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Original Article

Comparing Proton to Photon Radiotherapy Plans: UK Consensus Guidance for Reporting Under Uncertainty for Clinical Trials

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Abstract

In the UK, the recent introduction of high-energy proton beam therapy into national clinical practice provides an opportunity for new clinical trials, particularly those comparing proton and photon treatments. However, comparing these different modalities can present many challenges. Although protons may confer an advantage in terms of reduced normal tissue dose, they can also be more sensitive to uncertainty. Uncertainty analysis is fundamental in ensuring that proton plans are both safe and effective in the event of unavoidable discrepancies, such as variations in patient setup and proton beam range. Methods of evaluating and mitigating the effect of these uncertainties can differ from those approaches established for photon therapy treatments, such as the use of expansion margins to assure safety. These differences should be considered when comparing protons and photons. An overview of the effect of uncertainties on proton plans is presented together with an introduction to some of the concepts and terms that should become familiar to those involved in proton therapy trials. This report aims to provide guidance for those engaged in UK clinical trials comparing protons and photons. This guidance is intended to take a pragmatic approach considering the tools that are available to practising centres and represents a consensus across multidisciplinary groups involved in proton therapy in the UK.

Key words: Clinical trials; guidelines; proton therapy; proton therapy comparison; uncertainty

Introduction

In December 2018, the first of two National Health Service (NHS) high-energy proton beam therapy (PBT) centres in the UK opened at The Christie NHS Foundation Trust in Manchester, with the second due to open at University College London Hospitals NHS Foundation Trust in 2020. Prior to this, patients for whom PBT was deemed of significant benefit compared with photon therapy were sent abroad to facilities in the USA, Switzerland and Germany [1]. With the new UK NHS centres, there is an opportunity to significantly increase the number of patients eligible for PBT. However, further research and clinical trials are

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required to help identify those patients who will most benefit from this resource.

Many existing radiotherapy trials, both national and international, have focused on photon radiotherapy. As such, limited guidance on how to plan or evaluate proton treatments exists. The fundamental behaviour of proton beams is different from that of photons. As PBT facilities and treatment planning systems have evolved, so have the associated planning and treatment delivery techniques, diverging from those used for photon therapy. The plan evaluation methods that have been applied to photon treatments may not be appropriate for evaluating PBT plans. However, there has not been consistency in the reporting used for clinical trials or comparison studies and often the concepts integral to modern PBT are entirely neglected.

In the UK, the National Cancer Research Institute-funded Clinical and Translational Radiotherapy Research Working Group (CTRad) established a PBT Clinical Trial Strategy Group, which has published an eight-point framework to assist in the development and delivery of high-quality clinical trials [2]. Subsequently, a CTRad PBT quality assurance subgroup was formed in February 2019 to provide guidance to the radiotherapy clinical trial community regarding PBT clinical trial reporting. This multiprofessional group of clinicians, radiographers and physicists comprises CTRad and National Radiotherapy Trials Quality Assurance group members, as well as staff from the two UK NHS PBT centres with clinical experience in both photon and proton radiotherapy.

The aim of this report is:

- To provide advice for those designing and participating in clinical trials involving PBT in the UK.
- To support radiotherapy quality assurance programme development, implementation and review.
- To provide a resource for those interpreting the outcomes of clinical trials and the reasons behind the methodology used.
- To improve consistency in the reporting of clinical trials involving PBT.

Overview of the Uncertainty Problem

In the context of clinical trials comparing photon and proton therapy, an appreciation of the differences in treatment plan reporting is important to ensure meaningful comparison. This extends to uncertainties in the treatment planning and delivery processes, which are outlined below (see Table 1 for definitions of those phrases in bold and other commonly used terms).

Setup uncertainties in radiotherapy are typically accounted for using expansion margins in the form of planning target volumes (PTVs) and planning organ at risk volumes (PRVs) [3,4]. However, this approach may not be adequate for proton therapy, where the effect of setup **errors** on the treatment plan is not well approximated by rigid shifts of the dose distribution [5,6].

Although protons stop at an energy-dependent distance within the patient, their exact range is uncertain – they are subject to **range uncertainty**. This is due, in part, to uncertainties in the calibration of the patient's computed tomography (CT) scan to relative proton **stopping powers**, uncertainties in the mean excitation energies of different tissues and the handling of heterogeneities by analytical dose algorithms [7].

Uncertainties in proton therapy can result not only in a displacement, but also a distortion of the delivered dose. As proton Bragg peaks may be positioned throughout the target volume, when these uncertainties are realised this can result in regions of underdose within the clinical target volume (CTV), overdose of critical organs at risk (OARs) and other unexpected hot spots. Thus, plan creation and evaluation using a simple geometric expansion of the CTV (e.g. PTV) or OARs (e.g. PRV for critical serial architecture structures) may be insufficient. This is illustrated in Figure 1.

Instead of using PTVs and PRVs, a more appropriate assessment of plan quality for proton plans can be achieved by evaluating plans 'under uncertainty' in different **uncertainty scenarios**. These uncertainty scenarios are evaluated by calculating what a given plan would look like if the patient was shifted (in the case of setup uncertainties) or if the stopping power of each tissue was systematically higher or lower (in the case of range uncertainties). This results in a number of dose distributions that can be evaluated to ensure that the plan is safe and effective when inevitable variations in patient setup and image calibration are considered. Figure 2 shows how these uncertainty scenarios may be visually represented using dose volume histograms (DVHs), together with the DVH of the **nominal scenario** (the error-free distribution that is usually considered when evaluating a plan).

To help distil this increased amount of information into something that is practically useful to those reviewing plans, a '**worst case**' from these uncertainty scenarios is often reported. For the CTV this may be the minimum value of a given coverage metric over each of the scenarios and for OARs this may be the maximum value of a given dose constraint.

Although it can be relatively straightforward to evaluate setup and range uncertainties, anatomical changes present an arguably larger source of uncertainty [8]. The impact of changes such as weight loss, organ filling, tumour progression etc. may not be comparable between photon and proton plans and this should be considered within the context of a clinical trial. For example, the TORPEdO trial (a phase III trial of proton therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer; CRUK/18/010) mandates repeat CT mid-treatment, with an evaluation of the dose to relevant structures and replanning required to maintain some minimum standard [9]. Anatomical changes are more difficult to predict than setup and range uncertainties and may only occur in a small number of patients [8].

Table 1
Glossary of terms relating to uncertainties in proton therapy

Error	A realised uncertainty. It should be noted that, in this context, an error is not the same as a mistake. Errors are the result of unavoidable residual uncertainties.
MFO/IMPT	Multi-field optimisation or intensity-modulated proton therapy. Optimisation technique with which all fields are optimised simultaneously resulting in inhomogeneous but complementary fields which combine to provide highly conformal target coverage. However, this can be more sensitive to uncertainty than single-field optimisation (**SFO**).
Nominal scenario	The error-free scenario.
Range uncertainty	Uncertainty in the range of proton beams, typically evaluated as a systematic 3.5–5% error on the relative proton **stopping power** of all tissues.
RBE	Relative biological effectiveness. The ratio of biological effectiveness of different modalities. Protons are known to be more effective than photons and an RBE of 1.1 is typically used but this is uncertain and may vary along the proton path and especially in the Bragg peak.
Robust optimisation	The inclusion of uncertainties explicitly in the optimisation process. Plans are optimised with the aim of meeting objectives even when defined **errors** (such as patient setup errors) occur.
Robustness	The extent to which an aspect of a treatment plan is insensitive to defined conditions. e.g. clinical target volume coverage may be considered robust to **setup** and **range uncertainties** of defined magnitudes if the minimum dose to the clinical target volume in each of these scenarios meets the treatment aims.
Robustness evaluation/ uncertainty analysis	The evaluation of a plan under uncertainty by assessing the plan recalculated in different **uncertainty scenarios** to ensure that it is still safe and effective when defined errors (such as patient setup **errors**) occur.
Setup uncertainty	Uncertainty in patient setup assuming rigid shifts of the patient position, typically of the order of a few millimetres.
SFO	Single-field optimisation. Optimisation technique with which all fields are optimised independently, each aiming to satisfy the optimisation objectives. This results in fields with fewer in-field dose gradients compared with multi-field optimisation (**MFO**)/intensity-modulated proton therapy (**IMPT**).
Stopping power	A measure of how much a material slows down the proton beam. It is calculated from the loss of energy per unit path length and often expressed relative to water. Lung tissue has a low relative stopping power and bone has a high relative stopping power.
Uncertainty scenario	Potential or anticipated **errors** for which the dose distribution is recalculated. These may be used during **robust optimisation** or during plan evaluation. They are sometimes referred to as error scenarios.
Worst case	Often applied in different contexts, the worst-case dose may be the worst reported dose for a given metric over all **uncertainty scenarios** (e.g. the highest reported maximum dose over all scenarios for an organ at risk). The 'worst-case scenario' is typically a physically realisable scenario (either a setup shift or a systematic change in relative stopping power) in contrast to the 'worst-case dose distribution', which can sometimes be used to describe a composite distribution taking, e.g. the highest voxel value over all scenarios for each point outside the target volume and the lowest voxel value within the target volume.

Robustness to uncertainty is often a trade-off against plan quality; robustness to greater uncertainty results in increasing detriment to the nominal plan quality. This concept is like having larger PTV margins resulting in irradiation of a greater volume of normal tissue in the patient. As such, where changes are unlikely, where they occur in a small proportion of patients or where there are multiple ways in which they could manifest, it may be more appropriate to take a reactive approach to their mitigation.

Additional uncertainty can result from intrafraction motion such as breathing. The interplay of organ motion and PBT scanned delivery can result in significant deviation from the planned dose distribution, particularly in regions with large density heterogeneities, such as the lung, because of greater changes in proton beam range. Motion management techniques, such as abdominal compression, breath-hold delivery and gating, can help to minimise motion during treatment delivery. Furthermore, the reduction of in-field dose gradients with single-field optimisation (**SFO**) techniques and the use of multiple fields (even duplicating fields and dividing into multiple deliveries as a type of rescanning [10]) to blur out the delivered dose distribution can help to reduce the effect of residual motion on the delivered dose [11,12].

Plan robustness is not a new concept to proton therapy. Planning strategies have long been used to reduce sensitivity to range and anatomical uncertainties; careful beam selection to avoid heterogeneity or variable anatomy remains a key consideration in producing robust proton therapy treatment plans [13].

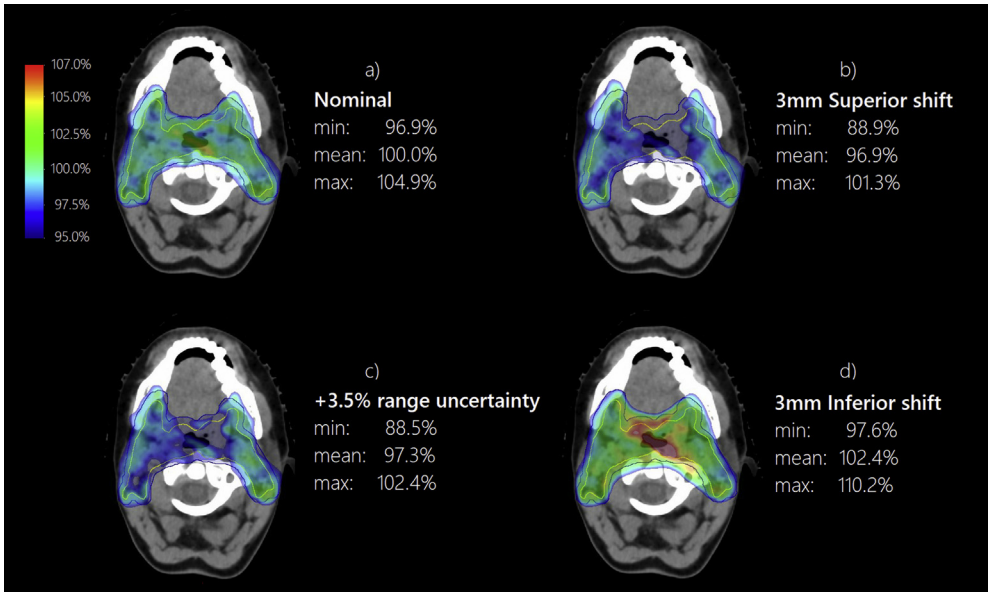

Fig 1. Axial slices showing the dose distribution for a treatment plan optimised for planning target volume (PTV) coverage of a nasopharyngeal carcinoma. Dose statistics for the clinical target volume (CTV; yellow) on the slice displayed are given. (a) In the nominal plan, coverage of the PTV (blue) is good. Doses above 95% of the prescription dose are shown. (b, c) Under example setup and range uncertainties, coverage of the CTV is poor and cold spots are observed within the CTV itself. (d) Some scenarios can result in unexpectedly higher doses; here the CTV receives dose >110% of the prescription dose.

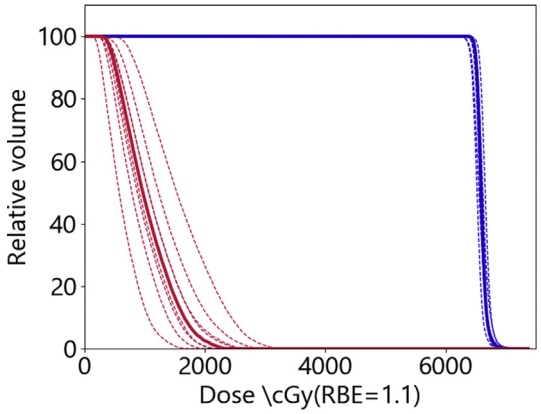

Fig 2. Evaluation under uncertainty results in multiple dose-volume histogram (DVH) curves for each structure. Here, the DVH curves for the clinical target volume (CTV; blue) are closely grouped reflecting robust coverage of the target volume – if uncertainties occur the planned dose would not be significantly different. In contrast, the DVH curves for the spinal cord (red) show greater variation under uncertainty. Despite this, even in the worst case (the rightmost DVH curve) the planning objectives are still met, ensuring that the plan will be both safe and effective.

Apart from plan evaluation, uncertainty scenarios can be used to include uncertainty explicitly in the optimisation process, so-called **robust optimisation**. As treatment fields are modified during the optimisation process, the resultant dose distribution and its uncertainty scenarios can be evaluated against the planning objectives and modified to satisfy the planning aims under uncertainty. This has recently been introduced into most commercial treatment planning systems, although different approaches have been adopted by each vendor [14–16]. In some implementations, robust optimisation is carried out probabilistically by optimising the (mathematically) expected plan quality [16], in others the plan is optimised for the worst uncertainty that has been considered, so-called minimax optimisation [15]. For the latter, the worst case may be: (i) a physically realisable scenario, such as the plan under a 3 mm shift to the patient's left; (ii) an objective-wise worst case in which the worst-case value for each planning objective is considered independently; (iii) a voxel-wise worst case, where, for example, the highest voxel value is taken for each point outside the target volume and the lowest voxel value within the target volume [17]. At present, not all planning systems support robust optimisation and evaluation for photon planning [18]. Further application in addressing changes in anatomy [19] and biological issues, such as variable proton relative biological effectiveness (**RBE**) [20], has been considered. A detailed review of robust plan generation for both photons and protons, as well as a discussion on the limitations of the PTV concept, is presented in a recent review by Unkelbach et al. [6].

As with the wide variation in robust optimisation approaches, the evaluation of robustness is equally nuanced. The importance of accurately describing how uncertainty analysis is carried out is presented by Yock et al. [21] who identify the influence of uncertainties on the delivered dose as a key consideration in the meaningful comparison of different modalities. Various sets of uncertainty scenarios may be valid, but these should be adequately described so that they may be replicated. Different approaches are not necessarily comparable. For assessing the dosimetric effect of uncertainties, Yock et al. [21] present a hierarchy of descriptors with full three-dimensional dose distributions for

all scenarios as the most complete but impractical dataset, down through DVH bands, to uncertainties on individual metrics. It is noted that there exists considerable scope for ambiguity in both the description of uncertainty scenarios and the dosimetric effect, emphasising the need for detailed, precise reporting.

Robust Optimisation/Analysis Practices within the Literature

Reported practice in the comparison of photon and proton plans has been disparate and the difference in uncertainties between the two modalities has frequently been neglected. This is reflected in a review of the recent literature. A literature search was carried out using PubMed with the search terms 'photon' AND 'proton' AND 'comparison' and 'proton therapy comparison'. Publication date was limited to between 1 January 2016 and 1 July 2019 to ensure that both photon and proton techniques were relevant to future clinical trials practice. All papers relating to radiotherapy were reviewed. Thirty-five English-language papers were identified as treatment plan comparisons between photon and protons, representing a wide range of tumour sites, of which 27 detailed treatment planning or delivery of pencil beam scanning proton therapy (references are given in Appendix A). Most studies were planning comparisons where patients were treated with one modality and retrospectively planned for comparison, with only one reported prospective study of treated patients. Ten studies reported tumour coverage using CTV, whereas 17 reported PTV coverage. Four studies reported both CTV and PTV coverage. Four reported neither, instead focusing on toxicity and secondary cancer risk.

Robust optimisation was used in the treatment planning process in nine studies and seven studies reported evaluation under uncertainty. In each case a variety of setup and range uncertainty scenarios was used, in part reflecting the diversity of tumour sites being assessed. In total, 13 studies considered uncertainty in the treatment planning process through either optimisation or evaluation. No study detailed how the uncertainty scenarios were applied to the assessment of OARs/PRVs.

This snapshot of the literature represents a wide range of tumour sites and treatment plan comparisons. Less than half of the publications including pencil beam scanning reported on aspects of robustness. Those publications that did used a wide range of uncertainty scenarios for setup and range uncertainty, the magnitude and application of which were highly variable.

Practice in Other Proton Beam Therapy Centres

The challenge posed in producing robust treatment plans is common to PBT centres worldwide. An informal survey of established centres suggests that most use robust analysis of the final treatment plan to determine the degree of robustness (personal communication). Dose metrics in uncertainty scenarios are compared with clinical protocol constraints, and either required to be met for the worst-case scenario, for a given majority of scenarios, or merely reported for assessment with a final decision made by the responsible clinician. The decision process used varies between centres and tumour site protocols. Due in part to the functionality available in treatment planning systems for robust analysis, most centres assess robustness for scenarios of fixed values of setup shift and range uncertainty, which are either treated independently or combined, as illustrated in Table 2 (note the values used in the table are illustrative only and are not recommended values).

Of interest is the approach adopted by the Dutch proton centres who use a model-based patient selection requiring meaningful comparison of plans under comparable robust target coverage [22]. With this approach two distributions

Table 2
Illustration of the difference between treating setup and range uncertainty independently (creating eight scenarios, left) and combining the two uncertainties (creating 14 scenarios, right)

	Independent				Combined			
	X	Y	Z	Range	X	Y	Z	Range
1	0 mm	0 mm	0 mm	+3.5%	0 mm	0 mm	0 mm	+3.5%
2	0 mm	0 mm	0 mm	−3.5%	0 mm	0 mm	0 mm	−3.5%
3	+3 mm	0 mm	0 mm	0%	+3 mm	0 mm	0 mm	+3.5%
4	−3 mm	0 mm	0 mm	0%	+3 mm	0 mm	0 mm	−3.5%
5	0 mm	+3 mm	0 mm	0%	−3 mm	0 mm	0 mm	+3.5%
6	0 mm	−3 mm	0 mm	0%	−3 mm	0 mm	0 mm	−3.5%
7	0 mm	0 mm	+3 mm	0%	0 mm	+3 mm	0 mm	+3.5%
8	0 mm	0 mm	−3 mm	0%	0 mm	+3 mm	0 mm	−3.5%
9					0 mm	−3 mm	0 mm	+3.5%
10					0 mm	−3 mm	0 mm	−3.5%
11					0 mm	0 mm	+3 mm	+3.5%
12					0 mm	0 mm	+3 mm	−3.5%
13					0 mm	0 mm	−3 mm	+3.5%
14					0 mm	0 mm	−3 mm	−3.5%

taken from the minimum and maximum dose for each voxel over all scenarios are generated to evaluate the CTV coverage and hot spots, respectively. Acceptance criteria for these distributions are calibrated against PTV metrics for historic photon plans. This enables plans to be compared with comparable confidence levels but does rely on the generation of dose distributions that are not available in all treatment planning systems.

Guidance

Comparing two different planning/treatment modalities presents many challenges. This guidance is intended to provide a pragmatic approach representing a minimum standard for the comparison of photon and proton therapy plans, and for reporting doses in proton plans from planning studies or clinical trials within the UK. This has considered our current understanding in what is a rapidly developing field and the technological solutions available within commercial treatment planning systems. We have attempted to draw from a growing consensus within the international proton therapy community, with consideration of the tools that are commercially available to practicing centres in the UK.

- **Uncertainty analysis** should be carried out and reported for all proton plans against defined **uncertainty scenarios**. The treatment plan should be recalculated and evaluated in these **uncertainty scenarios**, which should be based on expected **setup** and **range uncertainties** for each treatment site.
- When assessing PBT treatment plans against corresponding photon plans, coverage of the CTV for all **uncertainty scenarios** in the PBT plan is considered the best equivalent of PTV coverage for photon radiotherapy.
- Sparing of an OAR for all **uncertainty scenarios** should be considered the best equivalent to the use of a PRV in photon practice for assessing dose to an OAR.
- The exact magnitude and combination of **uncertainty scenarios** used to assess PBT plans should be defined in the trial protocol. These should be applied consistently by all centres as different methods may not produce comparable results. The **uncertainty scenarios** used should be stated explicitly in all reporting of the trial results such that they can be assessed against other work and recreated later as required.
- It may not always be appropriate for all dose constraints to be met under the full range of **uncertainty scenarios**. Dose escalation, sequential treatment plans (e.g. two phase treatments) and very complex sites may require more tailored approaches that should be defined based on the specific clinical need of the trial, e.g.
  - where satisfying dose constraints to OARs in close proximity to the target volume can lead to unacceptable compromise and where the treatment aims may justify the additional risk. However, it is still recommended that doses under uncertainty are reported such that they can be used to inform toxicity outcome data.
  - Combining sequential treatments such as two phase plans may result in the addition of uncertainties from contradictory uncertainty scenarios, e.g. opposing range uncertainties.
- It is recommended that the **worst-case** dose is reported in a physically realisable **uncertainty scenario** (as opposed to a composite worst-case dose distribution) although these scenarios may be different for different plan quality metrics. For example the dose to 1 cm^3 in the brainstem may occur in a x-3 mm scenario and the dose to 1 cm^3 in the spinal cord may occur in a z-3 mm scenario.

Caveats

- The planning method used to achieve a plan that meets the **robustness evaluation** criteria does not necessarily need to be stipulated. Treatment plan creation is highly dependent on the specifics of the treatment delivery equipment, treatment techniques and even the treatment planning system used by different centres. As such, a single approach may not be feasible.
- Producing a plan with **robust** coverage of the target and OAR does not remove the need for due diligence and appropriate monitoring to identify patient changes along with associated dosimetric review. There are many factors that can affect proton treatment delivery that are not accounted for within this assessment of robustness, including, but not limited to:
  - weight change
  - non-translational systematic setup variation
  - internal organ motion
  - organ filling
  - tumour response to treatment (growth/shrinkage)
  - normal tissue responses, such as shrinking of the parotids.
  - All treatment centres should have a strategy in place to deal with these factors should they arise in clinical practice. Regular monitoring of patients through online imaging, and, where appropriate, the use of additional offline imaging modalities, such as magnetic resonance imaging, is strongly recommended. Although some form of daily online imaging and correction is recommended, the frequency of volumetric imaging, on which non-geometric changes can be evaluated, will depend on the expected likelihood, impact and frequency of these factors for different treatment sites.

- These techniques do not compensate for the effects of moving targets, i.e. tumours subject to breathing motion, and strategies will be needed to minimise motion and mitigate the effects of interplay between the scanned delivery of PBT and organ motion where such targets are treated.
- Evaluation against **setup** and **range uncertainties** do not account for the variability in **RBE** inherent in PBT. This is very difficult to evaluate and subject to much uncertainty. Despite this, the potential effect of **RBE** variability should be considered in the planning process, e.g. by avoiding all beams terminating on critical OAR and using multiple fields from different directions to dilute the effect of enhanced RBE.
- Variation in contour delineation remains a significant source of systematic uncertainty, particularly with the development of more conformal radiotherapy techniques. The use of multimodality imaging to aid delineation of both the target volumes and OARs, together with adherence to delineation protocols and guidelines, is recommended.

This article sets out guidance focused on the comparison of photon and proton plans in the context of UK-based clinical trials. It is motivated by the development of a clinical PBT service within the NHS, and clinical trials currently in development for this service. Although this guidance document may be applied to standard clinical practice, currently the assessment of robustness, the number, method and combinations of scenarios assessed should be at the discretion of individual treatment centres based on their own experience and confidence. As this field develops, we expect to revise this document based on future developments to ensure that it continues to reflect the best achievable practice.

Conflicts of Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2020.03.014.

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