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Position Paper

Development of clinical trial protocols involving advanced radiation therapy techniques: The European Organisation for Research and Treatment of Cancer Radiation Oncology Group approach

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Abstract The European Organisation for Research and Treatment of Cancer (EORTC) Master Protocol for phase III radiation therapy (RT) studies was published in 1995 to define in a consistent sequence the parameters which must be addressed when designing a phase III trial 'from the rationale to the references'. This was originally implemented to assist study investigators and writing committees, and to increase homogeneity within Radiation Oncology Group (ROG) study protocols. However, RT planning, delivery, treatment verification and quality assurance (QA) have evolved significantly over the last 15 years and clinical trial protocols must reflect these developments. The goal of this update is to describe the incorporation of these developments into the EORTC-ROG protocol template. Implementation of QA procedures for advanced RT trials is also briefly described as these essential elements must also be clearly articulated. This guide may assist both investigators participating in current ROG trials and others involved in writing an advanced RT trial protocol.

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1. Introduction

Properly conducted trials in radiation oncology are required to establish new treatment approaches in terms of improved tumour control and/or lower complication rates. Interest in the quality of radiation therapy (RT) delivered within a clinical trial setting has increased in parallel with the growing complexity of diagnostic and therapeutic procedures, cost of studies and numbers of patients accrued.[1] The amount of new knowledge generated from each trial must be maximised to optimise shrinking resources.[2] Uncertainties in terms of volume delineation, target and normal tissue doses and machine output may not only decrease the effectiveness of therapeutic management, but increase complication rates and reduce patient quality of life.[3] The worst case scenario is that non-compliant RT in a comparative phase III trial may contribute to a negative statistical conclusion regarding the primary end-point, reflecting the value of treatment of low quality, and thus failing to assess the benefit of the planned RT.[4,5] Such instances also call into question the feasibility of the study treatment.

RT protocols should define all critical procedures in order to minimise variation between investigators.[1] Modern trials are often multidisciplinary, multi-centric and international, further focusing attention on the critically important issue of a clear, well-written protocol, especially if participants' first language is not English. Although a protocol is usually written by experts in a certain disease site, institution investigators may not be familiar with the subject to the same extent. RT protocols must serve the informational needs of many disciplines, such as radiation oncologists, medical physicists, radiotherapy technologists, study nurses and clinical research associates. Therefore, protocol writing should be supported by an infrastructure of experts in areas including data management, bioinformatics, pharmacovigilance and regulatory affairs. Although it can be difficult to write a simple, straightforward but thorough RT protocol on a complex treatment technique, the aim should be to create this document in a manner that addresses potential areas of ambiguity in all steps of treatment preparation, delivery and reporting.

The European Organisation 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 phase III randomised trials. The EORTC also conducts early phase combined modality trials investigating optimal integration of new molecular agents with radiotherapy, and protocols exploring new RT delivery methods. The concept of a Master Protocol for phase III studies was originally considered by the EORTC Radiation Oncology Group (ROG) in the 1990's in order to help facilitate writing and increase consistency of study protocols.[6] The Master Protocol was also instituted to help address disappointing quality assurance (QA) in RT results of past EORTC ROG studies, which has been explained by misinterpretation of protocol instructions.[7–11] In some cases, this inter-centre variation was significant enough to have triggered protocol amendments.[9–11]

The aim of this consensus document is to describe the current EORTC ROG approach to protocol writing of RT trials, focusing on the requirements of advanced external beam delivery techniques in multicentre clinical trials. In addition to the CONSORT guidelines for interpretation and reporting of clinical data,[12] ROG protocols should be clearly aligned with the recommendations of the International Committee on Radiation Units & Measurements (ICRU) Report 83 on prescribing and reporting of intensity-modulated radiation therapy (IMRT).[13] The following parameters must be included in all EORTC ROG clinical protocols unless their omission is clearly justified (Table 1).

2. Radiation therapy

A key component of an effective process improvement and workflow management infrastructure is consistent RT structure and terminology. As such, the use of international recommendations on terminology and prescription practices is mandatory, together with inclusion of uniform naming conventions in a common language.[13]

2.1. Facility and equipment

Describe minimum technical requirements and procedures with which institutions must comply. Allowed equipment and treatment techniques should be described and under which circumstances each may be used. Give information about beam quality, the minimum (and/or maximum) beam energies allowed and required technical capabilities (e.g. intensity-modulated radiation therapy [RT], cone beam CT). Consideration should be given to the foreseen development of new treatment techniques within the lifetime of the trial and a provision for their future use should be included whenever possible.

2.2. Patient positioning and simulation

Explicit patient preparation guidelines should be given, such as bowel and bladder filling instructions. Requirements for the treatment planning CT that should be included are: recommendations on patient positioning and immobilisation; anatomic references for the minimum scan volume; use of contrast or other visualisation aids; range of acceptable slice thickness and maximum inter-slice gap. All potential beam entrance and exit areas should be included in the planning CT range in order to

Table 1
Summary of required protocol components.

Title	• Include information on the trial design
Summary table	• Provide a concise outline of key points such as main inclusion criteria, treatment arms and target accrual
Background and rationale	• Describe the evidence base for the rationale, importance and choice of treatment arms including doses and fractionation schedules • Include the hypothesis on which the main statistical considerations are based
Trial objectives	• State the main clinical question(s) to be addressed by the trial • Define briefly the main primary and secondary end-points
Patient selection	• List eligibility and ineligibility criteria
Trial design	• State the type of trial and whether it is randomised • Include an easily understandable study schema or flow diagram with an overview of treatment schedules, primary objective and total sample size
Pre-treatment evaluation	• Explain the schedule of investigations needed to evaluate eligibility (including histologic confirmation), prognostic factors and baseline values of parameters to be used as end-points • Include any other pre-treatment assessments such as specialist consultations
Surgery (if any)	• Outline any invasive staging and therapeutic procedures, peri-operative care and surgical quality assurance
Radiation therapy	• Describe minimum requirements for facilities and equipment, along with instructions pertaining to all phases of RT preparation and delivery • Expected toxicities, their management, dose and schedule modifications and withdrawal criteria should be described
QA for radiation therapy	• Define the level(s) of QA to be implemented, specifying timing of each (prior to site activation versus during patient accrual)
Systemic therapy	• Outline types of agents, dose, route, schedule, and treatment duration • Expected toxicities, their management, dose and schedule modifications and withdrawal criteria should be described • Logistics to be considered include supply, packaging, dispensing, storage, reconciliation and QA
Central review procedures	• Explain objectives and procedures for central (pathology, imaging, other) review
Follow-up	• Summarise methods used for assessing study end-points (clinical evaluation, lab tests, imaging, other) and their timing
End-points and response criteria	• Clearly define primary and secondary end-points, how they will be measured as well as length of required follow-up • State the data required to determine the types of response and confirm progression • Give guidelines for treatment at relapse, if any
Registration and randomisation	• Explain procedures for assignment of patient identification number, registration, randomisation, allocation ratio, blinding/unblinding and stratification
Administrative procedures	• Methods of data collection and other administrative requirements of investigators must be described • Data control procedures and foreseen on-site quality control should be mentioned
Adverse event and pregnancy reporting	• For toxicity, specify definitions, grading, assessment tools and reporting procedures • Explain regulations regarding pregnancy reporting
Ethical considerations	• Refer to laws, regulations, and guidelines which will govern conduct of the study, and include a patient consent form and patient information sheet
Statistical methods	• Discuss end-point calculation and stratification factors • Provide a sample size estimate, its underlying assumptions and expected accrual rate • Describe the statistical methods and populations to be used in the analysis • Protocol early stopping rules and interim analyses should be explained, along with the roles of the Independent Data Monitoring Committee and Data Safety Monitoring Board
Quality of life (if any)	• Specify objectives, assessment tools, schedule and statistical considerations
Translational research	• Explain objectives; material to be obtained; schedule; instructions for handling, transfer and storage of samples and statistical considerations
Additional administrative sections	• Administrative responsibilities • Trial sponsorship and funding • Trial insurance • Publication policy • Administrative signatures • References
Appendices	• Staging system • Performance status • Imaging acquisition protocols • Guidelines for target volume selection and delineation • Method of response evaluation • Acute and late toxicity grading scale • Form submission schedule • Patient consent form • Quality of life instruments

avoid areas of inadequate dose calculation. Allowed methods for motion management during the CT simulation scan must be described (eg respiratory gating, 4DCT). If information from other imaging modalities (MRI, PET) will be required for volume selection, clearly define the acquisition protocol to be used. Specify whether co-registration and fusion is mandatory and if it is to be implemented, state whether it should be performed with a deformable or non-deformable algorithm.

2.3. Volume selection and definition

If the protocol includes multiple target volumes (GTVs/CTVs), clear descriptions for volume selection should be given for each. Sources of additional information (e.g. diagnostic imaging, surgical report, pathology report) to be consulted should be given. Guidelines for PTV design (including any requirement for an internal target volume) should be given.

Volume definition should be in accordance with ICRU Report 83.[13] Specific attention in the protocol description should be focused on areas where known variation in practice between centres exists. This section should refer to published contouring atlases, if in existence. It is preferable not to duplicate descriptions in the protocol but rather reproduce appropriate extracts from the source publication in an appendix. Delineate all volumes on all slices.[14]

The CTV to PTV margin depends on the set-up verification and correction method applied and may thus be institution specific. Heterogeneity of protocol treatment implementation (e.g. differences in specific IMRT techniques) may necessitate the specification of a range of acceptable CTV to PTV margins. The protocol should provide a rationale for the choice of margins allowed.[14]

An organ at risk (OAR) section describing all normal tissues plus any planning at risk volumes (PRV) to be contoured is required.

2.4. Planning aims and dose–volume constraints

Specify the total dose, dose fractionation schedule, minimum inter-fraction interval (if applicable) and allowed overall treatment time for each PTV. For sequential phases, state the sequence and timing of treatment delivery for each. Adoption of the ICRU 83 Report dictates prescription based on the PTV parameter of median dose (D_{50}). D_{nearmin}, and D_{nearmax} for PTVs and D_{nearmax}, average dose or V_{d} (volume receiving a dose 'd') for organs at risk must be specified.[13] Dose–volume constraints (maximum dose, dose per volume) for each relevant OAR and PRV are also required.

2.5. Treatment planning

In advanced RT delivery techniques, there is no longer a need to predefine a specific beam arrangement, since forward or inverse planning is iteratively employed to produce a compliant dose distribution. Provided protocol-specified dose homogeneity requirements and OAR dose constraints are met, investigators select the best combination and orientation of beams. If both three-dimensional conformal RT and IMRT are allowed in the protocol, the dose homogeneity for the PTV should be similar for both modalities.[14] During plan optimisation, priority levels should be defined in terms of primary goals (mandatory to achieve), secondary goals (highly recommended) and tertiary goals (optional). Avoidance structures and other volumes used in the optimisation process are left to the discretion of the dosimetrist, physicist or treatment planning radiation therapist. A structure called 'non-delineated tissue' (all tissues contained within the skin but not otherwise included within any other contour) may be useful in plan QA and comparison.[14]

2.6. Dose computation

Provide dose calculation details such as the calculation grid size. Corrections for density inhomogeneity must always be performed and, when relevant, the type of heterogeneity correction algorithm could be further specified.[15,16] Advanced technology protocols should explicitly require that the treatment machine monitor unit setting generated by the treatment planning software (TPS) should be checked independently before the first treatment.[13]

2.7. Treatment verification

Requirements for patient set-up and positioning must be defined, along with guidance for set-up correction protocols (e.g. frequency and type of imaging). Recommend adherence to specific correction protocols, if applicable. Dictate the minimum acceptable treatment verification and action levels, such as weekly electronic portal images with an action level of >5 mm. Consider implications of the total verification imaging dose and incorporate this into treatment planning monitor unit calculation if necessary. In general, automated matching of treatment and planning images should be performed. When using fiducial marker-based treatment imaging and correction, consider including maximum corrections which can safely be employed.

2.8. Acute toxicity during radiation therapy

Describe the schedule of clinical evaluation and investigations required to assess toxicity during RT as well as the grading scale. List expected acute toxicities (incidence, grade), including side-effects of any concurrent systemic therapy, prophylactic strategies, management approaches and any applicable reporting procedures. Specify prohib-

ited concomitant medications. Define modifications of doses and/or schedules to be followed in case of toxicity (including reasons for discontinuation of one or more components of protocol therapy). Describe any planned treatment interruptions. The maximum duration of any unplanned treatment interruptions and any recommended method of compensation or adaptation of the RT schedule must be included in this section.

2.9. Additional considerations for combined modality trials

In the case of combined modality treatment, outline the relationship of each modality to the other, the treatment sequence, permitted and optimum time intervals. For concomitant systemic therapy, specific timing of drug injection in relation to RT administration should be defined, if applicable; consider requesting review of this section by an experienced medical or clinical oncologist, if the drug regimen to be employed warrants.

3. Quality assurance in radiation therapy (QART)

3.1. General overview

In this section of the protocol, provide an overview of the trial QART program, clearly stating which EORTC levels (i.e. levels 1–5) will be included.[3] Prospectively define procedures aimed at detecting relevant deviations from protocol criteria, when they will occur, and corrective actions which will be taken. The protocol will detail what constitutes acceptable RT and list minor and major deviations. Procedures required before sites can be authorised to enter the study, those which take place during the course of accrual, and any required after the completion of patient treatment need to be clearly distinguished. State if there is a separate document describing QART requirements and where it is available.

3.2. Complete prior to site authorisation

3.2.1. Facility questionnaire and external reference dosimetry audit (EORTC level 1)

Centres at authorisation must complete a facility questionnaire (FQ) describing department infrastructure, staffing levels and treatment workload.[3] Instructions for completion must be included, either in the protocol or in a separate QART start-up letter. Additionally, all centres prior to authorisation must provide evidence of an independent external reference dosimetry audit (ERDA) demonstrating that beam calibration has been performed to a certain standard. Accepted level of agreement between the reference audit and the centre's own measurement is within 5%.

3.2.2. Digital data integrity QA and dummy run (EORTC level 2)

Digital data integrity QA (DDIQA) ensures participating institutions can upload all protocol-specified data to the network which will be utilised. Review for correct data format, absence of corruption, uniformity of structure contour names and recalculation of DVHs is performed, which is required to ensure RT plans created with different TPS can be compared. Successful DDIQA demonstrates understanding of the protocol data export and transfer requirements and confirms the dataset can be analysed for dosimetric end-points of interest.

Details about a dummy run (DR) procedure to be carried out before authorisation or prior to using a specific technique must be specified.[3] State the method of DR case evaluation (e.g. independent central review followed by discussion with local investigators). Include procedures to be followed in the case of inability of an institution to meet the required standard at first or subsequent attempts. In ROG clinical trials of advanced RT delivery techniques, a DR necessarily includes a check of DDIQA.

Explain procedures for cross-validation, if applicable. Describe in which circumstances successful DDIQA or DR completion in a previous trial will result in a waiver being granted for the current protocol.

3.2.3. Complex dosimetry check (EORTC level 5)

Details about a required complex dosimetry check (CDC) procedure (e.g. physical phantom[17–19] or digital benchmark case[20]) must be specified. Provide criteria for passing these requirements, as well as procedures to be followed in the case of inability to pass at first or subsequent attempts. Similar to QART level 2, include a statement on CDC cross-validation if applicable.

3.3. Patient-specific

3.3.1. Individual case review (EORTC levels 3 and 4)

Explain the patient population to be reviewed (e.g. a limited number of patients per site [EORTC level 3] versus all participating patients [EORTC level 4]), the timing in relation to the start or finish of RT, and in what format data must be submitted. Specify if the extent of review differs per RT delivery technique or randomisation arm. Define a priori what constitutes major and minor deviations, the method of case of review and who will be performing it. Procedures for how investigators are informed, how deviations are addressed (e.g. discussion with local investigators) and what corrective action will be pursued must be described.

3.4. Other QART procedures

Include any other planned QA procedures specific to trial RT delivery, such as site visits or dosimetry audits.

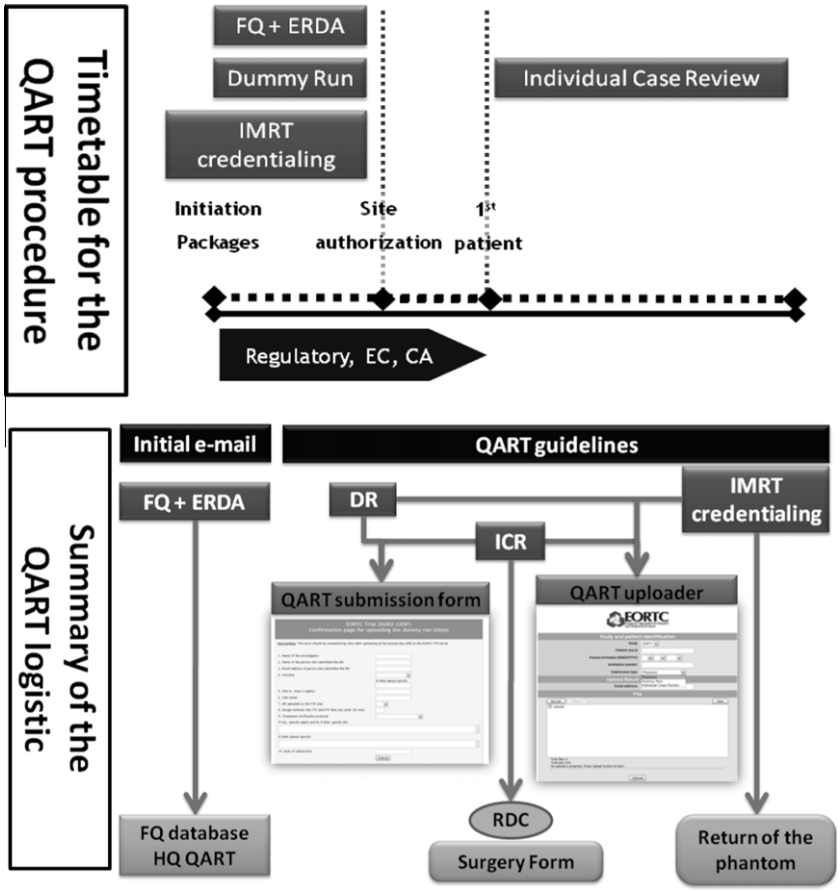

Fig. 1. Example of EORTC ROG trial QART requirements and timelines (figure courtesy of Dr. A. Gulyban).

Specify the aims and expected timelines, define deviations, and clearly state the impact on trial participation if minimum criteria are not met (see Fig. 1).

4. Conclusions

A clear description of the design and conduct of any clinical trial can avoid variations in practice that make it impossible to provide a definitive answer about the effectiveness of a new approach. The implementation of this updated RT protocol outline as a result of collaboration between the EORTC Headquarters and the ROG has significantly increased data reliability. For trials involving advanced radiation therapy techniques, the minimum acceptable degree of protocol compliance must be described to mitigate unacceptable variation between institutions. This is operationalised via implementation of RT quality assurance, which is mandatory for all EORTC ROG protocols. Development of high quality clinical study protocols and vigilance during trial accrual ensures the EORTC ROG remains a global leader in high quality radiotherapy delivery within multicentre clinical trials.

Conflict of interest statement

None declared.

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