Chapter

Credentialing Proton Centers for Clinical Trials

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Abstract

This chapter will provide an overview of quality assurance processes to credential proton therapy centers for clinical trial participation. There are a number of credentialing audit steps, including independent output verification, anthropomorphic phantom audits, image guidance credentialing, knowledge assessments, and on-site dosimetry review. The purpose of these credentialing steps is to ensure consistency across proton centers participating in clinical trials, and well as comparability with photon centers for randomized trials. This uniformity ensures high quality data for measuring patient outcomes, which are pivotal at a time when proton therapy is being assessed for superior outcomes.

Keywords: proton therapy, quality assurance, credentialing, Imaging and Radiation Oncology Core, phantoms, dosimeters, image guidance, benchmarks, audits

1. Introduction

1.1 Importance of clinical trial quality assurance (QA)

Clinical trials are designed to give us confidence in a course of care. For cancer treatment, clinical trials have played a crucial role in the advancement of treatment for a variety of disease sites over the last century. As discussed in the chapter on clinical trials, there are a number of active protocols seeking to better understand the role of proton therapy within modern radiotherapy. Clinical trials have varied points of emphasis and radiation therapy may be an important aspect of the trial but not the trial endpoint. Phase II and III trials often require many participants to reach a statistically significant conclusion. With limited numbers of patients of various disease sites seen at an individual institution, it is common for proton therapy trials to be conducted among multiple institutions. When a trial includes multiple institutions, variability in treatment practices increases. One way to minimize differences across participating centers is to require QA of the trial treatment. QA helps minimize deviations within trials, and can improve clinical outcomes such as overall and progression-free survival [1–4]. This is particularly important for many proton therapy clinical trials, as insurance companies want to see quantification of superior outcomes before agreeing to cover the cost of therapy.

1.2 National Cancer Institute (NCI) proton guidelines

In 2007, the NCI formed an ad-hoc panel of proton experts to outline guidelines for the use of proton therapy in clinical trials. The original guidelines included

recommendations about beam calibration protocol, relative biological effectiveness (RBE), target volumes, and clinical trial audits. The guidelines have been updated several times since then, most recently in 2019, to include requirements for modulated pencil beam scanning delivery, robust optimization, advanced treatment planning algorithms, and recommendations about clinical trial credentialing [5].

2. General proton approval

2.1 Output checks

Regular remote output checks are part of clinical trial QA around the world [6]. In the United States (US), output checks are required on an annual basis for all proton beams used in the NCI's National Clinical Trial Network (NCTN) protocols. The purpose of these QA audits is to verify the output of a uniform field. Typically institutions use their reference calibration (International Atomic Energy Agency Technical Report Series 398) field for this purpose. Use of the same field year after year can catch drifts in output or dramatic changes that may be caused by an error in calibration.

2.2 On-site audit

In addition to the remote output check, all proton therapy centers in the US receive an on-site dosimetry audit as part of the baseline approval process for clinical trial participation. With relatively few proton centers in the US (as compared to photon clinics), many personnel are coming to work at new proton facilities without prior experience with proton therapy. On-site audits are perhaps the most crucial component of proton approval, as they allow a deep dive into the dosimetry and clinical operations of a facility, and check for practice consistency across these new facilities.

The on-sites audit consists of a number of dosimetric measurements, including beam calibration, calibration equipment intercomparison, depth dose profiles, lateral beam profiles of reference and patient fields, imaging vs. radiation isocenter coincidence, and Hounsfield Unit (HU) – Relative Linear Stopping Power (RLSP) calibration. On-site audits allow for greater dosimetric accuracy and complexity than remote audits. Recommendations are made to the institution about how they can improve their clinical practice and make it more consistent with other proton centers on multi-institutional trials. The most common recommendation relates to the HU-RLSP conversion curve that institutions use to predict proton range within a patient [7, 8]. The curve is sensitive to errors at low densities (e.g. lung tissue) and variability is observed across institutions at both low and high densities. Accuracy of this calibration is critical to accurate proton beam modeling and by minimizing deviations in the calibration, treatment delivery deviations can also be mitigated.

The on-site audit also includes a review of clinical practices, covering topics like CT simulation and re-simulation over the course of treatment, patient immobilization, treatment planning and robustness evaluation, and image guidance. The goal is to ensure consistency across institutions, in an effort to minimize deviations on trials. For example, if an institution is not performing any kind of rectal sparing technique for prostate treatment, a recommendation might be made to investigate and adopt a technique in order to follow standard clinical practices. The machine QA practices are also reviewed to ensure compliance with recommended standards [9–12]. The proton QA standards are relatively new, so the review of QA practices provides useful feedback on ways to implement different tests, benefits and drawbacks of different equipment, and failure modes within the system.

3. Protocol-specific credentialing

3.1 Anthropomorphic phantoms

Anthropomorphic phantoms are one of the most robust options for remote audits of a radiotherapy modality. They encompass an end-to-end test of simulation, treatment planning, setup, and delivery of radiation. Proton therapy presents some unique challenges for phantom tests. The plastics typically used for QA of photon beams are not necessarily "tissue-equivalent" in a proton beam, thus appropriate phantom materials need to be tested to ensure they fall on a clinical proton HU-RLSP curve [8].

The phantoms currently available for proton credentialing test a variety of different clinical requirements: conformality (brain, head and neck (H&N), spine), organs at risk (OAR) avoidance (H&N, prostate), motion management (liver, lung), heterogeneities (lung, spine), and multiple targets (liver) [13, 14]. Proton anthropomorphic phantom credentialing has already led to improvements in accuracy of treatment dose calculations for clinical trials. The lung phantom credentialing for the Radiation Therapy Oncology Group's (RTOG) randomized proton vs. photon trial for non-small cell lung cancer (NSCLC) (RTOG 1308) found gross overestimates of dose when using an analytic algorithm for dose calculations in low-density heterogeneities [15]. The NCI has updated their proton therapy guidelines to require Monte Carlo or advanced algorithms for future trials with low density heterogeneities [5].

3.2 Image guidance

Image guidance is a crucial component of proton therapy because the beam range is dependent on the density of the material in its path. If you plan a field in soft tissue and then a bone is in the beam path at the time of treatment, you could entirely miss your target. Alternatively, if high density tissue is in the beam path at the time of planning but not at the time of treatment delivery, you risk delivering full dose to the tissue distal to the target. Most proton centers began by using orthogonal kV image guidance, but many now have in-room volumetric imaging capabilities with CT or cone-beam CT (CBCT) [16, 17].

There are many components of image guidance that are important to verify: image quality, geometric accuracy, imaging dose, imaging system communication, and safety [9–11]. Some of these components, like imaging dose and image-guided radiotherapy (IGRT) safety checks, are left to the institution's physics team to test. Other elements are verified through clinical trial credentialing. Many protocols require IGRT credentialing for both photon and proton therapy if "reduced margins" (typically less than 5 mm) are used. The IGRT credentialing requires submission of actual patient IGRT data for central review, as well as completion of a questionnaire outlining IGRT practices. The images are reviewed for registration to reference treatment planning data as well as consistency from day-to-day. The goal of this credentialing is to ensure consistency of IGRT processes and quality across institutions.

Of course, there could be accurate in-room images, but if the proton beam is not coincident with the IGRT isocenter, the accuracy of the beam delivery is negatively impacted. For this reason, the coincidence of the IGRT and proton beam isocenters is verified for proton therapy centers participating in clinical trials. This is done with a Winston-Lutz type test as part of the baseline approval process for clinical trial participation [18].

3.3 Motion management

Motion management is of particular importance in proton therapy due to the sensitivity of the beam range to changes in tissue density [19, 20]. Several anthropomorphic phantoms (liver, lung) assess the end-to-end process of motion management, but there are some clinical trials that also require a motion management questionnaire. This questionnaire assesses the standard clinical practices for assessing and accommodating target motion, such as the upper limit for motion magnitude, simulation practices, respiratory management system, and patient setup requirements. Many of these aspects are also reviewed during the on-site audit, so a separate motion management questionnaire for a specific clinical trial may not be necessary.

3.4 Knowledge assessments

A knowledge assessment asks questions about a clinical trial to ensure that participants have carefully reviewed the protocol and understand its requirements. Knowledge assessments are used for credentialing in a handful of NCTN clinical trials. Knowledge assessments can be useful for randomized proton vs. photon trials because there are intricacies of treating with two modalities, such as accounting for RBE, different definitions of target structures, and partnerships among multiple institutions. Unfortunately the knowledge assessment only captures the knowledge of a few personnel at a specific point in time, so it does not ensure that everyone involved over the course of the trial has carefully read the protocol. For this reason, most new NCTN proton clinical trials do not require knowledge assessments.

3.5 Benchmark cases

Benchmark cases have commonly been used for clinical trial credentialing [21, 22]. The objective is to have a standard sample case that all participants plan on. The reviewer can then assess quality of contours, beam arrangement, and target coverage. Often an independent dose recalculation is also performed to assess the accuracy of the institutions' treatment plan dose calculations. Benchmarks can be a great way to identify variability across centers and offer a platform to provide feedback to participants for improving their practices.

In addition to planning benchmark cases, there is also an image-fusion benchmark case that is used for some central nervous system (CNS) trials. The benchmark reviews an institution's fusion of CT and MR images. For proton therapy, this benchmark can be particularly useful. Proton therapy cannot be planned directly on MR images because the HU values from CT are required for beam range calculations, and the proton range is sensitive to anatomical changes, so proper fusion of MR and CT images is important for treatment delivery accuracy.

There are two challenges with benchmarks; one general and one proton-specific. There have been a few instances where a clinical trial required a benchmark and hundreds of institutions completed the benchmark, but then when it came to patient enrollment, only a small fraction of those initial institutions enrolled patients on-protocol. Reviewing benchmarks is time-intensive for the QA office and at times this method of up-front verification does not yield commensurate reward. For proton therapy specifically, the NCTN QA group does not yet have an independent dose calculation that can be used for all proton therapy centers, so benchmarks can only be used as a qualitative assessment rather than a quantitative one. For these reasons, clinical trial QA is shifting away from standard benchmark cases.

3.6 Pre-treatment, on-treatment and post-treatment review

In lieu of benchmark cases, many clinical trials are shifting toward pre-treatment or on-treatment review of actual patients enrolled in the trials. A pre-treatment review is the submission of the actual treatment plan for a patient intended to be treated on protocol. The plan is rapidly reviewed by clinical trial staff or volunteers and feedback is provided to the participating institution before the start of that patient's treatment. Most commonly, the contours, target dose coverage, and dose to critical structures are reviewed. For proton therapy, the beam arrangement and potential sources of range uncertainty are also evaluated.

The advantage of pre-treatment review is that it can reduce the number of protocol deviations. If an institution receives feedback about ways to improve one patient's treatment, this benefits the individual patient and can also benefit subsequent patients treated at the same institution. The biggest drawback of pre-treatment review is the time-sensitivity of the plan review. Typically the turnaround for such reviews is three business days, but sometimes this is done more quickly. This requires that there is always personnel available to review cases, and does not allow for the reviewer to batch reviews at a time convenient to them. To balance the demands of pre-treatment review, some protocols will require pre-treatment review for the first few (e.g. five) patients from an individual institution. Other trials might place a quantitative criterion for when to require pre-treatment review; one trial requires pre-treatment review if the high dose goal for the target is not met. This is a good compromise to allow early feedback to shape an institution's practices throughout the protocol.

On-treatment reviews, performed while the patient is being treated, can allow similar timely feedback as pre-treatment reviews. They are less time-sensitive, but can have a similar positive down-stream impact on subsequent patients treated by the same institution. Another benefit of the pre- and on-treatment reviews is they give the reviewers a chance to see common issues across multiple institutions, which can be addressed during investigator discussions during the trial and help ensure consistency as the trial moves forward.

Post-treatment reviews are typically performed for all plans, regardless of whether pre- or on-treatment reviews were performed. They assess many of the same criteria, as well as protocol compliance for duration of treatment time.

4. Conclusion

Independent peer review is an important component in clinical trials with radiation therapy, particularly in the emerging field of proton therapy. The credentialing efforts required by the NCI are a paradigm for other proton clinical trials. With the future of proton therapy relying on results of many clinical trials, it is important to get the basics right. Through standard checks of consistency and comparability, we ensure high quality trial data for strong statistical analysis of outcomes.

Conflict of interest

The author declares no conflict of interest.

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