Quality assurance for prospective EORTC radiation oncology trials: The challenges of advanced technology in a multicenter international setting

Damien C. Weber\textsuperscript{a}, Philip M.P. Poortmans\textsuperscript{b}, Coen W. Hurkmans\textsuperscript{c}, Edwin Aird\textsuperscript{d}, Akos Gulyan\textsuperscript{e}, Alysa Fairchild\textsuperscript{a,\ast}

\textsuperscript{a}Geneva University Hospital, Switzerland; \textsuperscript{b}Institute Verbeeten, Tilburg, The Netherlands; \textsuperscript{c}Catharina Hospital, Eindhoven, The Netherlands; \textsuperscript{d}Mount Vernon Hospital, Northwood, UK; \textsuperscript{e}EORTC, Brussels, Belgium

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A B S T R A C T

The European Organization for the Research and Treatment of Cancer (EORTC) is a pan-European structure charged with improving cancer treatment through the testing of new therapeutic strategies in phases I–III clinical studies. Properly conducted trials in radiation oncology are required to demonstrate superiority of a new treatment over the current standard. The Radiation Oncology Group (ROG) has initiated a complex quality assurance (QA) program to ensure safe and effective treatment delivery. Most modern trials are multicenter and multidisciplinary, further increasing the importance of early, strict and consistent QA in radiotherapy (RT). QART measures confirm whether a site possesses minimum staff and equipment for participation. Dummy runs, reviews of patient treatment plans and complex dosimetry checks verify the ability of an institution to comply with the protocol. Data required for evaluation are increasingly exchanged digitally, allowing detailed plan reconstruction, evaluation of target volume delineation and recalculation of dose-volume parameters for comparison against predefined standards. The five tiers of QA implemented in EORTC trials are reviewed, along with past, current and future QART initiatives. As substantial human and financial resources are increasingly invested in QART, the importance of cost-benefit analysis of QA and its impact on clinical outcome cannot be overstated.

\ast Corresponding author. Address: EORTC, 83 Ave. E Mounierlaan, Brussels 1200, Belgium.
E-mail addresses: alysa@ualberta.ca, alysa.fairchild@eortc.be (A. Fairchild).

Radiation therapy (RT) planning and delivery have changed substantially over the last three decades, starting with the introduction of three-dimensional (3D) treatment planning in the 1980s, followed by intensity-modulated RT (IMRT), image-guided RT (IGRT), and stereotactic radiosurgery, often requiring dedicated treatment units for specific indications [1,2]. The evaluation of these potentially error-prone techniques in clinical trials followed by their introduction into daily clinical practice requires careful and thorough quality assurance (QA) programs.

QA in RT (QART) is defined by all of those procedures that ensure consistency of the RT prescription and the safe fulfillment of that prescription with regard to the dose to the target and organs at risk (OARs), minimization of exposure of personnel, and patient monitoring aimed at determining the results of treatment [3]. The practice of QA includes the environment in which care is delivered (structure), how operational standards are maintained (process), and what is achieved for patients (outcome) [4]. A QA program is aimed at defining the range of acceptable deviations, detecting potential causes for larger deviations, and developing mechanisms of action for correction and prevention of these deviations [5]. The goal is to reduce variability and uncertainties related to the different steps of treatment planning and actual patient irradiation, including but not limited to patient positioning and precise dose delivery to the target volume [6].

Interest in the quality of clinical trials in radiation oncology has increased in parallel with the growing complexity of RT techniques, associated cost of studies and increased numbers of patients accrued to trials [6]. Only the results of well-conducted studies with a documented QA program in which patients are treated in a technically optimal fashion can be considered credible [5,7,8]. Optimal RT is pivotal in the interpretation and reliability of trials, ensuring that potentially practice-changing results are regarded as robust, definitive and generalizable. Modern clinical trials are often multidisciplinary and international, further increasing potential points of discordance and focusing attention on the critically important issue of global harmonization of QA procedures. Specific considerations of QART in a multicenter research setting include:

- determination of protocol ambiguities that may affect treatment delivery;
- education of sites in RT-specific trial guidelines;
- promotion of consistency between centers.
Variations in compliance with protocol treatment can decrease therapeutic effectiveness that may lead to loss of tumor control and/or increase RT-induced toxicity. Such deviations may ultimately contribute to negative clinical trial results. In a recent prospective trial in advanced head and neck cancer randomizing between radical chemoradiotherapy with or without tirapazamine, patient outcomes correlated with protocol deviations [7]. In patients who received at least 60 Gy, those with major deficiencies in their treatment plans had a markedly inferior outcome compared with those whose treatment was initially protocol-compliant: 2-year overall survival was 50% vs. 70%, and 2-year locoregional control was 54% vs. 78% (both p < 0.001). While other factors likely contributed, radiotherapy quality undeniably determined trial outcomes [9]. While noncompliant RT may waste time, effort and money and could more importantly harm patients, there is some evidence that the process of participating in protocol QA activities improves treatment delivery not only for enrolled patients but also for those treated off-trial [6,10].

In this paper, we will briefly review the history of the QART program of the European Organization for the Research and Treatment of Cancer (EORTC) Radiation Oncology Group (ROG), discuss current requirements for participation, and review digital data exchange within this context. The central review platform of the EORTC will be introduced followed by remarks on securing dedicated funding and future QA challenges.

Center credentialing requirements

In 1982, the EORTC ROG activated its QA strategy. Over the past 30 years, the QA program has included site visits, evaluations of institutions’ staffing and infrastructure, direct mechanical and dosimetric checks of treatment units, verification of clinical data in institutions’ staffing and infrastructure, direct mechanical and planning exercises demonstrated insufficient or excessively large irradiated volumes in about one-third of cases [13]. Deviations observed in mechanical output checks of accelerators and simulators were smaller compared to those of cobalt units, possibly related to the advanced age of the latter, up to 20 years [14]. The European TLD program revealed deviations >7% between the dose measured and the dose stated by some centers [15,16]. In 1993, more than 90% of beams with deviations >3% were from departments which had not participated in external audits in the previous 5 years [17]. Bentzen et al. used radiobiological modeling to calculate the possible clinical impact of dosimetry data obtained from 140 mailed TLD measurements from 35 departments, performed from 1993 to 1996 for 26 cobalt machines and 114 linear accelerators. In this theoretical study, the 10% most “underdosed” beams would result in a 7–8% loss in tumor control probability (TCP), whereas the 10% most “overdosed” beams would increase the grades 1–2 complication rate by 19–22% and grades 3–4 rate by 4–5% [18].

Based on these initial efforts, a consensus statement on QA within the framework of RT clinical trials was published in 1993 [19]. Recommendations were made for minimum requirements for participation in EORTC ROG protocols [11,20] and recently updated [5]. A summary of former and current requirements for infrastructure, personnel, and workload is presented in Table 1.

A QART program is currently implemented across all studies involving RT in the EORTC, which includes involvement in early protocol development. Importantly, the level of QA and its budget are determined very early in protocol conception. As the introduction of new treatment techniques within clinical trials often precedes general acceptance by the oncological community, a trial protocol must be written in such a way as to anticipate the challenges presented by this technological evolution. The protocol should define all critical procedures in order to minimize practice variation between investigators [6]. Clearly written qualitative and quantitative parameters are pre-defined. Protocol deviations are usually classified into three tiers: no deviation, minor, and major deviation.

Since 2006, QART requirements for sites participating in EORTC trials have been classified into five different levels (Table 2). Within these levels, there are: (a) general procedures which apply to all trials; and (b) trial-specific credentialing implemented depending on the complexity of the technologies involved. General credential-
ing (level 1) helps to ensure delivery of RT of minimum acceptable quality across all sites. It consists of the satisfactory completion of a facility questionnaire (FQ) and external reference dosimetry audit (ERDA); both are mandatory before site activation.

### Facility questionnaire

The FQ assesses department infrastructure, medical and technical staffing levels and treatment workload. Although it is assumed that the availability of resources influences process and directly impacts treatment results, this is difficult to prove [4]. However, it is evident, for example, that a department with several linear accelerators is more likely to be able to absorb the impact of unexpected machine breakdowns, essential to minimize treatment interruptions, or treat patients in a timely fashion as per protocol.

An institution more experienced in a given disease site may be more likely to recruit and more likely to be able to adhere to a complex protocol [21–23]. Multidisciplinary regimens require significant coordination of workflow including precise scheduling, collaboration with diagnostic services and communication with site research staff. Detailed reporting, either through paper forms or electronic data capture, takes time on the part of local investigators, data managers, and study assistants. Since the quality of submitted data is the backbone of all clinical trial outcomes, site staff should be well-trained and able to dedicate sufficient time to this activity [24,25]. Investigators handling a high number of patients per year may have difficulties complying with the logistical and administrative burden of clinical trials. This may translate into difficulty meeting submission timelines, compromised data quality, or preventable deviations from protocol treatment.

Such crucial information on these putative quality indicators is collected through the FQ at the time the center applies for ROG membership, prior to site activation of every new trial, or every 2 years, unless major changes in the RT delivery process occur. Currently, after each institution completes the web-based FQ, it is reviewed by one RO and one physicist from the ROG [5]. The data contained in the FQ database also presents an opportunity for research, for example investigating a possible correlation between site infrastructure and patterns of care illustrated by surveys of the EORTC network [26,27].

### ERDA

It has long been recognized that there may be differences in the calibration of individual RT treatment units; accuracy of calibration depends on the skill of the local staff, the instrumentation used, familiarity with appropriate procedures, and the secondary standard dosimetry laboratory (SSDL). The uncertainties inherent within this process are usually in the range of 1–2%, but errors can increase this to an unacceptable level. Before patients participate in a multicenter RT clinical trial, it is vital to determine the accuracy of a site’s machine output to avoid the introduction of bias due to different delivered doses [28]. Agreement between the reference audit and the center’s own measurement should ideally be within 2–3% but 5% agreement is within EORTC ROG tolerance.

Various external bodies can provide an audit. The earliest were initiated by the IAEA (1966) and radiological physics center (RPC; 1968), who both used mailed TLDs [29,30]. Various publications describe the extent of variation discovered using these procedures [31–33]. The EORTC’s program started in 1987, but has since been taken over by ESTRO [34,35]. Another approach, commonly used in the UK, is the interdepartmental or ‘peer-to-peer’ audit. This initially utilized ion chamber measurements with a simple anthropomorphic phantom, and later concentrated on photon and electron output measurements only [36–38]. While effective, since these types of audits are not based on a single secondary standard, the results show a larger variation [39].

The EORTC ROG requires proof of satisfactory ERDA every 2 years, in comparison to RPC, who performs these audits yearly. The implications of this differential time assessment are currently under study. The ERDA can be performed by any provider, including the UK approach, as long as there is a traceable pathway through a SSDL to an accepted primary standard. Audit of the following is currently required: the lowest and highest photon energy, and the lowest and highest electron energy, not necessarily on the same treatment unit. After submission of an ERDA certificate to EORTC headquarters (HQ), it is reviewed for approval.

### Protocol-specific institutional tests

The role of protocol-related institutional tests is to verify that external beam RT planning and delivery is congruent with study guidelines. The dummy run (DR), EORTC QART level 2 (Table 2), was introduced in 1987 to quantify both the incidence and range of possible protocol deviations of RT planning for an index case and provide an opportunity to practice application of protocol instructions. It documents the ability of the center to participate adequately in the study and identifies potential ambiguities in protocol wording. In a DR procedure, investigators are provided with relevant clinical and radiologic information on an index patient, and are asked to treat the case as if it were entered by their institution on that protocol. The DR case is usually study-specific and performed ideally before site authorization or within the early stages of the trial. Aspects which can be evaluated include the ability to delineate OARs and target volumes, and produce a treatment plan according to trial specifications. Data is analyzed by independent QA reviewers who report to the local principal investigators [40]. Major deviations trigger compulsory DR resubmission and a hold on patient accrual if the DR is a sine qua non condition for site authorization. Widespread or repeated deviations may trigger a protocol amendment [41].

The individual case review (ICR) verifies protocol compliance with RT parameters including target delineation, beam configuration and dose homogeneity (QART levels 3 and 4). The ICR is ideally carried out early in trial accrual so that deviations from protocol treatment planning, which may critically reduce the reliability of trial conclusions, can be rectified. It was a previously common practice at EORTC to perform the ICR only in centers accruing a certain number of patients, usually 10% or more [42]. However, the current approach is to review patients from all centers to assess overall RT quality. ICRs can be performed retrospectively or prospectively, each with defined timelines. Although the former approach predominated at EORTC for many years, under the current QA strategy, ICRs will be increasingly performed before RT starts, as currently required in the EORTC 22042–26042 meningioma study.

ICR of all trial patients (QART level 4; Table 2) is time-consuming and costly and for this reason, a selection of cases per department (QART level 3; Table 2) is usually performed [11]. This may be a random sample, a number of even/odd study number cases,

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time-dependent sequential selection, or the first 1–3 patients accrued. When done prospectively, significant improvement in protocol adherence is seen in the form of an increased number of evaluable and appropriately treated patients, especially after feedback is communicated to all trial participants [6,43]. The review package could be a mixture of hard copies (such as isodose distributions) and digital data (diagnostic images, RT plans, digitally reconstructed radiographs or position verification images) on CD-ROMs or via a web-server.

To verify that an institution can actually deliver advanced RT techniques according to the plan generated by their treatment planning system (TPS), a complex dosimetry check (CDC) may be required (QART level 5; Table 2). Most commonly, this comprises irradiation of a physical phantom. An anthropomorphic phantom is mailed to the institution and upon receipt, is CT-scanned. Thereafter, a treatment plan is made according to specific instructions and the phantom is irradiated. Measurement and calculations performed are evaluated based on predefined criteria by an independent central team. Experience with phantoms was initially gained in EORTC trials in the 1980s and 1990s [13,44], and this procedure has been recently relaunched as a collaborative effort with RPC for protocols allowing IMRT [45]. Other trial organizations have also utilized CDC inter-comparison [46–48]. In the UK, CDCs performed for IMRT trials such as PARSPORT are supported by the Radiotherapy Trials QA Group [49], and TROG recently performed a comprehensive audit of Australian and New Zealand centers participating in two IMRT trials [50]. Among clinical trial QA groups, the RPC has the largest set of phantoms available and the most experience with physical phantom dosimetry to date [51–54]. To minimize the QA burden on sites wishing to use IMRT in EORTC trials, consideration is currently being given toward waiving the CDC requirement after successful participation in a national or international IMRT audit performed outside of a trial [55–57].

There are a number of challenges related to IMRT credentialing by physical phantoms, however. The handling of a phantom not used routinely by the institution is prone to mistakes, distribution by mail is time-consuming and expensive, a number of identical phantoms are needed to credential a large number of sites for one trial, and maintaining and updating phantoms for new technologies is costly and labor-intensive. There are also limitations with respect to the interpretation of treatment errors. Ibott et al. reported in 2008 that approximately 30% of institutions irradiating a head and neck phantom failed to deliver a dose in agreement with their own treatment plan within gamma values of 7% or 4 mm [52]. However, this included a substantial number of errors related to obvious erroneous positioning on the couch. Since CDC procedures are often executed by physicists, who are less experienced with set-up, it is debatable whether these errors truly reflect substandard clinical practice.

To address these issues, a new procedure has been developed by the EORTC ROG, named “virtual phantom credentialing”. In this procedure, a CT dataset is provided to site investigators who generate a treatment plan based on predefined planning objectives. This plan is then copied to the image dataset of the institution’s own QA phantom. The dose distribution is recalculated without plan modifications. Measurements are performed on the QA phantom. The calculated and measured (2D or 3D) dose distributions in the QA phantom are uploaded to the EORTC and evaluated for acceptance based on gamma analysis [58]. Although this analysis is straightforward, results are dependent on the type of phantom used. Suitable acceptance criteria were acquired in a small multi-institutional, multi-phantom pilot study performed by the AAPM TG 119 [59]. Currently, the EORTC together with the AAPM clinical trials working party and AAPM IMRT QA working party are establishing an open, NCI-based website from which digital phantoms can be downloaded and results can be uploaded. This will enable pooling of results and establishment of detailed criteria. EORTC virtual phantom credentialing is expected to be instituted as part of QART level 5 as early as 2012.

Electronic data transfer and the EORTC platform

Traditionally, DRSs and ICRs were performed using paper documents. As QA requirements have increased in complexity in parallel with evolution of RT delivery techniques, a pressing need to facilitate inter-institutional digital data exchange has emerged. Clinical trial QART programs, including those of the EORTC, have played a pioneering role [60,61]. Collection of digital data carries significant advantages over paper, especially for RT treatment, where detailed information about target volumes and dose distributions is simply not available in any other format. With the widespread use of DICOM-RT, it is now possible to expand local networks to include other institutions and cooperative group data centers.

This expansion, however, presents new challenges. Integrating computerized central review of treatment delivery requires careful validation, and implementation of multicenter digital exchange may reveal previously unknown incompatibility issues. These may include the requirement to overcome the institutional firewall for file transfers, possible inability to export the data in the proper format, different versions of software coexisting, uniform structure naming requirements, or discrepancies introduced in the course of performing anonymization. Building central reviews of diagnostic imaging and RT data requires proper setup and a dedicated team for the collection, data process and analysis.

Assuming data export is properly performed, the images, structure and dose files must be reassembled to reproduce the local plan for review. However, submitted DVHs lack consistency as a result of the various TPS algorithms in use internationally, with a small difference in the method of volume calculation resulting in up to a 30% difference. Recalculation of DVHs must be performed and these recalculated DVHs used for comparison to ensure consistency; this could result in different values compared to those calculated by the site [62,63]. This must be taken into consideration when defining tolerance doses in trial protocols. TPS vendors should insist on the DICOM-RT standard for storing the original DVH parameters within the dose matrix. Caution is also required with inverse-planning systems, where the optimization procedure creates special volumes and DVHs.

To address difficulties with digital data submission, it is important that the clinical trial group provide IT and DICOM troubleshooting support for participating institutions. Based on the US experience through the Advanced Technology Consortium, 26–29% of digital submissions required intervention to correct data integrity problems [64]. This process often requires iterative communication with site personnel. Similar to case report forms’ cross-checks and validation procedures, digital data submission requires dedicated support to ensure smooth data exchange.

Given the above, the EORTC ROG determined that the essential requirements for a new integrated modular central review facility were: broad applicability; secure and easy access to data without on-site hardware installation; integration within the EORTC HQ’s existing clinical remote data capture system; and the ability to both customize the platform to specific studies and adapt to currently unforeseen future needs. A streamlined process for electronic data transfer also facilitates international and inter-group cooperation.

The resulting QA platform, which also integrates image analysis software, permits timely, secure, and fully digital central DICOM-RT based data review (Fig. 1) [65]. Participating sites upload requested data through a standard secure upload webpage. Supplemental information is submitted in parallel through web-based forms, such as type of TPS and description of the position
verification protocol. An internal data integrity check by EORTC HQ reviews format, consistency, completeness of protocol-required elements, and anonymization. Review of contouring compliance, recalculation of DVHs, check of the dose prescription and dose heterogeneity takes place. Central reviewers have remote online access to the DICOM-RT data through a terminal server, and are provided relevant clinical data by HQ QART. They evaluate submissions for protocol compliance through a standardized online evaluation matrix. Comments are collected by EORTC HQ and participating institutions are informed of the results. After retrospective testing within several clinical trials, the platform was introduced in phases to participating sites and study reviewers. The digital era at the EORTC began with the DR of EORTC 22042 in 2008.

Other important applications of a digital platform are the ability to store data centrally for future research, and the avoidance of returning hard copy RT records to participating centers [66]. Data storage, security, and archiving are among the most rapidly developing aspects of information technology, and allow creation of a structured data warehouse for future analysis. Amalgamating imaging databases with clinical and translational data depends critically on cross-referencing de-identified patient data. Therefore, anonymization should be performed in a consistent way for different types of information pertaining to the same patient.

Integral to the EORTC ROG platform, the Visualization and Organization of Data for Cancer Analysis (VODCA) software is a software package for digital data submission, archiving and review of volumetric RT data [67]. Through VODCA, it is possible to collect complete digital data for patients enrolled in clinical trials in a standardized and comprehensive manner. This presents an unprecedented level of complexity and a previously unavailable level of data. VODCA allows analysis of the influence of treatment technique and dosimetric parameters on patient outcomes. Other applications include development of dose–response models and correlation of trial results with QA compliance.

Variability in volume definition by clinicians can be a significant factor affecting outcomes [68]. This variability may be due to methodology used for delineation, training and experience of physicians, or subjective interpretation of imaging [6]. With the EORTC platform, a comprehensive estimate of the degree of variability between patients and between institutions in both tumor and OAR volumes can be developed from multi-institutional data. Other current initiatives include combining dosimetric variation with clinical parameters to build models to predict TCP, normal tissue complication probability and quality of life.

**QA for advanced RT techniques**

An evolution in the paradigm has occurred regarding QA of treatment techniques and equipment. In the past, QA has focussed more on equipment specifics like type of treatment machine, beam energy, minimum allowed field size, number of treatment fields, etc. With advanced techniques like static and rotational IMRT, and modern equipment like helical Tomotherapy, Cyberknife and flattening filter-free treatment units, this is no longer feasible. Instead the focus has shifted to confirmation that an institution is able to deliver a dose in agreement with its own treatment plan. IGRT is also sometimes considered an advanced RT technique. However, portal imaging, which is a form of IGRT, has already been extensively used within EORTC trials. With the advent of new imaging modalities like cone beam or megavoltage CT and highly conformal treatment plans, the focus of QART for IGRT has also progressed. The relation between target and OAR volume delineation, margins, imaging and set-up correction strategies is vital, and often cannot be separated. Thus, QART of IGRT now aims to define the adequacy of these components within the trial protocol; this is assessed as part of both DR and ICR procedures.

**Funding for QA**

Clearly, there is an investment required in terms of time and money to support implementation of QA in the framework of clinical trials. QA activities impose significant additional workload on participating departments and on clinical trial organizations like the EORTC. The incorporation of QA as a standard part of the conduct of clinical trials, including ensuring sufficient financial and technical support, requires budgeting early in protocol development. Dedicated funds should be negotiated with industry, cancer...
leagues, academic funds, granting agencies, clinical trial groups, national and international networks to ensure inclusion of these essential requirements.

In Europe, the question of long-term, stable funding is not yet solved. Most of this work is currently done by volunteers and by fellows financially supported by grants from cancer leagues. With the growing complexity of RT and in fact all aspects of clinical and basic scientific research, this is likely untenable in the long term. In response, a thorough evaluation of the organization and the financial support for QA has been made by the EORTC ROG QART strategic committee. In cooperation with EORTC HQ, a QART office was established in 2008 with the appointment of a QART Manager (medical physicist). Dedicated financial support for a QART fellow (physician) has actually been in place since 2001 with the generous support of the Vlaamse Liga tegen Kanker. The QART office expanded in early 2011 with the addition of a QART Officer (RTT).

Conclusions

Each step in the process of treatment preparation and delivery can contribute to the total uncertainty in the dose delivered to the patient [4]. Therefore the validity of conclusions relating to a specific protocol may be questioned if appropriate QA has not been performed [68]. The selection of the appropriate levels of QA for a given trial is highly dependent on the aim of the trial and the complexity of the RT techniques used.

Current clinical trial QA programs help to ensure that participating departments deliver prescribed radiation doses that are clinically comparable and consistent. They help to improve compliance, reduce deviations, identify protocol ambiguities, and detect systematic errors in sites’ clinical practice. This has improved the quality of care of all patients by education of site personnel in safe implementation of new methodologies and techniques [10]. This should prove to be a cost-effective means to correctly translate new procedures from research to bedside.

As modern technologies are incorporated into clinical trials at a progressively faster rate, QART challenges will also increase. By expanding the number and complexity of correlates examined to try to relate treatment technique to clinical outcome, substantial demands are put upon QA processes [68]. However, data collection, credentialing and central review using the EORTC’s integrated, web-based platform will reduce the risk that trial outcomes are compromised through inadequate RT.

Several issues remain to be satisfactorily addressed, however. Knowledge dissemination should be integral to QART programs to ensure that difficulties encountered within trials are not reproduced in future studies or when attempts are made to implement trial results into standard practice [6]. Cooperative groups should continue to investigate the impact of QA on clinical endpoints, what RT deviations are predictive of substandard outcomes and how they should be corrected [67]. Finally, as QA represents a substantial investment of time and money on the part of both trial organizations and participating departments, there is an urgent need for thorough cost-benefit analyses.

Conflict of interest statement

There are no actual or potential conflicts of interest to declare.

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