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**Article:**

Amos, R, Bulbeck, H, Burnet, NG et al. (9 more authors) (2018) Proton Beam Therapy – the Challenges of Delivering High-quality Evidence of Clinical Benefit. *Clinical Oncology*, 30. pp. 280-284. ISSN 0936-6555

<https://doi.org/10.1016/j.clon.2018.02.031>

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**Running title:- Proton beam therapy - The challenges of delivering high quality evidence of clinical benefit**

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## **Short abstract**

The use of proton beam therapy (PBT) offers the opportunity to improve greater conformality of radiotherapy treatment delivery in some patients. However, it is associated with a high capital cost and the need to build new dedicated facilities. We discuss how the global radiotherapy community can respond to the challenge of producing high quality evidence of clinical benefit from PBT in adult patients

In the UK, the National Cancer Research Institute funded Clinical and Radiotherapy Translational group (CTRad) has established the PBT Clinical Trial Strategy Group. An eight point framework is described that can assist the development and delivery of high quality clinical trials.

Proton Beam Therapy (PBT) is an important treatment modality in the modern radiotherapy (RT) armamentarium. The high capital cost, the need to build new dedicated facilities and the limited high-level evidence of clinical benefit in adult malignancy creates a major challenge for the global radiotherapy community. This article will discuss the different approaches that can be used to generate the necessary evidence base.

## **Background**

Despite the continuing rise in gross domestic product (GDP) spend on healthcare in developed countries, this is failing to keep up with the rapid pace of new treatments in clinical medicine [1]. There is a well-defined pathway for the evaluation of new systemic cancer treatments and in some countries mechanisms are in place to assess their cost effectiveness and availability. There is typically a substantial investment in the evaluation of such treatments from the pharmaceutical industry.

In contrast, as new technological developments are introduced, evaluation is initially focused on safety rather than efficacy. Its development and subsequent adoption is commonly based on theoretical or perceived benefit and other incentives including potential financial benefit in some health care systems. High quality evidence for clinical benefit is less common and frequently based on observational studies. The generation of high quality evidence generally requires significant academic funding. In radiotherapy, it is not uncommon for the clinical trials to be performed after significant adoption of the new treatment approaches.

In the surgical domain, the introduction of robotic surgery centres was achieved by major financial investment relying heavily on charitable and philanthropic sources. However high quality randomized clinical trials against the standard of care for this new approach are uncommon. However, a recent Cochrane review [2] did not find evidence of significant benefit for the use of robotic assisted prostate cancer surgery. Aggarwal et al [3] have recently reported changing patterns of radical

prostatectomy centres. The increased use of robotic surgery has played a significant role, as well as minimum patient volume requirements, in contributing to closure of some cancer surgery units. In rectal cancer, Jayne et al [4] reported no evidence of clinical benefit for robotic compared with laparoscopic surgery in an international phase III trial of patients with rectal cancer. The new expensive technology does not always lead to better patient outcomes.

### **Evaluating PBT**

How can the radiotherapy community respond to the challenge of delivering the high quality evidence that demonstrates the clinical benefit of proton beam therapy? We have a significant track record of generating high-level evidence through practice changing clinical trials using photons. Many were performed as two arm phase III trials. An example of the breadth and depth of these achievements in the last two decades are summarized in a recent review of five tumour sites (breast, prostate, head and neck, bladder and anorectal [5]. However, some of these trials required up to a decade to achieve their large sample size to assess long term outcomes including loco-regional control and survival.

Most of the trials in the review evaluated the delivery of 3D conformal external beam photon radiotherapy. However, the widespread introduction of external beam photon based stereotactic ablative radiotherapy (SABR) and intensity-modulated radiotherapy (IMRT) has taken place without randomized clinical trials. Retrospective single centre cohort series lack the rigour of prospective trials including quality assurance of contouring, planning and treatment delivery. However, for example, the UK performed two randomized trials of 3D conformal versus IMRT in breast and head and neck cancer, demonstrating reduced toxicity with IMRT [6,7]. Interestingly, the head and neck trial reported an increase in fatigue in the IMRT arm. A possible mechanism for this finding was an increased radiotherapy dose to the cerebellum and brainstem with the use of IMRT [8]. This unexpected but important clinically relevant finding was only identified through standardised prospective toxicity collection and the randomized comparison of IMRT with 3D conformal radiotherapy.

## **Generating high quality evidence**

Anthony Zietman has described, in this issue, the precarious path of PBT development in the United States leading to demands from health care providers for high quality clinical evidence to justify the increased costs [9]. In the case of PBT, the significant capital cost investment and the relatively small number of facilities are key factors driving the demand for high quality evidence to support its use. Whilst there is consensus regarding the indications for PBT therapy in paediatric and skull base indications, there remains a significant lack of high quality clinical evidence for the majority of adult patients and including randomized clinical trials. This article will focus on this adult patient population.

There is no international consensus on the best approach to generate the highest-level evidence for PBT therapy. A model-based approach has been proposed for the selection of patients for PBT therapy [10]. This will be used in the Netherlands to select patients most likely to benefit from PBT, those who should be treated with conventional photons, and a minority of patients where there is uncertainty and where (randomized) clinical trials could be used to compare the two treatment modalities.

The emphasis with this approach is to generate high quality prospective multi-centre data for the majority of patients treated with PBT. Some of the challenges associated with this approach include the need for high quality contemporary normal tissue complication probability (NTCP) models for optimized IMRT. Further variables include the dynamic delivery and motion effects, range uncertainties along with variable linear energy transfer (LET) and related variable radiobiological effectiveness (RBE) with protons.

Other countries are conducting or planning clinical trials. In the USA, there is increasing support from insurers to fund PBT treatment in clinical trials although the full cost of PBT therapy may not be met. As well as the UK, the Netherlands and Denmark will due to open their first PBT centres in 2018. In the UK, Manchester will

open in the Autumn 2018 and University College London Hospitals in 2020. As the international critical mass of PBT centres increases, how should we design and deliver high quality clinical trials? In this issue Anthony Zietman comments that the UK is very well placed to design and deliver the trials that other countries find difficult to perform [9].

So how can the UK respond to this challenge? In the UK, radiotherapy clinical trials and radiotherapy research is co-ordinated by the National Cancer Research Institute funded Clinical and Radiotherapy Translational group (CTRad) [11]. Our aim is to maximize quantity and quality of life for patients receiving radiotherapy by optimising tumour control and minimising toxicity [12]. CTRad has a broad multi-disciplinary membership with four workstreams covering the breadth of radiotherapy research from basic science, all phases of clinical trials to new technology and radiotherapy quality assurance. It brings together research active National Health Service professionals, University academics and patients. We hold clinical trial proposals meetings twice yearly to evaluate new concepts and assist in their development prior to and after funding. However, the PBT trial development is more complex and requires special attention [13]. The CTRad PBT clinical trial strategy group was therefore first convened in August 2017 to specifically address proton beam clinical trials development. Collectively, we have identified an eight point framework to address the challenge (Figure1):-

**i] Identifying the important scientific question** – across the adult tumour sites there is a need to decide whether clinical trials will focus on the reduction of long term treatment-related toxicity and/or the improvement of cancer specific end points including loco-regional control or survival. Efficacy trials may consist of dose escalation and/or new agent radiotherapy combinations. CTRad led a recently published consensus statement regarding the development of the latter approach [14]. Long term follow up is essential to adequately characterize late failures and determine the pattern and severity of long term toxicities. Co-ordinated planning and the availability of pilot or earlier phase clinical data across a range of tumour

sites is essential to estimate the anticipated event rates with both photons and PBT therapy for effective clinical trial design.

ii] **Clinical trial design and methodology** – Radiotherapy is a complex intervention, and additional care is required in choosing trial methodologies [15,16]. In addition, pressures from both funders and the advances in personalized medicine is leading to significant changes in the approach to clinical trial design. The future of conventional large-scale phase III two-arm design is under threat; although they have a role in common tumour sites, it is clear other approaches are also needed.

Mishra et al recently reviewed the PBT clinical trial landscape [17]. They identified a total of ninety-six adult interventional clinical trials with a median planned sample size of sixty-eight patients. The interventional trials consisted of Phase I (17%), phase II (53%) and phase III (15%). Only five active studies at the time of the review randomized patients between PBT and photons. Three further completed studies were noted.

The UK has experience of using a clinical trial design that uses two experimental treatment arms in prostate and breast cancer trials [18,19]. This may help address efficacy and toxicity-related clinical trials questions using PBT including the uncertainties regarding the RBE of protons.

We will develop a network of NCRI accredited clinical trial units who plan to prioritise PBT trials as part of the core strategy to support trial development. Novel statistical and methodological expertise is essential [20]. Different approaches where only relatively small sample sizes may be feasible, as described by the International Rare Cancer Initiative (IRCI) Network studies, previously employed in systemic therapy trials [21]. The UK Advanced Radiotherapy Technologies Network (ART-NET) project group [22] aims to optimise SABR MRI radiotherapy and protons. It includes a clinical trial methodology workstream that focuses on clinical trial methodology for PBT trials and will provide advice to investigators on future clinical trial design.



We will also review large scale UK funded clinical trials to determine whether an amendment to the existing clinical trial design will allow an embedded PBT trial question to be added. Different disease settings and the scientific questions will determine the design. There are efficiencies to this approach including a single step funder approved amendment to an open trial. Irrespective of the embedded design a tightly defined framework for evaluation of clinical end points is used for both photon and PBT treated patients.

**iii] Patient and public involvement and equipoise** – In the UK the opening of two PBT NHS facilities in England will require many patients to travel and stay at the PBT facility for treatment and return to their referring centre for follow up. The very strong Patient and Public Involvement in CTRad and site specific groups will be of crucial importance to help patients understand the key issues. These include the need for a stronger evidence base, to understand PBT, dispel misunderstandings and help design clinical trials that are of interest and relevance to patients. The involvement of referring photon centres is crucial to understand and improve the level of clinical and centre equipoise. These are particular strengths in the UK radiotherapy community.

**iv] Disease specific trial development** - CTRad will engage with the NCRI Clinical Study groups (CSG) that exist for each tumour site. They play a key role in identifying the key scientific questions and which tumour characteristics should be considered in framing a clinical trial question. We will encourage investigators interested in developing future trials to work collaboratively with both CTRad and the parent CSG. CTRad will host its first PBT trials workshop to encourage existing and new clinical study concept development in May 2018.

#### **v] Collaboration and development**

The complex nature of PBT clinical trial design and delivery requires close collaboration and leadership from both the PBT centre and surrounding referring photon cancers. A key aim of the CTRad PBT Clinical trial strategy group is to encourage and accelerate study development, ensure fit with the overall site-specific

portfolio and avoid the development of competing studies by bringing the interested parties together. We seek to encourage the next generation of clinical trial leaders to work with an experienced clinical trial unit and to receive senior mentoring, preferably from experienced Chief Investigators of previous successful photon clinical trials. We are also keen to engage with other countries to identify the opportunities for international cooperation in PBT trials including international groups such as Particle Therapy Co-operative Group (PTCOG) [23]. There are different models of collaboration that would encourage the development of international recruitment to a common protocol. When this is not feasible, a common template for assessment of toxicity and efficacy to standardize outcome reporting in a parallel and complementary trials should be considered.

**vi] Radiotherapy Quality Assurance** - clinical trials deliver the highest multi-centre quality assurance in both treatment planning and delivery. The UK RTTQA group has demonstrated a clear track record in the delivery of IMRT trials in the UK [24]. Further work is required to deliver the additional quality assurance demands of PBT treatment delivery including proton specific margins, motion management dosimetry, imaging and adaptation. Dedicated and adequately resourced radiotherapy quality assurance is of critical importance to the delivery of high quality clinical trials.

**vii] Engagement with funding bodies** – A coordinated approach is required within the UK and internationally to ensure funders of clinical trials appreciate the importance of the evaluation of PBT and the greater challenges associated with a limited number of geographically spread PBT facilities. The patient benefits and health care savings associated with the reduction in long term treatment-related toxicity is not fully appreciated in the curative setting of cancer treatment. We also need to assess the different models of funding that would incentivise international recruitment.

**viii] Translationally rich clinical trials** - Personalised medicine has led to a significant increase in clinical trials that combine novel therapy evaluation with a strong

translational research component or stratify patients according to their tumour biology. The evaluation of novel therapies in combination with radiotherapy should include the assessment of PBT as the treatment modality. The opportunity exists for translational researchers, particularly in the fields of DNA damage repair, tumour micro-environment and immune-oncology to work with the PBT community to deliver such studies.

## **Conclusion**

We have an unprecedented, once-in-a-lifetime opportunity to initiate practice-changing clinical studies, including randomized trials, to clarify the role of PBT for patients and society. This requires engagement with the whole RT community, as well as with patients, carers and the wider public. Trial design must also include clearly defined translational components. CTRad is uniquely placed to guide this process in the UK and looks forward to the opportunity of working with the international community to achieve these goals. However, we must move with some speed in order to exploit the opportunity that beckons.

Word count 2420

## **Acknowledgements**

NGB, KJK and RIM are supported by the NIHR Manchester Biomedical Research Centre

MAH is funded by MRC grant: MC\_UU\_00001/2

DSM,EH,MAH,KJK,RM are supported by a Cancer Research UK Centres Network Accelerator Award Grant (A21993) to the ART-NET consortium.

The National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRad) is funded by the following NCRI Partners: Cancer Research UK, Medical Research Council, Department of Health and Social Care (England), Chief Scientist Office (Scotland), Health and Care Research

(Wales) and Public Health Agency Research and Development (Northern Ireland).  
The CTRad PBT Clinical Trial Strategy Group is coordinated by Aifric Müller and  
Carolyn Chan from the NCRI.

The RTTQA group is funded by the National Institute of Health Research.

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