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Redesigning Radiotherapy Quality Assurance: Opportunities to Develop an Efficient, Evidence-Based System to Support Clinical Trials:

Report of the National Cancer Institute Work Group on Radiotherapy Quality Assurance

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Abstract

Background—In the context of national calls for reorganizing cancer clinical trials, the National Cancer Institute (NCI) sponsored a two day workshop to examine the challenges and opportunities for optimizing radiotherapy quality assurance (QA) in clinical trial design.

Methods—Participants reviewed the current processes of clinical trial QA and noted the QA challenges presented by advanced technologies. Lessons learned from the radiotherapy QA programs of recent trials were discussed in detail. Four potential opportunities for optimizing radiotherapy QA were explored, including the use of normal tissue toxicity and tumor control metrics, biomarkers of radiation toxicity, new radiotherapy modalities like proton beam therapy, and the international harmonization of clinical trial QA.

Results—Four recommendations were made: 1) Develop a tiered (and more efficient) system for radiotherapy QA and tailor intensity of QA to clinical trial objectives. Tiers include (i) general credentialing, (ii) trial specific credentialing, and (iii) individual case review; 2) Establish a case QA repository; 3) Develop an evidence base for clinical trial QA and introduce innovative

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Conflicts of Interest Notification

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prospective trial designs to evaluate radiotherapy QA in clinical trials; and 4) Explore the feasibility of consolidating clinical trial QA in the United States.

Conclusion—Radiotherapy QA may impact clinical trial accrual, cost, outcomes and generalizability. To achieve maximum benefit, QA programs must become more efficient and evidence-based.

Keywords

clinical trial design; credentialing; radiotherapy; quality assurance

INTRODUCTION

Modern radiotherapy employs complex modalities and techniques with the goal of optimizing the radiation dose received by the tumor and target tissues while minimizing the dose and possible toxicities to nearby normal tissues. Over the last two decades, many new planning and delivery systems and techniques have been developed and implemented for clinical use. Since these techniques and systems show potential for improving the therapeutic ratio, they have been rapidly and widely integrated into clinical trials.

Clinical trial radiotherapy quality assurance (QA) programs have become more comprehensive and labor intensive, and have increasingly been seen as barriers to trial accrual in some centers. In this context, concerns have been raised about trial generalizability and patient safety when new techniques/processes are extrapolated from a QA-intensive trial setting to routine-QA clinical practice. Furthermore, failure to conduct needed trials has led to some new modalities becoming widely used in clinical care without adequate evaluation of their comparative benefits, risks and costs.

Several recent reports from the Institute of Medicine (IOM) and the National Institutes of Health (NIH) have called for a transformation in cancer clinical trials, from a complex system hampered by delays in trial initiation and inadequate accrual to a limited number of high-priority trials to a more efficient and effective system focused on advancing forward the highest priority research efforts (1, 2). In light of these reports, the National Cancer Institute (NCI) convened a Workshop to address the current challenges in radiotherapy QA for clinical trials and to explore the potential for leaner, more efficient QA. Entitled “Methods and Issues for Redesigning Clinical Trial QA in Radiotherapy”, the conference was held in Rockville, MD on September 7–8, 2010.

The conference was sponsored by the NCI Radiation Research Program. This NCI agency is responsible for evaluating radiotherapy technology and QA in cancer clinical trials. The conference goal was to identify opportunities for developing an efficient, evidence-based QA system to support radiotherapy in cancer clinical trials. The objective of this report is to present the workshop’s findings and recommendations.

CHALLENGES FACING CLINICAL TRIAL RADIOTHERAPY QUALITY ASSURANCE

Clinical trial radiotherapy QA has served the cooperative groups well over the last forty years (3–6). The purpose of clinical trial QA is to ensure that institutions participating in clinical trials deliver prescribed radiation doses that are clinically comparable and consistent with clinical trial protocols. QA centers (Table 1) have improved compliance with protocols, reduced major and minor deviations, detected systematic errors in clinical practices, reduced the misunderstanding and misinterpretation of guidelines, reduced equipment failure modes, and identified QA issues resulting in improved treatments for the next generation of studies

(3–6). These efforts have attempted to assure that the radiotherapy delivered on clinical trials is comparable among patients treated within and between centers and to minimize variations in treatment that may confound patient outcomes. These endeavors have also indirectly improved the quality of patient care at participating institutions by training and education of personnel in safe implementation of new radiotherapy methodologies and techniques.

There is wide consensus that an appropriately rigorous level of institution and provider credentialing should be required by regulatory authorities. This is particularly necessary for participation in trials utilizing radiation therapy advanced technologies. The principal reasons are to: 1) protect patients who volunteer to participate in federally-funded cancer clinical trials and 2) prevent confounding of the study question by variations in the quality of radiation therapy administered.

Although intuitively QA programs must be seen as beneficial in a broad sense, there is relatively limited evidence supporting the value of either general QA or trial specific QA. Some data on the effect of QA are available in the published literature and have shown that vigorous quality assurance results in fewer deviations from protocol (7–9), but evidence for a clinical trial specific benefit is limited. Participation in modern-day clinical trials that utilize radiotherapy advanced technologies requires institutions to submit the protocol patients' volumetric treatment planning and verification data electronically to QA Centers, which is a worthwhile but significant challenge. Such data are also a potential resource for secondary analyses and development of robust dose-response models. Yet, it is not clear what kind of credentialing and case QA is most cost-effective in terms of detecting and preventing deviations of potential clinical relevance. Furthermore, standardization of various aspects of radiotherapy clinical trial QA (via standardized data reporting and submission conventions) would enable streamlined benchmarking, transparency, and easier auditing of participating institutions. Lastly, the possible influence of QA on clinical outcomes, including health-related quality of life and overall survival, has not been clearly defined.

LESSONS LEARNED FROM RECENT MULTI-INSTITUTIONAL CLINICAL TRIALS

Multi-institutional clinical trials involving radiotherapy encompass a range of trial designs and objectives, from investigating the safety or efficacy of new radiotherapy technologies or fractionation schemes to examining more conventional radiotherapy approaches as an adjuvant to novel chemotherapy or biologic agents to studying symptom management interventions. While current QA processes in the United States tend to be “one size fits all,” there may be opportunities to tailor clinical trial QA to the objectives of specific trials. In this section, we present examples of multi-institutional clinical trials with different trial objectives, describing radiotherapy QA challenges and lessons learned.

Radiation Therapy Oncology Group (ROTG) 0126 (NCT00033631)

RTOG 0126 was a Phase III randomized study of high-dose 3-dimensional conformal radiation therapy/intensity-modulated radiation therapy (3DCRT/IMRT) versus standard dose 3DCRT/IMRT in patients treated for localized prostate cancer. The primary objective was to determine whether 3D-CRT/IMRT to 79.2 Gy in 44 fractions would lead to improved overall survival in patients treated for prostate cancer compared to a group of patients treated with 3D-CRT/IMRT to 70.2 Gy in 39 fractions.

The QA and site accreditation process involved a site facility questionnaire, an IMRT/3DCRT dry run case and an IMRT phantom study. The IMRT Facility Questionnaire requests information regarding the training and experience of the IMRT team; the IMRT

treatment planning and treatment equipment; and the in-house QA procedures. A dry-run (the term “dummy run” is used for European Organization for Research and Treatment of Cancer (EORTC) protocols) case provided trial specific treatment planning training to the institution and helped detect ambiguities in the protocol during the early phase of the trial. In 2003, (after the trial had been underway for nearly 2 years), RTOG 0126 was modified to allow IMRT because of the growing availability of the modality and the desire to further reduce normal tissue radiation dose volumes. However, if IMRT was used, each participating institution was required to pass an IMRT phantom test conducted by the Radiological Physics Center (RPC).

Having both 3DCRT and IMRT required modification of the dose prescription parameters. To be consistent with IMRT planning technology, a *minimum* dose prescription to the PTV was required rather than the point dose prescription to the International Commission of Radiation Units (ICRU) reference point (isocenter). It was expected that IMRT may result in more heterogeneity in dose coverage than forward-planned 3DCRT; the impact of this on trial results remains to be seen.

Like other IMRT trials, this study required the planning and physical irradiation of an anthropomorphic phantom. Alternative treatment planning assessments have been proposed, including a digital phantom. While the former is an end to end test of planning and delivery capabilities, the latter only tests the ability to optimize the radiation dose distribution. Thus far, there has been no peer reviewed analysis of the benefits achieved by requiring an IMRT phantom test rather than the IMRT benchmark developed by Quality Assurance Review Center/Advanced Technology Consortium (QARC/ATC).

RTOG 0236 (NCT00087438)

RTOG 0236 was a Phase 2 trial of Stereotactic Body Radiotherapy (SBRT) in the treatment of patients with medically inoperable stage 1 non-small cell lung cancer. The primary objective of the study was to determine if radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieved acceptable local control in frail patients with medically inoperable early stage non-small cell lung cancer.

SBRT involves the use of several advanced technologies including small field targeting, motion management, extremely compact dosimetry, and image guidance. Proper implementation of these technologies is required in order to deliver the extremely potent hypofractionated (i.e., ablative) dose fractionation characteristic of SBRT and is unique from treatments that use forms of these technologies to deliver conventional fractionation.

The RTOG 0236 QA and site accreditation process involved demonstration of motion control, phantom irradiation, and a dry run. The accreditation process required the institutions to submit data related to motion control to the study committee physics Co-Investigator who would determine whether RTOG 0236 criteria could be achieved. Phantom irradiation for accreditation was managed by the RPC. For accreditation, centers demonstrated targeting, treatment planning with compact high dose distributions, and treatment delivery to moving targets. The last step of the accreditation process involved central committee scrutiny of the first enrolled case. If major deviations from protocol parameters were noted, treatment was held until resolution of the deviations. The initial dry run review was completed using the Image-guided Therapy QA Center (ITC) resources typically in less than 48 hours.

Prior to the activation of RTOG 0236, few centers affiliated with the RTOG had started a SBRT clinical program. Despite having few sites poised to treat at activation, the committee leaders decided to move forward with the trial using the QA framework developed

specifically for the trial as a training and education template. This way, the cooperative group could systematically train sites to develop a program that would meet protocol objectives.

The 3 year clinical results demonstrated very high primary tumor control, acceptable toxicity, and excellent survival despite the frailty of the treatment patient population (10). The results have been the basis for studying SBRT in patients with more favorable performance status (e.g., American College of Surgeons Oncology Group (ACOSOG) Z4099/RTOG 1021 in high risk operable lung cancer) as well as in other disease sites. The RTOG 0236 QA plan facilitated the implementation and evaluation of this technologically intensive treatment during its early development.

HeadSTART (NCT00094081)

The HeadSTART clinical trial evaluated the role of hypoxic cell cytotoxin Tirapazamine in a randomized clinical trial in patients with locally advanced (Stage 3 and 4) squamous cell carcinoma of the head and neck (11). Patients were treated with chemoradiotherapy with Tirapazamine as the point of randomization on study.

Participating centers were required to submit diagnostic imaging and treatment plans for patients entered onto the trial to QARC by the end of the first week of radiotherapy. These materials were reviewed by QARC clinical and dosimetry staff, and feedback was provided to the investigators to either confirm that the plan was protocol compliant or to recommend modifications if the plan was noncompliant. On study analysis, patients with protocol deviations had a significant decrease in both survival and local control (11). As part of data review, patients with deviations were re-reviewed to assess the significance of the deviation. If the deviation was thought to be clinically significant, patient survival was similar to those patients who had plan adjustment during the first week on treatment. Interestingly, the survival of both groups was worse than those patients who had protocol-compliant plans de novo. Patients who had non protocol-compliant plans with clinical significance had a statistically significant decrease in survival and local control.

The HeadSTART trial provided several opportunities for process improvements in clinical trials. Because of significant international participation, the clinical trial management committee did not feel that pre-therapy review was feasible, hence the reason for the review during the first week of treatment. With modern digital technology for imaging and radiation therapy, tools are now facile and pre-therapy review is performed routinely in both imaging and radiation therapy in international clinical trials. This study demonstrated the association of a protocol-compliant radiation therapy treatment plan with patient outcomes as well as the importance of designing and reviewing appropriate treatment planning parameters prior to initiating therapy on clinical trials.

RTOG 0831 (NCT00931528)

RTOG 0831 is an ongoing randomized, double-blinded, placebo-controlled phase III trial to evaluate the effectiveness of a phosphodiesterase 5 inhibitor, tadalafil, in prevention of erectile dysfunction in patients treated with radiotherapy for localized prostate cancer. The primary objective is to determine whether tadalafil maintains spontaneous (off-drug) erectile function, as measured by the International Index of Erectile Function (IIEF), as compared to placebo at weeks 28–30 after initiation of radiotherapy for prostate cancer. Patients are stratified by external beam or brachytherapy and proton therapy is not permitted. Study questions are focused on the efficacy of the symptom management intervention and not the efficacy of radiotherapy; however QA of the treatment modality was integral to the trial design.

The RTOG 0831 QA and site accreditation process utilizes the current standard approach for IMRT, 3DCRT, and brachytherapy treatment modality credentialing, involving a facility questionnaire, a phantom study for IMRT performed with the RPC, and review and successful completion of the “Dry-Run” QA evaluation with the ITC. For sites performing prostate brachytherapy, submission of a Knowledge Assessment Form and Clinical Test Case (for physicians) and a Knowledge Assessment Form, a Credentialing Questionnaire, and Reference Cases (for physicists) is required.

Standard credentialing of treatment modalities on a trial that asks a symptom management research question (rather than a radiotherapy research question) was cause for significant discussion among the study team. Radiation quality and dose to critical structures may impact the symptoms following radiation therapy. However, symptom management trials in the clinical trials cooperative groups are conducted through the Community Clinical Oncology Program (CCOP), and the goal of the CCOP is to facilitate research in the community where most cancer care is given. The concern for undue burden on the sites was significant but needed to be balanced with the concern for ensuring quality care while on clinical trials. While the credentialing was determined to be necessary, overburdening sites with significant imaging data submissions not directly related to the study aims was minimized.

Children’s Oncology Group (COG) Trials

The radiation oncology committee of the Children’s Oncology Group (COG) has a long history of active involvement in the QA process and conduct of the clinical trials supported by their group. Until 1990 the review of imaging and radiation therapy information was done as a retrospective process by study investigators. However, the committee reviewed process of QA after review of data generated from the Pediatric Oncology Group (POG) P8725. This study evaluated and randomized the role of radiation therapy after 8 cycles of hybrid chemotherapy in patients with intermediate and advanced stage Hodgkins lymphoma (HL). Initial review and publication of results revealed no advantage to the addition of radiation therapy (12). However, retrospective review revealed a 10% survival advantage to patients treated with radiation therapy when the therapy fields were compliant to study objectives (3).

The POG RT committee required that the next generation of studies P9425 (intermediate risk HL) and P9426 (low risk HL) include pre-therapy review of the RT plan after chemotherapy before radiation treatment could be initiated. This intervention significantly decreased deviations on study with remarkably strong institutional compliance to pre-therapy review (13). For the recently completed COG study of intermediate risk HL AHOD0031, all response imaging and radiation therapy treatment plans were reviewed in real time for uniform response assessment and treatment execution (14). The real time review strategy for imaging and radiation therapy has now been applied to most disease sites in COG, Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group (ECOG), and ACOSOG. However, there are times the processes are decreased based on experience and evolution of study processes. For example, the COG decided to no longer collect central nervous system (CNS) treatment images of patients treated for leukemia after publishing evidence that academic and community medical centers have identical rates of study deviation (15).

POTENTIAL OPPORTUNITIES FOR CLINICAL TRIAL RADIOTHERAPY QUALITY ASSURANCE

Normal Tissue Toxicity, Tumor Control Metrics

Normal tissue toxicity is one of the most important limiting factors in the delivery of radiotherapy. An optimal clinical trial radiotherapy QA program might incorporate estimates or observations of normal tissue outcomes. It is not clear to what extent the knowledge of how dose distributions affect normal tissue outcomes can be utilized as part of radiotherapy QA.

The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) effort summarized normal tissue complication data, but was primarily associated with late effects, thereby limiting its suitability as a guidance document to refine clinical trial QA (16). Models based on the generalized equivalent uniform dose (gEUD) or other forms of EUD may be marginally preferable (e.g. EUD based on equal damage for volume effect organs or tail max doses for serial organs). gEUD has the potential to be quite valuable in the clinical trial context as it can quickly identify differences (or equivalence) among cohorts, especially with respect to target coverage. However, questions and challenges remain. For example, does the subtraction or inclusion of the “high dose” planning target volume (PTV)/normal tissue rind (as is a common planning practice) influence analyses? Should target coverage analyses be based on PTV coverage or gross tumor volume (GTV) dose actually received? Does a small miss in PTV coverage actually translate to worse clinical outcomes? One strong, and not easily testable, assumption underlying the EUD is that over-dosage in one region can be off-set by under-dosage in another region. It is not clear if this assumption is valid in general for tumors or for critical normal tissues.

Biomarkers of Radiation Toxicity

Biomarkers have been defined as characteristics that can be objectively measured and evaluated as indicators of normal physiologic or pathologic processes, or as pharmacologic responses to a therapeutic intervention. They represent a heterogeneous group of characteristics (proteins, nucleic acids, lipids, small metabolites, biophysical profiles) and diverse methods of quantification and analysis (genomic, proteomic, other –omics technology, biomedical imaging) and offer promise as surrogate, predictive, prognostic, pharmacodynamic and pharmacokinetic markers. There is a need for ongoing identification of biomarkers that predict both acute and late toxicities, offering the possibility to personalize therapy with respect to toxicity (not just disease tumor control). Some recent examples include TGF β 1, XPC gene induction as a measure of acute toxicity and p53 as a measure of stress response and tissue biodosimetry (17). It is an enticing possibility that biomarkers could be used to guide QA efforts, though such efforts would require substantial preliminary work and validation.

New Radiotherapy Technologies and Multi-modality Imaging

New technologies continue to be developed and implemented in radiation oncology at a progressively higher rate. As the use of these new technologies makes their way into clinical trials, they pose new challenges for cooperative groups and the QA centers. It is becoming increasingly clear that ensuring 5% accuracy in delivered dose to patients with 95% confidence interval with advanced technology radiotherapy techniques is very challenging. (18, 19) Proton radiotherapy presents a particular challenging area for clinical trials QA. While there are potential advantages to patients from proton therapy, there are substantial concerns as protons are less tolerant than photons of inadequacies in the planning, optimization, and execution of radiotherapy processes. This reflects the nature of the

interactions of protons with matter, and hence the need for credentialing and QA procedures that are specific for proton therapy. In addition, there are several other modalities that present opportunities for clinical trials QA including compliant data export for stereotactic-specialized treatment systems and new processes such as adaptive radiotherapy with the use of deformable registration software tools. The increasing use of multi-modality imaging used for tumor/target volume and organs at risk (OAR) definition will require the involvement of imaging physicians and physicists to a much greater degree.

International Harmonization of Clinical Trial Quality Assurance

One of the most important opportunities facing the cooperative groups and QA centers is the potential for harmonization of both national and international radiotherapy credentialing and QA requirements in clinical trials. Harmonization is urgently needed for some clinical trial sites in order to achieve sufficient patient accrual for the required statistical power in a timely manner. Other benefits include broader acceptance of the trial results and thus greater impact of the trial. A consortium of groups involved in clinical trial QA (the Clinical Trials QA Harmonisation Group) including the NCI, EORTC, RTOG, Trans Tasman Radiation Oncology Group (TROG), ATC, and International Atomic Energy Agency (IAEA) have begun to work toward harmonization under the umbrella of the IAEA. An example of such an effort is the RTOG/EORTC phase III trial evaluating both erlotinib and chemoradiation as adjuvant treatment for patients with resected head of pancreas adenocarcinoma, which is currently open for accrual. Achieving global harmonization of clinical trials QA in general within the international radiotherapy clinical trials community is a major challenge.

RECOMMENDATIONS

Recommendation 1: Develop a tiered system for clinical trial radiotherapy QA and tailor intensity of QA to clinical trial objectives to achieve maximum efficiencies. Tiers include (1) general credentialing, (2) trial specific credentialing, and (3) individual case review

Clinical trial QA should be optimized for any given trial by tailoring QA to trial objectives and trial design. We propose 3 tiers of clinical trial QA that should be utilized incrementally with increased radiotherapy complexity or importance of radiotherapy to the trial design. A standardized submission process which incorporates automated procedures and builds on prior submissions would ease the burden on participating institutions and could potentially improve the quality of submitted data for individual trials.

Tier 1 - General Credentialing—This level is to be completed by all participating radiotherapy sites and mainly aims to ensure basic RT quality is available. This consists of: (1) completing a facility questionnaire documenting staffing and contact information, treatment planning and delivery systems available, and other pertinent information depending on the protocol and modality used; and (2) successful completion of an external audit of machine calibration by an expert center such as RPC.

Tier 2 - Trial Specific Credentialing

- a. **Dry Run/Dummy Run:** This credentialing exercise applies to protocols that require a demonstration of an understanding of the protocol planning and data submission requirements. Dry runs ensure that institutions have reviewed protocol requirements, but do not guarantee protocol compliant radiotherapy delivery in patients. Protocols should include training efforts for participating physicians in target delineation and include delineation guidelines and atlases (if available).
- b. **Advanced Dosimetry Checks:** These credentialing exercises would be done only on protocols utilizing advanced modalities and require that dose delivery does not

deviate from the treatment plan within pre-defined limits. Considerable thought should be given to replacing physical phantom dosimetry tests by digital phantom dosimetry, wherein an image dataset is provided on which a treatment plan is generated by the participating institution. The actual irradiation is then performed on the institution's own phantom. American Association of Physicists in Medicine (AAPM) Task Group (TG) 119 has proven the feasibility of this approach.

Tier 3: Individual Case Review (ICR)—The ICR process should be tailored to trial objectives and applied only to trials that require intensive review of radiotherapy technique at participating institutions. The need for intensive review should be identified based on consensus among study investigators, the sponsoring clinical trial organization, and the QA center. In order to reduce the ICR burden, some trials already incorporate an adaptive ICR review mechanism, i.e., institutions that fail their first dummy run attempt or have a higher ICR failure rate get more frequent ICRs. To ensure maximal effect, ICR should be performed as early as possible during patient accrual. Further refinement of the ICR process will be important to reduce institution burden, increase clinical trials QA efficiency and maintain safe and effective treatment for patients who require re-planning. Consideration should be given to establishing methods to verify that institutions continue to maintain appropriate processes throughout trial accrual.

Recommendation 2: Establish a case quality assurance repository

Expansion of the existing ATC data repository infrastructure is needed to one that provides a robust environment in which institutions can submit and QA Centers can receive, share, and analyze radiation oncology protocol specific volumetric multimodality imaging/treatment planning/verification (ITPV) digital data, the associated pre- and post-treatment (quantitative) diagnostic imaging data, and associated metadata including outcomes. Collecting this data provides an opportunity to examine dose and volume relationships and their impact on clinical outcomes as part of secondary research analyses.

Recommendation 3 - Develop an evidence base for clinical trial QA and introduce innovative prospective trial designs to evaluate radiotherapy quality assurance as part of clinical trials

Several alternatives exist to develop the evidence that support the radiotherapy QA benefits in clinical trials. These include prospective study designs to evaluate QA programs as part of larger clinical trials, secondary analyses of clinical trials to estimate impact of non-compliance on treatment effects, and development of an individual patient case review registry to enable observational studies of compliance involving multiple clinical trials or patient registries.

a. Prospective randomized evidence—Randomized controlled trials of intense versus less intense QA could be feasible as a trial within a trial. Including such a factorial randomization among QA strategies generally does not require an increase the sample size requirements of the existing trial and enables “two questions to be answered for the price of one.” This design is being used for testing image-guided radiotherapy in the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial. Randomization could occur at the patient-level or at the cluster-level, allowing groups of facilities to be randomized to one type of QA versus another. Routine radiotherapy QA as per any institution's usual care standard would remain regardless of which clinical trial QA program arm an institution was randomized.

b. Adaptive QA designs and Bayesian methods—Adaptive designs have been introduced to clinical trials to allow mid-trial adjustments based on the interim data such that

informed decisions can be made earlier with fewer patients. Bayesian methods provide great flexibility but frequentist designs have also been used.(20) How much and what type of QA is necessary? By specifying the criteria for acceptable QA, adaptive QA designs can be constructed with a variable sample size. A potential promising area of clinical trial development will be whether QA assessment can be altered using adaptive trial designs as soon as sufficient QA evidence is obtained.

c. Prospective non-randomized evidence—Full randomization among QA strategies is not always feasible. In some cases, a design may be used in which institutions can choose whether to participate in the QA randomization for individual patients or whether to use a fixed QA strategy for all of their patients. This approach permits QA strategies to be compared with less concern about confounding of compliance with prognostic factors than is often the case. When treatment effects differ substantially based on QA strategies, non-randomized evaluations of this type can be effective. Even if a randomized clinical trial (RCT) came out with a significant benefit from a certain type of QA or high-intensity QA, it may still be unclear as to “what kind” or “how much” of QA is required. Hybrid designs, where institutions can opt-in to different QA paradigms, may provide useful data on the importance of components of QA involved in the rigorous framework of an RCT. Even if not randomized, such studies could be prospectively powered to detect a given effect size from the QA intervention, and accrual could be adjusted in the QA strata as the trial progresses, though selection bias involving those institutions who opt to participate in the QA intervention would have to be mitigated.

d. Retrospective Analyses—An important complement to prospective evidence may be secondary analyses of clinical trials combined. One possibility would be to examine the relationship between dosimetric uncertainty and clinical outcomes in simulation studies using clinical trial data from the RTOG database. An alternative is to develop a repository of case-based QA on individual patients as part of a larger radiotherapy patient registry. Several groups have begun to explore the possibility for a national radiation oncology registry, including the Radiation Oncology Institute (ROI).(21) Constructing a repository of case-QA data objects as part of this registry would enable retrospective review of the impact of dosimetric variability in “real world” clinical settings. Such analyses would have to carefully examine and adjust for confounding between compliance and prognostic factors.

Recommendation 4: Explore feasibility of consolidating clinical trial radiotherapy quality assurance in the United States

We propose to capitalize on the infrastructure and strengths of the nation’s existing QA programs including the Image-Guided Therapy Center (ITC), Radiotherapy Oncology Group (RTOG), Radiological Physics Center (RPC), and the Quality Assurance Review Center (QARC) to form a true consortium (single funding source). This consortium would support all U.S. cooperative groups and be available to support other country’s clinical trials via fee for service. This consortium would work with international cooperative groups and QA Centers with a mandate to reach world-wide harmonization. One approach to consider is for QA centers to be independent organizations separate from the administrative structure of Cooperative Groups.

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Table 1

Overview of Clinical Trial Quality Assurance Centers

Quality Assurance Center	Year Established	Reason Established
Radiological Physics Center (RPC)	1968	To insure the validity of physical data entered into clinical trials
Radiation Therapy Oncology Group (RTOG)	1971	To conduct radiation therapy research and cooperative clinical investigations
Quality Assurance Review Center (QARC)	1980	To establish QA services in support of cancer clinical trials
European Organization for Research and Treatment of Cancer Radiation Oncology Group (EORTC-ROG)	1982	To provide QA for member centers of the EORTC
Image-guided Therapy QA Center (ITC)	1994	To provide QA for prostate dose escalation study using 3DCRT
Advanced Technology Consortium for Clinical Trials QA (ATC)	1999	To establish a consortium of U.S QA Centers that includes the ITC, RTOG, RPC, and QARC and make use of each group's strengths and avoid duplication of existing programs

Table 2

Lessons Learned from Recent Multi-Institutional Clinical Trials

Clinical Trial	Year Initiated	Disease	Trial Design	Primary Endpoint	Clinical Trial QA Lessons Learned
RTOG 0126 NCT00033631	2002	Localized Prostate Cancer	RCT Phase III: High dose 3DCRT/IMRT vs. standard dose 3DCRT/IMRT	Compare the overall survival of patients with stage II adenocarcinoma of the prostate treated with high- vs standard-dose three-dimensional conformal or intensity-modulated radiotherapy.	Timely individual case review provides important training to the participating institution early on in protocol requirements and required structures delineation. Whether IMRT phantom test rather than the IMRT benchmark will be required for future 3DCRT/IMRT prostate trials is unclear.
RTOG 0236 NCT00087438	2004	Medically Inoperable Stage I/2 Lung Cancer	Phase II: Stereotactic body radiotherapy	Determine whether treatment with stereotactic body radiotherapy results in acceptable local control (i.e., 80%) in patients with medically inoperable stage I or II non- small cell lung cancer.	QA plan facilitated the evaluation of the technologically intensive treatment in its early development. Whether this trial's QA structure and degree will be necessary for future trials as SBRT treatment becomes commonplace is unclear.
HeadSTART NCT00094081	2002	Locally Advanced Head and Neck Cancer	RCT Phase III: Chemoradiotherapy with Tirapazamine vs. chemoradiotherapy	To compare the efficacy and safety of concomitant chemoradiation with tirapazamine, cisplatin and radiation versus cisplatin and radiation.	Patients with deviations from protocol had significantly poorer outcomes.
RTOG 0831 NCT00931528	2009	Localized Prostate Cancer	RCT Phase III: External beam/brachytherapy with Tadalafil vs. External beam/brachytherapy alone	To study the efficacy of tadalafil in preventing erectile dysfunction in patients with prostate cancer treated with radiation therapy.	Limit QA requirements that are burdensome to accruing institutions and that do not contribute to the study's main endpoint
COG AHOD0031 NCT00025259	2002	Intermediate- risk Hodgkin's lymphoma	Chemotherapy: RER patients: additional chemo +/- radiotherapy; SER patients: chemo + radiotherapy	Compare response- based chemotherapy and/or radiotherapy in children with intermediate-risk Hodgkin's lymphoma.	It is feasible to provide central and interventional reviews for response- based therapy in a large, multi-center trial. Digital imaging accelerates the ease and timeliness of scan submission to QARC and sharing for remote review.

Table 3**Recommendations for Clinical Trial Quality Assurance**

1	Develop a tiered (and more efficient) system for clinical trial QA and tailor intensity of QA to clinical trial objectives. Tiers include (1) general credentialing, (2) trial specific credentialing, and (3) individual case review
2	Establish a case quality assurance repository
3	Develop an evidence base for clinical trial QA and introduce innovative prospective trial designs to evaluate quality assurance as part of radiotherapy clinical trials
4	Explore the feasibility of consolidating clinical trial quality assurance in the United States and harmonizing QA and credentialing requirements across cooperative groups