U.S. Nuclear Regulatory Commission
Advisory Committee on the Medical Use of Isotopes

Subcommittee on Patient Intervention

Final Report
April 6, 2020

Subcommittee Members:
Gary Bloom
Vasken Dilsizian, MD
Ronald Ennis, MD
Michael Sheetz (Chair)

NRC Staff Resource: Said Daibes Figueroa, PhD

Subcommittee Charge:

During the September 10-11, 2019 Advisory Committee on the Medical Uses of Isotopes (ACMUI) Meeting, ACMUI Chairman, Dr. Christopher Palestro, established a subcommittee to evaluate the definition of "patient intervention" and other actions and circumstances that are exclusive of Medical Events.

As part of its evaluation, the subcommittee looked at the different aspects of patient intervention, discussed below, such as 1) active actions taken by the patient to interrupt treatment delivery, 2) anatomical, physiological, or changing medical conditions which cause a deviation in the administration, and 3) extravasation. It also looked at the applicability of these events with respect to the Medical Event reporting requirement.

Background:

A medical misadministration reporting rule was first proposed by the Atomic Energy Commission (AEC) in response to an August 1972 Government Accounting Office (GAO) report, which identified 20 cases of wrong doses or overdoses between 1961 and 1972, which involved human error. In March 1973, the AEC published a proposed misadministration rule that would have required licensees to notify the AEC of misadministrations which may result in a demonstrable effect on the patient.[1] The Nuclear Regulatory Commission (NRC) was established as the AEC's regulatory successor in 1975, and in July 1978, it published a proposed Misadministration Reporting Requirement that noted, "The purpose of a misadministration reporting requirement is to allow NRC to investigate the incident; evaluate the corrective action taken by the licensee to minimize the chance for recurrence; and, if other licensees could make the same errors, begin generic corrective action which would, as a minimum, inform other

licensees of the potential problem".[2] A final rule was published in May 1980 which included criteria for misadministration reporting at 10 CFR 35. 41.[3] For this Part, a misadministration was defined as the administration of:

> (a) A radiopharmaceutical or radiation from a sealed source other than the one intended;
> (b) A radiopharmaceutical or radiation, to the wrong patient;
> (c) A radiopharmaceutical or radiation by a route of administration other than that intended by the prescribing physician;
> (d) A diagnostic dose of a radiopharmaceutical differing from the prescribed dose by more than 50 percent;
> (e) A therapeutic dose of a radiopharmaceutical differing from the prescribed dose by more than 10 percent; or
> (f) A therapeutic radiation dose from a sealed source such that errors in the source calibration, time of exposure and treatment geometry result in a calculated total treatment dose differing from the final prescribed total treatment dose by more than 10 percent.

At that time, the NRC did however specifically exclude extravasation, or the infiltration of injected fluid into the tissue surrounding a vein or artery, as a misadministration. It stated, "Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections. It is virtually impossible to avoid. Therefore, the Commission does not consider extravasation to be a misadministration."

In August 2000, the NRC issued a revised Medical Use Policy Statement, to focus its regulatory emphasis on those medical procedures that pose the highest risk.[4] The policy statement outlined the intent of the NRC to regulate the medical use of radioisotopes based on the following four guiding principles:

1. The NRC will continue to regulate the medical use of radioisotopes as necessary to provide for the radiation safety of workers and the general public.
2. NRC will not intrude into the medical judgements affecting patients, except as necessary to provide for the radiation safety of workers and the general public.
3. NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's direction.
4. NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety.

In April 2002, the regulations in 10 CFR 35 were revised to be more risk-informed and performance-based, in alignment with the revised Medical Use Policy Statement.[5] The term "Misadministration" was changed to "Medical Event", and the reporting criteria was revised to include different types of deviations from that which was prescribed (wrong dose or dosage, wrong radioactive drug, wrong route of administration, wrong patient, wrong mode of treatment, wrong treatment site, or implant of leaking sealed source) and to also include a dose threshold that must exceed 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin (10 CFR 35.3045a). It was stated again that the purpose of reporting Medical Events was for the NRC to evaluate if there was a breakdown in the licensee's program for ensuring that byproduct material or radiation from byproduct material was administered as directed by the Authorized User (AU), or if there was a generic issue that should be reported to other licensees, thereby reducing the likelihood of other medical events. A specific exclusion was listed for permanent implant brachytherapy for sources that were implanted in the correct site but migrated outside the treatment site. There was also an exclusion from the Medical Event reporting requirement for an event that results from "patient intervention", where "patient intervention" is defined as: "actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration" (10 CFR 35.2) However, a licensee must report any event resulting from intervention of a patient or human research subject in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician (10 CFR 35.3045(b)).

In the 2018 amended 10 CFR 35 regulations for the reporting and notification requirements for a Medical Event, no changes were made to the patient intervention exclusion.

Previous ACMUI Subcommittee Recommendations Regarding Patient Intervention:

A previous 2017 ACMUI Patient Intervention Subcommittee, looking into unintentional treatment outcomes with Y-90 microsphere therapy, introduced the concept of "passive" rather than "active" patient intervention.[6] It stated, "Unintentional treatment outcome due to anatomic or physiologic anomaly and/or imaging uncertainty falls into the category "the Art of Medical Practice" provided that the standards of medical practice are met. Reporting such unpredictable and unavoidable patient-specific medical events will not help to prevent such events in the future, and therefore cannot be regulated". This type of "passive" patient intervention was intended to address situations where there was a stasis of arterial flow or shunting of microspheres through aberrant vessels, resulting in a medical event for the Y-90 microsphere therapy. The subcommittee also recommended that such unintentional treatment

outcome exceptions should apply to ALL current and future treatments, and not limited to Y-90 microspheres.

A 2019 ACMUI Subcommittee on Extravasation reviewed the NRC decision in 1980 to exclude extravasation, or the infiltration of injected fluid into the tissue surrounding a vein or artery, from being considered a misadministration (Medical Event).[7] The subcommittee agreed with the 1980 assessment that extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections and is virtually impossible to avoid, and concluded that extravasation is a practice of medicine issue and not an item that needs to be regulated by the NRC. The subcommittee reconfirmed that the exclusion of extravasation from Medical Event reporting was appropriate for both diagnostic and therapeutic procedures. However, one of its recommendations was for extravasation to be considered a type of passive "patient intervention" and that extravasation that leads to "unintended permanent functional damage" be reportable as a Medical Event under 10 CFR 35.3045(b).

Discussion of Issue:

At issue is what types of events are intended to be captured by the term "patient intervention" and what should or should not be considered a Medical Event. As noted by the definition of "patient Intervention", it was intended to address physical action taken by the patient (intentional or unintentional) which caused a deviation in the administration of byproduct material or radiation from byproduct material, from that which was directed by the AU. It is also assumed that the licensee did everything it should to prevent patient intervention during the treatment that resulted in a Medical Event, and that the actions taken by the patient were practically out of the licensee's control. For example, a patient pulls out a vaginal applicator during an HDR treatment, and then refuses completion of the treatment. However, there could also be a situation where physiological changes in the patient's medical condition causes a deviation in the administration of byproduct material or radiation from byproduct material, from that which was directed by the AU. For example, a patient experiences severe cardiac arrhythmias half-way through a gamma knife treatment, requiring urgent medical care, thus preventing completion of the treatment. In both cases, the patient caused a deviation from the prescribed treatment which would meet the medical event reporting criteria; and in both cases, the events could not have been reasonably prevented by the licensee. Therefore, it would seem reasonable for both of these examples to be considered a type of patient intervention.

A reportable Medical Event is meant to be an event that occurred due to treatment errors on the part of the licensee. If the Medical Event criteria are met due to a patient death, patient choice, or because of a changing medical condition that is out of the control of the licensee, it should not be reportable as a Medical Event, however, the licensee should note the reason in

the patient's record. Reporting such unavoidable patient specific Medical Events will not help to prevent such events in the future. The subcommittee recognized that the condition "that is out of the control, or that could not have been reasonably prevented by the licensee" is subjective and may result in varying interpretations. However, decisions on what constitutes reasonable medical practice for the level of patient control should be left to the physician's professional judgement, as they have the primary responsibility for the protection of their patients. The NRC's responsibility, as part of its charge to provide for the radiation safety of patients, is to regulate against unacceptable risks from improper procedures or careless use, while avoiding intrusion into the practice of medicine. Medical Events resulting from intervention of a patient that result in unintended permanent functional damage to an organ or a physiological system should still be reported by the licensee.

It should be noted that a Medical Event may also be due to a device failure or equipment malfunction, with no error on the part of the licensee. These events still need to be reported as a Medical Event, as it may indicate a generic defect or problem that would be of benefit for other licensees to know.

Specific Exemptions to Medical Event Reporting in 10 CFR 35.1000:

Several patient specific events have been incorporated in Part 35.1000 licensing guidance which are also exempt from the Medical Event reporting requirement. Each of these events or situations involves an anatomical, physiological, or changing medical condition, which could cause a deviation in the administration of radioactive material from that prescribed by the AU, resulting in a Medical Event. The events are appropriately excluded from the Medical Event reporting requirement because they cannot be controlled by the licensee and fall into the category of "the practice of medicine".

In the "Low Activity Radioactive Seeds Used for Localization of Non-Palpable Lesions and Lymph Nodes" Licensing Guidance, October 07, 2016, Revision 1,[8] there is an exemption from Medical Event reporting for cases involving: (a) intervention of a patient, (b) the patient failing to return for his/her explantation by the scheduled surgery appointment date and time, and (c) a physician determination not to explant the seed due to various patient conditions (e.g. doing so would jeopardize the patient's well-being). Here, "various patient conditions" is intended to address situations where either the implanted seed may have migrated close to sensitive nerves or vessels where surgical removal may cause significant patient harm (e.g. brachial plexus), or the patient's medical condition has changed such that the patient may be at a high risk to physically tolerate the surgical procedure.

In the "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®" Licensing Guidance, November, 8, 2019, Revision 10,[9] there is an exemption from

Medical Event reporting if the procedure must be modified due to emergent patient conditions that prevent administration in accordance with the written directive (e.g., artery spasm or sudden change in blood pressure). There is also an exemption if the total dose or activity administered was less than that prescribed due to stasis, or if a dose to the wrong treatment site is due to shunting, when shunting was evaluated prior to the treatment in accordance with the manufacturer's procedures. All of these exemptions are intended to address an anatomical or physiological condition of the patient that may affect the administration of the therapy in accordance with written directive, and are out of the control of the AU or licensee.

Examples of Medical Events Not Due to Patient Intervention:

There have been two Medical Events that were discovered by the NRC during routine inspections where the licensee initially determined it to be the result of patient intervention and therefore did not report the event. These are described in NRC Information Notice 2006-11 "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures".[10] In both cases, which involved a Gamma Knife, the patient's head frame had moved during treatment resulting in a dose to the wrong treatment site. In both cases, the licensee attributed the movement as a result of "patient intervention", and since it did not result in permanent functional damage, the licensee concluded that it did not meet the reporting criteria for a Medical Event. However, the NRC concluded that neither licensee provided sufficient evidence to exclude equipment set-up error as the cause of its Medical Event, rather than patient movement.

There have been multiple cases involving Y-90 microsphere treatments where the micro-catheter becomes occluded and prevents complete administration of the prescribed dosage from the delivery device. This has created confusion among some licensees as to whether this type of event is reportable as a Medical Event, or it constitutes a type of stasis or patient intervention. However, in the most recent Y-90 microsphere licensing guidance document[9], it states that "The inability to complete administration due to clogging or kinking of the catheter is not considered stasis.", and therefore this would need to be reported as a Medical Event.

Recommendations:

The purpose of the Medical Event reporting rule is to evaluate if there was an error or problem in the licensee's program for ensuring that byproduct material or radiation from byproduct material was administered as directed by the AU, or if there was a generic issue that should be reported to other licensees, thereby reducing the likelihood of other Medical Events. If a Medical Event occurs during a properly performed clinical procedure, and results from actions taken by the patient which could not have been reasonably prevented by the licensee, or from an anatomical or physiological condition of the patient which falls into the realm of the practice

of medicine, then it should not need to be reported. Reporting such unavoidable patient specific medical events will not help to prevent such events in the future, and doing so would potentially infringe on the practice of medicine. The term "patient Intervention" should be interpreted to include all such events. Intentional or "voluntary" actions would include physical actions taken by the patient, such as removing an implanted brachytherapy source or applicator, or refusing to continue with a prescribed course of treatment. Unintentional or "involuntary" actions would include medical outcomes resulting from the anatomical or physiological conditions of the patient, such as extravasation, migration of implanted radioactive seeds, arterial spasm, and the onset of other underlying medical diseases and disorders which interfere with the prescribed treatment. This expansion of the term "patient intervention" is consistent with the original objective for which it was developed in 2002.

Medical Events resulting from patient intervention in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician, should be reported as required by 10 CFR 35.3045(b). This will allow for those events resulting in serious patient harm to be evaluated for any program deficiencies in the safe use of radioactive material, help ensure that corrective actions are taken, where possible, to prevent recurrence, and identify any generic issues or concerns that may be of benefit to other licensees.

A Medical Event resulting from patient intervention (whether it causes permanent functional damage or not) should still be internally reported to the institution's Patient Safety Committee in accordance with the institutional patient safety reporting and review process. This review is both appropriate and important in ensuring a strong patient safety culture.

Summary of Recommendations:

1. The current definition of "patient Intervention" in 10 CFR 35.2 should be interpreted to include both intentional (or voluntary) actions taken by the patient, such as removing an implanted brachytherapy source or applicator, or refusing to continue with a prescribed course of treatment; and unintentional (or involuntary) actions which would include medical outcomes resulting from the anatomical or physiological conditions of the patient, such as extravasation, migration of implanted radioactive seeds, arterial spasm, and the onset of other underlying medical diseases and disorders which interfere with the prescribed treatment.

2. The subcommittee agrees that Medical Events resulting from "patient intervention" should not need to be reported as it would potentially infringe on the practice of medicine, and it will not help to prevent such events in the future.

3. Medical Events resulting from patient intervention in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician, should be reported as required by 10 CFR 35.3045(b).

References:

1. History of the NRC's Misadministration Reporting Rule, Norman L. McElroy, J Nuc Med. 1986;27:1104
2. Federal Register, 29297, July 7, 1978, Volume 43, Nuclear Regulatory Commission, Misadministration Reporting Requirements, Proposed Rule
3. Federal Register, 31701, May 14, 1980, Volume 45, Nuclear Regulatory Commission, Misadministration Reporting Requirements, Final Rule
4. Federal Register, 47654, August 3, 2000, Volume 65 Nuclear Regulatory Commission, Medical Use of Byproduct Material, Policy Statement; Revision
5. Federal Register, 20330, April 24, 2002, Volume 67, Nuclear Regulatory Commission, Medical Use of Byproduct Material, Final Rule
6. ACMUI, Subcommittee on Patient Intervention, Draft Report, Part II, April 27, 2017
7. ACMUI, Subcommittee on Extravasation, Final Report, October 23, 2019
8. Nuclear Regulatory Commission, "Low Activity Radioactive Seeds Used for Localization of Non-Palpable Lesions and Lymph Nodes" Licensing Guidance, October 07, 2016, Revision 1
9. Nuclear Regulatory Commission, "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®" Licensing Guidance, November, 8, 2019, Revision 10
10. Nuclear Regulatory Commission, Information Notice 2006-11 "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures", June 12, 2006

The ACMUI unanimously approved this report and its recommendations, as presented, during its spring 2020 meeting on March 30, 2020.

Respectfully submitted,
Subcommittee on Patient Intervention
Advisory Committee on the Medical Use of Isotopes
U.S. Nuclear Regulatory Commission