideline to actually help and assist people who -- as you quoted, in bad situations -- that's what they -- I think that would be really valuable. I'll stop there and let you comment.	type of medical event should not be reported, and others be reported. Either a medical event meets reporting criteria or not.
DR. VAN DER POL: Yes, well I -- I think the way you perform your trace injections -- it's very important, of course. And I know from my older colleagues who already retired a few years ago that -- not so long ago, for instance, they used straight needle injections and they saw a lot of extravasations in that line. That's where we use the (audio interference), which in -- it doesn't seem to be a much problem anymore. And I think there must be some -- some other reporting, like I said before, of -- local reporting of extravasation as well because that's the reasons of which you're enjoying your daily job, you're busy, and -- and it's something that -- it's possibly forgotten. So you have to think of a system, how to -- to do that in a very user-friendly way. And actually we have integrated these kinds of local reporting in our PET system and that -- we hope in the future that makes it easy and doable for anybody to -- to -- to report any -- any kind of events, like tracer extravasation.	Dr. van der Pol indicates this is NOT a patient issue, but a clinician issue. Centers that routinely extravasate are not handling isotopes properly.
CHAIR METTER: Thank you. Any other questions or comments from the ACMUI members? MEMBER MARTIN: This is Melissa Martin. I was just wondering -- thank you, first of all, for a wonderful presentation. We really appreciate it. But there tends to be a punitive aspect to documenting extravasations -- sometimes dealt with primarily on -- or by, or with the technologist. And I was just wondering how you handle that process. Do you penalize your technologists for extravasations? Do you track how many each technologist is doing? Or -- what is the attitude that you would recommend that we handle reported extravasations?	The concern regarding punitive aspects of reporting is not relevant to whether an event is classified as a medical event.
DR. VAN DER POL: Well, I think that's -- that's a personal -- an opinion for myself. But I don't think it works to penalize people in any way to -- in order to -- to improve their work. I think you should always do it in a very positive way. And -- yes. Again, that's how we work. We don't penalize, but we try -- for instance, we have an open complication meeting every -- every three months. So in the Netherlands, we are already merged with -- with radiology. So we have one big medical imaging department. So we do a complication meeting for all the complications on the department. And that way we know the -- we try to take care of it in a positive way and -- we don't try to penalize anyone if it's presented. And we have -- it's a	The documentation of how often an issue happens and the sharing of lessons learned justify reporting situations where byproduct material has not been handled properly.

meeting in which every event is respectfully presented and I think in such a positive atmosphere, then it's -- anyone should be able to -- to understand the importance of sharing such adverse events -- and the importance of understanding how -- how often it -- it happens. And to -- to see if there's need to change the way people work.	
MEMBER MARTIN: Thank you very much. CHAIR METTER: Thank you. Any other comments or questions from the ACMUI? (No audible response.) CHAIR METTER: Okay, hearing none -- Dr. Van der Pol and Mr. Sheetz, thank you so much for a very important and practical presentation on an issue that's really very important to educate our new clients and community on this important -- quality of imaging in the care we give our patients. And I want to thank you -- thank you very much for looking at this because it's -- the topic that needed to be looked at and I appreciate your time and your expertise. Thank you very much. DR. VAN DER POL: You're welcome. (Simultaneous speaking.) MEMBER EINBERG: This is Chris Einberg, I'm with the NRC. And on behalf of the NRC and -- we wanted to thank you for your research in this area. And then, yes, you know -- your valuable time making this presentation. This has helped clarify, you know, things in our mind as we move forward to look at the regulatory structure -- whether extravasations need to be reported as medical events. And our Advisory Committee -- they will be receiving a report shortly on our evaluation. We do an independent evaluation on this as well. So -- thank you so much. DR. VAN DER POL: You're absolutely welcome. And I -- I would like to hear if you have -- if you are going to change the regulations or not. Perhaps, Mr. Sheetz -- with whom I am already corresponding can -- can get me some information about that. I would be very interested in that.	
[Intervening topics]	
OPERATOR: I do have a question. DR. METTER: Yes, please. OPERATOR: Paul Wallner, you may go ahead. DR. WALLNER: Thank you very much. It's actually not a question. It's several comments. My name is Dr. Paul Wallner. I'm a radiation oncologist. I've been in practice for now 49 years and much of that time has been devoted to a clinical and research interest in the use of radiopharmaceuticals and that included my time as a branch chief at the National Cancer Institute. I had hoped to comment and speak with Dr. van der Pol earlier but was unable to do that. I wanted to compliment him on his lecture, which I thought was excellent, and his meta-analysis, which I think is terrific for educating and informing residents and practitioners in nuclear medicine and technologists but not for development of public policy because I think the conclusions that he drew were actually not correct based on the material he researched.	Dr. Wallner indicates that editors of peer-reviewed publications require that complications be listed very clearly. If the authors did not follow the patient (which they did not do in 3,013 of the 3,016 cases) then they cannot describe the complications. Furthermore, in a 1M + patient study of adverse events for radiopharmaceutical extravasations, injections issues were excluded from the study. Dr. Wallner also miscites the van der Pol literature review. 3,016 diagnostic extravasations were highlighted in this

First of all, I think his comments, his meta-analysis was really demonstrative of the weaknesses of meta-analysis. He sub-selected from 4,000 plus manuscripts that did not include anything about extravasations and clearly were not related to extravasations, 44 publications of which 37 were diagnostic and 8 therapeutic. In the United States, peer reviewed editors and reviewers will require that complications be listed very clearly. So the complications related to extravasation are clearly not a problem in the United States and not a problem worldwide based on his own analysis. He commented in one of his conclusions that extravasation is common despite the fact that his own data suggests that's not the case. In his diagnostic evaluation, he reported 3,000 cases, of which only three demonstrated radiation injury. Twelve of the reports that he cited, six of those reports, or 50 percent had three or fewer cases that were included. So you can see even in these individual reports, they are essentially anecdotal because they are so rare. Of the eight publications that listed therapeutic complications, all were single case reports except one, which, again, reported three cases. He also reported that there were no National Registries looking at this issue and that's absolutely incorrect. The Australian government has an Australian Registry, which has been reported in peer reviewed literature in the Medical Journal of Australia. Several years ago they reported 2.5 million procedures, that's 2.5 million diagnostic and therapeutic procedures, of which there were 7 extravasations that were reported. I think that extravasation issues are best handled in the clinic the way they are now using practice guidelines. I see no clinical or public health reason why there should be any change in those guidelines or regulations. Thank you very much.	review. Only three patients were followed. All three developed adverse tissue reactions. The remaining 3,013 were not followed. Furthermore, Dr. Wallner is not familiar with everyday nuclear medicine practice. Extravasations are far from anecdotal. They occur in nuclear medicine centers at a very high frequency compared to chemotherapy and contrast CT injections. The Canadian study of bone scan extravasations is particularly instructive. Nine centers participated. Each center reviewed 25 consecutive bone scans on two separate occasions. Extravasation rates ranged from 0-44% and averaged 17.5%. Stanford just reported on their first 44 Lutathera patients. They extravasated 6 (13%). The Australian government requires the reporting of extravasations and have for many years. That is why they have a significantly lower extravasation rate than in the US. Had they left this issue to the individual center to address, it is likely that they would have a similar extravasation rates in Australia today as we have in the US.
DR. METTER: Thank you very much for your comments. And I do apologize. Dr. van der Pol was on a short timeframe, so we had very limited time on answering questions. But I really appreciate your insight and your expertise and thank you for your comments. Very valuable. Any other questions or comments from the public?	