

**Advisory Committee on the Medical Use of Isotopes (ACMUI)
Permanent Implant Brachytherapy Revised Final Report
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Permanent Implant Brachytherapy Subcommittee Members

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Recommendations

A. Proposed Definition for Medical Event for Macroscopic Permanent Implants

1. For the target, greater than 20% of the sources fall outside of the treatment site (not resulting from patient-related causes such as edema or source migration after placement)

OR

2. For normal-tissue structures,
 - a. For neighboring structures (such as the bladder or rectum in prostate implants as an example), the dose to at least 5 contiguous cm³ exceeds 150% of the dose prescribed to the CTV or PTV;

OR

- b. For intra-target structures (such as the urethra in prostate implants as an example), the dose to at least 5 contiguous cm³ exceeds 150% of *that structure's* expected dose based on the approved pre-implant, dose distribution.

OR

3. A treatment is executed
 - a. Using the wrong radionuclide;
 - b. Using the wrong activity or source strength (\pm 20%) as specified in the Written Directive;
 - c. Delivered to the wrong patient;
 - d. Delivered directly to the wrong site or body part, with the exceptions of seed migration, edema and other patient-related factors or source displacement following placement, as long as the criteria in 1. is not violated;
 - e. Delivered using the wrong modality or
 - f. Using leaking sources,

B. Written Directive Completion

After implantation but before the patient is released from the Authorized User's control, the Authorized User shall complete the Written Directive to include the radionuclide, treatment site, number of sources, and the total source strength permanently implanted in accordance with 10 CFR 35.40(b)(6). Unusual aspects of the procedure, including patient-related limitations should be documented in this Written Directive completion. The Authorized User should provide a statement in this Written Directive Completion attesting that the permanently implanted sources have been placed in accordance with the final planned distribution.

The permanent implant procedure shall be considered complete once the patient is released from the Authorized User's control.

Terminology

Gross Tumor Volume, GTV – The volume of the tumor proper as detected on imaging, visual observation or manual palpation on physical examination.

Clinical Target Volume, CTV – The volume containing the gross tumor and a margin that may contain malignant cells from the tumor. In the case of prostate implants, this usually is the whole prostate but can be more if there is “extracapsular extension” of disease.

Planning Target Volume, PTV – The volume within which the sources are placed to deliver the prescribed dose to the CTV. This would include the CTV plus any additional margin used to assure adequate coverage.

D₉₀ – The dose to 90% of the CTV

Treatment site – The anatomical description of the tissue intended to receive a radiation dose, as described in a written directive [10 CFR 35.2]. The Subcommittee recommends the description include the concept of GTV, CTV, or PTV.

Report Modification

Please note that a significant minority of the Subcommittee holds an opinion that differs substantially from the general body of this modified report. An additional section (“Minority Report” vide infra) details key aspects of this minority viewpoint.

In the period since the approval of the ACMUI Permanent Implant Brachytherapy Final Report dated October 18, 2011, several comments have been received regarding the practicality of the recommendations that report contained. Based on several follow-

up teleconferences and discussions on the subject, the Subcommittee has modified the final report into the form contained herein. The essential adjustments are:

- 1) Omission of the use of D_{90} to the treatment site as a criterion for Medical Event definition. Upon reflection, most members of the Subcommittee felt that after years of arguing against the use of dose to the treatment site as a metric for defining Medical Events, it was imprudent to resurrect its use presently.
- 2) Omission of the octet concept. While some members of the Subcommittee liked the concept, others felt this may prove too challenging in real, daily practice for the Authorized User to document and the regulator to effectively inspect.
- 3) Inclusion of the attestation by the Authorized User in the Written Directive Completion. This, along with A2a,b – overdosing of normal tissues, is meant to address the concern about bunched sources.

The rationale for these recommendations is discussed below. Importantly however, there was not complete agreement within the Subcommittee on several issues and this modified report does not reflect a unanimous opinion on the issues discussed. At the end of this document is a section entitled, Minority Report, which explains the dissenting perspective.

Discussion

The ACMUI has previously issued three reports providing recommendations on the definition of Medical Event for permanent implant brachytherapy. In the 2008 report¹, ACMUI provided comments and recommendations on the proposed rule² to redefine Medical Event for permanent implants. The ACMUI issued an interim report³ in 2010 at the NRC's charge to provide recommendations on regulatory changes or improvements to the NRC's processes for permanent implant brachytherapy programs. ACMUI's interim recommendations reiterated the principle that "a Medical Event should be potentially of true medical significance to a patient." In the time since the 2008 rulemaking², NRC and the medical community have discussed⁴ possible Medical Event definitions that would identify those permanent implants (and ideally only those implants), that fall below clinically acceptable tolerances. Most recently, the ACMUI

¹ Advisory Committee on the Medical Use of Isotopes (ACMUI) comments on the Proposed Rule for Medical Use of Byproduct Material – Amendment/Medical Event Definitions (RIN 3150-AI26, NRC-2008-0071-0058, November 5, 2008;

<http://pbadupws.nrc.gov/docs/ML0922/ML092220766.pdf>.

² 73 FR 45635, Proposed Rule for Medical Use of Byproduct Material – Amendment/Medical Event Definitions (RIN 3150-AI26, NRC-2008-0071, August 6, 2008;

<http://edocket.access.gpo.gov/2008/pdf/E8-18014.pdf>).

³ Advisory Committee on the Medical Use of Isotopes (ACMUI) Permanent Implant Brachytherapy Interim Report (October 20, 2010; <http://pbadupws.nrc.gov/docs/ML1035/ML103540385.pdf>).

⁴ Medical Rulemaking Workshops for Discussion of Topics Related to Medical Part 35 Regulations (New York, NY, June 20-21, 2011; Houston, TX, August 11-12, 2011; <http://www.blsmeetings.net/NRCMedicalRulemakingWorkshop/presentations.cfm>)

Permanent Implant Brachytherapy Subcommittee issued another report in October 2011, which was subsequently reviewed by the entire ACMUI and designated as "final". Since finalizing that report, a number of concerns were raised by experienced practitioners and stakeholder organizations including the American Society for Radiation Oncology (ASTRO). Upon review of these concerns, some members of this Subcommittee now believe that although the recommendations within the October 2011 report would work in an ideal world, there could be difficulties with some of these recommendations in the "real world" of brachytherapy. Therefore, this modified report contains different criteria defining Medical Event from the October 2011 report that some members of the Subcommittee feel will be more practical yet fully effective in the aim of capturing events that are truly clinically significant or of radiological importance. However, see the section entitled Minority Report at the end of this document, which reveals that the vote on this matter was not unanimous.

This modified ACMUI report proposes a definition that would capture appropriate Medical Events, utilizing metrics consistent with information currently required on the Written Directive and using standard medical guidelines for permanent implant brachytherapy. This proposed definition would identify cases where less-than-desirable dosimetry results from poor source distribution. Unlike previous definitions, dose changes due to edema or other patient-related factors would not trigger a Medical Event.

Because the vast majority of permanent implants are performed to treat prostate cancer, examples and guidance for these recommendations have drawn heavily on that procedure. However, the proposed definition (and everything else in this Subcommittee report) is intended to apply generally to all forms of permanent implants.

The Medical Event definition proposed in this modified report would catch an event where an inappropriate number of sources are bunched together through the requirement that the Authorized User provide an attestation in the Written Directive Completion that the final distribution of sources has been placed in accordance with that called for by the computer-calculated plan, or medical description why the surgical implant varied from the plan. As the computer-generated plan will invariably call for a source distribution that will be spread out within the treatment site (except for areas to be spared or dose-escalated as called for in the prescription), the final source distribution should reflect a reasonable approximation to that computer-generated source distribution. The Authorized User must attest in the Written Directive Completion that this aim has been achieved. For cases in which areas within the treatment site are physically unreachable (e.g., the pubic arch limited access to the anterior prostate) in which octants might therefore be underrepresented, the Written Directive Completion should reflect the clinical limitations encountered. Such cases should not be classified as Medical Events as long as the completed Written Directive documents why there might be octants with fewer sources than initially planned.

The Subcommittee feels that dose is an acceptable parameter for defining Medical Events that are due to overdoses to normal tissues and structures. For normal tissues

and structures, some form of dose-volume specification is needed for realistic regulatory implementation. The suggested D_{5cc} contiguous dose-volume specification avoids the high variation in dose sometimes seen in point doses and has literature to support it being a relevant quantity for toxicity. In the case of prostate therapy, the rationale for the distinction between the bladder and rectum versus the urethra is that the latter falls within the target volume. Thus, the suggestion for categorizing normal structures as neighboring normal tissues or intra-target normal tissues is included in this report.

This modified report also provides recommendations of how the NRC should apply the current requirements for a permanent implant Written Directive. As stated in 10 CFR 35.40(b)(6), a Written Directive must contain for permanent implants:

- “(i) Before implantation: treatment site, the radionuclide, and dose; and
- (ii) After implantation but before completion of the procedure: the radionuclide, treatment site, number of sources, and total source strength and exposure time (or the total dose).”

The Subcommittee recommends use of the current NRC definition for prescribed dose in manual brachytherapy which allows the Authorized User to use total source strength (number of sources) and exposure time (permanent). Completion of the Written Directive after implantation reflects NRC’s recognition of the need to allow final Written Directive documentation based on the medical situation encountered during the surgical procedure. The Subcommittee recommends that “completion” of the procedure should be considered the point when the patient is released from the Authorized User’s control. This time frame is consistent with other surgical procedures, allowing the physician to complete surgical documentation while the patient is in the surgical recovery area.

Adequate treatments require appropriate source-strength distributions that have been correlated over decades with successful clinical outcomes. As discussed in previous reports from this Subcommittee, post-implant evaluation constitutes an important component of Authorized User (and other members of the treatment team) self-assessment for correlating how actual source distributions compare with that on the pre-implant plan, and as modified by the Written Directive completion. It is acknowledged that dose distributions calculated on such post-implant dosimetry studies are fraught with problems, making calculated dose an unreliable metric for regulatory compliance purposes with regards to the treatment site. Nonetheless, post-implant evaluation of this type provides some valuable medical feedback to the Authorized User. Post-implant evaluation of the number of seeds located in the treatment site, as modified by the Written Directive completion, does provide the Authorized User and the regulating community with a more objective basis for inspecting implant compliance. Therefore, the Subcommittee has recommended that post-implant assessment be a mandatory component of the overall treatment process and is required implicitly through the requirement of an assessment of dose to the normal structures.

Basis for the Previous Subcommittee Recommendations

The Subcommittee has reaffirmed the principles that guided the definitions from the previous reports. The definition of a permanent implant brachytherapy Medical Event should be based on the following concepts:

A Medical Event ideally should be of true medical significance to a patient. The definition should be sensitive enough to detect any implant that is truly of potential harm to a patient from an unintended action during the surgical implantation, but not so rigid as to prevent an Authorized User from exercising his/her medical judgment for the benefit of the patient in changing where to implant seed during the surgical implant procedure.

NRC regulations categorize “harm” to a patient in these two ways:

- 1.) Radiological and medical harm medically due to overdosing of sensitive normal structures and tissues
- 2.) Medical harm due to unintended under-dosing the cancer and not curing the patient

An appropriate Medical Event definition for permanent implant brachytherapy must reasonably balance the identification of these potential ways of patient harm, but without causing the real harm of reducing or eliminating the patient’s access to this type of therapy, which historically has been proven effective in treating cancer, such as prostate cancer, with little to no side effects. This is a difficult task and the Subcommittee feels the proposed definition in this modified report reasonably meets this balance.

Meeting this reasonable balance is made even more difficult when attempting to encompass all forms of permanent implant brachytherapy under one Medical Event definition. The Subcommittee was previously in favor of proposing separate medical event definitions for prostate vs. non-prostate permanent implants. But, with the Medical Event definition proposed here, the Subcommittee no longer feels it is imperative to create separate definitions.

However, since overdose (item 1. immediately above) is irreversible whereas underdosing (item 2.) can be medically corrected (in some cases), the Subcommittee is not in full agreement with NRC’s traditional stance on the equivalence of these two forms of “harm”. It is felt by some Subcommittee members that, while overdosing of normal tissues remains clearly within the realm of NRC purview (protection of the public from inappropriate use/application of byproduct material), underdosing (to the target) falls into the realm of “practice of medicine” and should not remain a basis for NRC regulation. Furthermore, during the Summer 2011 Workshops, yet another concept of "harm" was introduced - psychological harm to the patient if his/her brachytherapy procedure has been labeled as a Medical Event. Despite the fact that

NRC has always insisted that the appellation, "Medical Event" does not necessarily imply clinically significant problems with the procedure, exaggerated negative media coverage may have spoiled the original NRC intent of this terminology and Subcommittee members now acknowledge the possibility of this additional form of "harm" as an unintended consequence of the Medical Event reporting process. This emphasizes the importance of developing a truly appropriate and relevant definition of Medical Events for permanent implant brachytherapy and all other brachytherapy procedures.

The Subcommittee recognizes that a dose-based definition for the treatment site, especially in prostate permanent implant brachytherapy, suffers from several limitations:

- 1.) True anatomic prostate volume or shape changes can occur during and after the implant procedure, particularly due to edema,
- 2.) Spurious differences in estimated prostate volumes can occur due to inherent limitations of identifying organ or target boundaries using CT and ultrasound (or any other modality),
- 3.) Volume estimate uncertainties due to artifacts caused by the seeds and the resultant indistinct prostate boundaries seen on post-implant CT images.

For these reasons, the Subcommittee opposes the use of dose to *the treatment site* (but is not opposed to appropriate use of absorbed dose to normal tissues) in defining Medical Events (however, please see the Minority Report at the conclusion of this modified report since not all Subcommittee members entirely oppose the use of dose to the target). The October 2011 report did use absorbed dose to the target in a limited fashion and some Subcommittee members are still in favor of that particular limited application). The Subcommittee also recommended in previous reports that if an apparent Medical Event were found to be due to true anatomic prostate volume changes (item 1. immediately above) after the administration, it should not be deemed a Medical Event. Such cases should be addressed in the fashion of other *patient-related or patient-specific factors* equivalent to a patient removing a temporary implant, migration of properly implanted radioactive seeds, or termination of a ^{90}Y microsphere administration because of stasis. Finally, consistent with the Subcommittee's opinion regarding target underdosing (an occasionally correctable situation), an implant with potentially undertreated regions should not be considered a Medical Event if imaging identifies regions requiring additional radiation therapy.

The previous reports also reviewed aspects of the old definition that dealt with normal tissues. Consider the part of §35.3045 that reads, "A dose to the skin or an organ or tissue other than the treatment site that exceeds by 0.5 Sv (50 rem) to an organ or tissue and 50 percent or more of the dose expected from the administration defined in the Written Directive." The Subcommittee feels that this definition is obsolete and inappropriate for use in modern permanent implant brachytherapy.

With the very high gradients in the dose distributions, small and clinically insignificant shifts in:

- a.) the source distribution,
- b.) the target organ, or
- c.) the normal tissues in question

can cause much larger changes than 0.5 Sv or 50% of the expected dose, with no consequences to the patient. For example, a 1-cm shift in the position of the prostate due to gas in the bowel (a common amount of movement) can produce a 94% change in the calculated dose to the skin. It is worth noting that the difficulties in post-implant dose reconstruction for the prostate might also affect dose calculations for certain normal tissues – for instance, the above example of a 94% increase in the dose to the skin might not be seen if the same procedure were done the very next day if the bowel gas resolved. Such perfectly normal and clinically acceptable implants should not be categorized as Medical Events.

Thus, if this §35.3045 criterion were applied strictly, some (perhaps many) properly executed and medically acceptable implants might inappropriately be categorized as Medical Events. This underscores the concept that, ideally, Medical Events should be of potential medical significance or at least should identify trends that could lead to consequences of medical significance if not identified and acted upon. The proposed Medical Event definition herein adheres to these principles.

Minority Report

One of the four members of the subcommittee preferred the definition for a permanent implant medical event in the 2011 draft of the report presented to the ACMUI to that definition in this draft. The reasons were:

1. **The ambiguity of the term, “treatment site” in the new proposed draft.** In the previous draft, the evaluation of the source placement explicitly tied with the “planning target volume (PTV).” Treatment site in the new draft is taken to mean the volume in which the sources are to be placed. In the prescription, the treatment site usually would mean the volume to receive the target dose, which would be the clinical target volume (CTV). This sets up a situation where the treatment site in the written directive and the treatment prescription are different, potentially leading to confusion and misunderstanding.
2. **The dissociation of the definition with potential harm to the patient.** The principle elucidated in the previous draft was that a medical event should be related to a situation that potentially could lead to harm to a patient. In many situations, an implant with more than 20% of the sources outside of the PTV can lead to a perfectly good implant with the proper dose coverage to the CTV, particularly in a case where just over 20% fall outside. This was the reason to

have the exclusion criterion in the previous draft that specified if the dose to 90% of the CTV (D90) was greater than 60% of the prescribed dose, the case would not be a medical event, preventing excessive reporting of adequate cases as medical events. Contrary to the interpretations of some members of the subcommittee, the criterion of $D90 < 60\%$ would not trigger a medical event classification for any case unless the source distribution fell into the criteria of $>20\%$ of the sources outside of the PTV or 5% not in each octant. The dose specification is an exclusionary criterion to narrow the application of the geometric criteria, not to expand and add another criterion. The dissenting member did prefer the use of 70% as the cut-off value for the D90, but the ACMUI changed that to 60%. The principle is still sound with either value.

Another objection to the use of this exclusionary clause was that the radiotherapy community has demonstrated that D90 should *not* be used to trigger a medical event for many reasons (e.g., edema, atrophy, timing of assessment different imaging modalities,) discussed very well in the 2008 report of the Permanent Implant Subcommittee. Those reasons still hold. There was concern in discussions about the current draft that the use of this quantity in any form could lead to the use of D90 as a criterion for a medical event rather than an exclusionary criterion. The dissenter felt that the NRC now understands the problems associated with the use of D90 to define a medical event, and as the 2011 draft was written, this hypothetical problem would not be realized.

3. **The lack of a distribution criterion in the current draft.** In the previous draft, the criterion for a minimal amount of source distribution was to catch egregious implants where a very large number of the sources unintentionally bunched within the target, and thus would not be caught in the 20%-outside-the-target criterion.
 - a. While the criterion specified 5% in each of the target's octants, it explicitly excepted cases where a non-uniform distribution was prescribed, for example to reduce or accentuate the dose in particular regions, or where the patient's anatomy precluded such a distribution.
 - b. Some discussion in the subcommittee focused on the complexity of octants. Octants are simply cutting the target in half on each of the three axes, which is very simple. Equivalently, it could be stated that 20% of the sources would occupy either half of the target, regardless of how the target was cut (again, except by prescribed differential distributions or due to anatomical constraints.)
 - c. The subcommittee had some discussion about potential disagreements between regulators and practitioners based on differing axes used for the evaluation. This could be solved by allowing this criterion to be satisfied if the distribution would exist for any set of orthogonal axes.
 - d. Again as with the 20% criterion, failure to satisfy this criterion only would have triggered a medical event if the D90 fell below 60%, i.e., if the poor distribution was clinically significant. The distribution need not be determined for any implant with the $D90 > 60\%$, which means most practices would never perform this determination.

4. **The attestation in the current draft.** In place of the criterion for a minimal distribution of the sources, the current draft has an attestation by the authorized user that the sources were placed as intended. The dissenting member felt that this was not good regulation, neither holding the user responsible for possibly harmful sources placement and encouraging some users faced with a potentially harmful implant to prevaricate. While this attestation was to replace the minimal distribution criterion, it could just as well replace the 20%-outside-the-target criterion, since the user could say that where ever the sources lie is the treatment site, now defined as the desired location of the sources. The attestation makes enforcement of this medical event definition mostly useless, unenforceable and a potential source of contention between users and regulators. There was discussion in the subcommittee asserting that the distribution of sources in the target was practice of medicine, and thus should not be included in the medical event definition. If that were the case, the attestation is unnecessary. Also if that were the case, holding the placement of the sources around the target, and possible outside of any defined target, would also be practice of medicine and outside the charge of the NRC. This assertion has been discussed many times in the ACMUI, always to be decided that the NRC does have the obligation to protect the public when practitioners fail to do so, and *not* to leave such cases to credentialing committees, where they exist.