Public and Patient Involvement (PPI) refine the design of ProtOeus: A Phase II Trial of Proton Beam Therapy (PBT) in Oesophageal Cancer

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Abstract/Summary:

Neoadjuvant chemoradiotherapy (nCRT) for oesophageal cancer vastly improves overall survival but is associated with high rates of severe post-operative complications. Proton beam therapy (PBT) may reduce these toxicities by delivering a lower dose to normal tissues compared to standard radiotherapy. ProtOeus is a proposed randomised phase 2 study of nCRT in oesophageal cancer that compares PBT to standard photon radiotherapy techniques. As PBT services are often centralised in academic centres in major cities, PBT trials raise distinct challenges for researchers and patients including coordination of treatments with local centres, patient acceptance of travelling for PBT and ensuring equity of access for patients.

Early patient and public involvement (PPI) in research are shown to improve the overall quality of research and increase likelihood of trial feasibility. To understand and improve trial acceptance, focus groups were held in different parts of the UK (Manchester, Cardiff and Wigan) ab initio of the trial development process to establish patient's views. Patients gave feedback on all aspects of trial design including treatment pathway and endpoint selection. The tangible impact of early PPI on the trial design is highlighted by significant trial design modifications including travel/accommodation provisions, choice of primary endpoint, randomisation ratio and fractionation schedule.

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Declarations

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Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery for operable oesophageal cancer has become an international standard of care after the CROSS trial reported a near doubling of overall survival compared to surgery alone.[1] However, trimodality treatment is associated with very significant toxicities with recent data reporting the incidence of post-operative Grade 3-5 pulmonary and cardiac toxicity of nearly 50%.[2] Concerns over these high rates of toxicity are partly responsible for the low usage of nCRT in the UK. [3, 4] Notably, the use of peri-operative multiagent (FLOT) chemotherapy, another standard of care, also results in post-operative complication rates of around 50%. [5]

PBT's intrinsic physical properties limit 'exit' dose, sparing normal tissue distal to the target volume. [6] In oesophageal cancer, this is shown to reduce dose to organs at risk (OARs) such as the lungs and heart, potentially decreasing severe pulmonary and cardiac toxicities in the immediate post-operative period and reducing long-term effects including ischaemic heart disease. [7, 8] However, evidence supporting the use of PBT in oesophageal cancer is limited with only one Phase II prospective study published to date. [9]

The efficacy and cost-effectiveness of PBT in many tumour sites remains subject to significant uncertainty. [10, 11] In Europe, the drive to systematically assess PBT is gaining momentum. The European Organisation for Research and Treatment of Cancer (EORTC) has recently published a report recommending the evaluation of PBT in tumour sites which may benefit from PBT as a research priority.[12] In the UK, the National Cancer Research Institute (NCRI)-funded Clinical and Translational Radiotherapy Group (CTRad) has established a PBT clinical trial strategy group which aims to deliver high quality clinical trials of PBT, the first of which, the TORPEdO study, commenced recruitment in early 2020. [13, 14] The National Health Service's (NHS) PBT service is based in two major academic centres; at The Christie, Manchester and University College London Hospital, London[15]. Once fully ramped up, it will have a treatment capacity of approximately 1500 patients/year, deliberately exceeding current patient demand based on UK criteria. In alignment with wider European strategy, the NHS has made systematic evaluation of PBT a central objective, allocating nearly 50% of treatment capacity for research. [14, 15]

Patient and Public Involvement (PPI) in PBT research

Involving patients in research is shown to improve the overall quality and relevance of research with these trials more likely to recruit and retain participants. [16-18] Emerging evidence suggests research which has meaningful input from patients with lived experience of the condition under study is likely to have a greater impact. [18] The UK National Institute of Health Research's (NIHR) recognises the value of PPI, founding INVOLVE, a national advisory group that promotes PPI in health research. INVOLVE recommends a model of co-production of research that involves patient contributions at every stage of the research cycle including at the development phase.[19]

Clinical trials of PBT in Europe present a distinct set of challenges for researchers and patients. Firstly, trial feasibility may depend on patients being willing to travel for treatment; away from home and their support networks for several weeks; to PBT centres which are often located in academic institutions in major cities. [20] For those unable or unwilling to travel, this raises the issue of inequity of access to PBT. Moreover, for neoadjuvant trials, patient pathways involving PBT are likely to be more complex, necessitating a more demanding level of coordination between PBT and tertiary surgical centres. Trial design in PBT also presents fresh challenges. PBT is often utilised to reduce the late effects of radiotherapy, such as in paediatric cancers, where benefits are not seen for several decades. New trials of PBT have the difficult task of selecting primary endpoints that are patient-focussed and scientifically robust yet deliverable within a research cycle timeframe. We describe the outcomes of partnership with patients and the public early at the trial development and solutions to specific challenges raised by the perioperative oesophageal setting.

Methods:

The ProtOeus study (Neoadjuvant Proton Beam Therapy in Cancer of the Oesophagus) is a proposed randomised phase 2 trial comparing nCRT with PBT to photons [Intensity modulated radiotherapy (IMRT)/volumetric arc therapy(VMAT)] for patients with resectable oesophageal cancer. Figure 1 shows the proposed trial design. Proposed patient pathway and trial endpoints are included in the appendix. As per INVOLVE's guidance, patients were consulted ab initio of trial development.

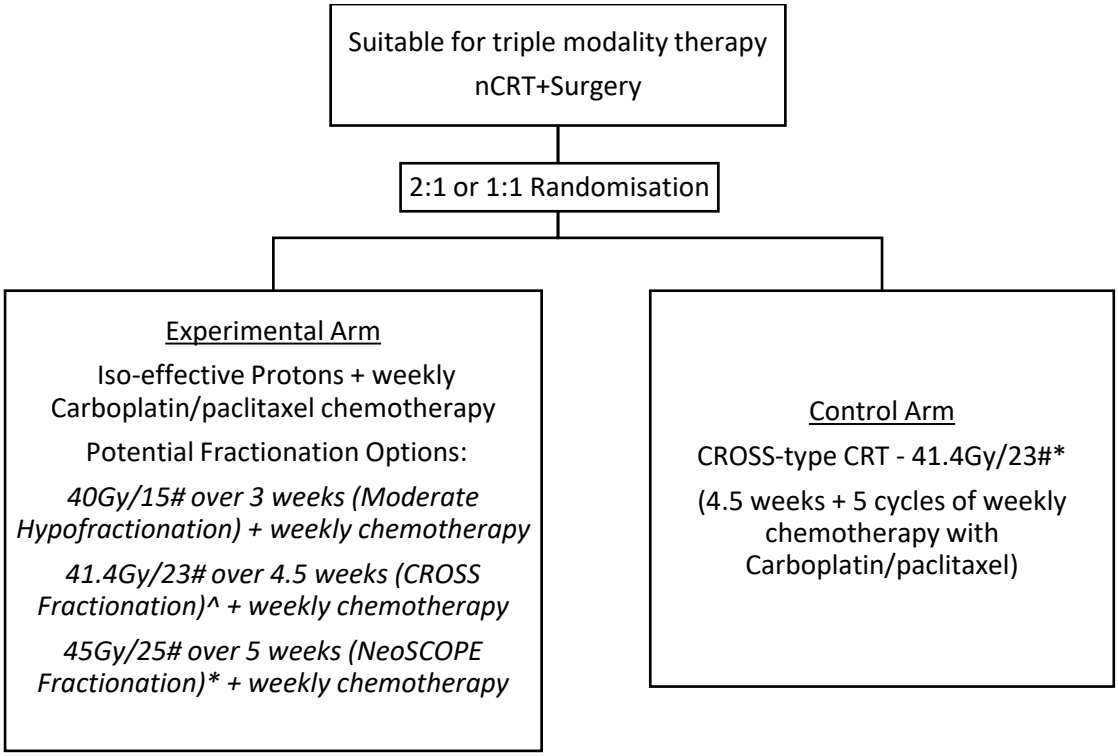

*Figure 1: Proposed Trial Design for the ProtOeus trial. Gy = Gray); # = number of radiotherapy fractions; ^Shapiro et al. [1]; *Mukherjee et al.[21].*

Three focus groups were held in separate UK locations; Manchester, Wigan and Cardiff; over a period of 7 months from November 2018 to June 2019. Invited participants included patients who had undergone treatment for oesophageal cancer, their spouses and experienced PPI contributors. The sessions were held in a facilitated focus group format with presentations and questions from the investigators organised around key themes.[22] Specific questions were asked on perception of PBT, acceptability of travel to PBT centre prior to surgery, patient pathway/trial design and patient information (see table 1). We presented possible clinical scenarios, including the need for admission to an acute hospital local to the PBT centre, in the event of an emergency. Data were interpreted by thematic analysis.

1) Perceptions of Proton Beam Therapy
2) Patient acceptability on travelling for PBT A) Would travelling to Manchester or London for PBT be acceptable? B) What additional support would be required at the PBT Centre?
3) Patient pathway and trial Design A) Thoughts on trial name B) What are your views on the patient pathway? C) What are your views on randomisation? D) What are your views on different fractionation schedules? E) Which trial endpoint is most important?
4) Patient information A) What type of patient information is would be most useful? Would any other form of media (e.g. videos, apps) be useful? B) How would you like the patient information presented?
5) Clinical Scenarios A) What are your thoughts about being treated at a local hospital for any emergencies? B) What are your views on being under the care of a different oncologist whilst at the PBT centres?

Table 1: Themes and questions asked to all PPI contributors

Results:

The focus groups were attended by 21 patients in total. There was a wide geographical representation with patients from as far afield as Pembrokeshire, Wales. Figure 2 highlights the geographical locations of patients and PBT centres.

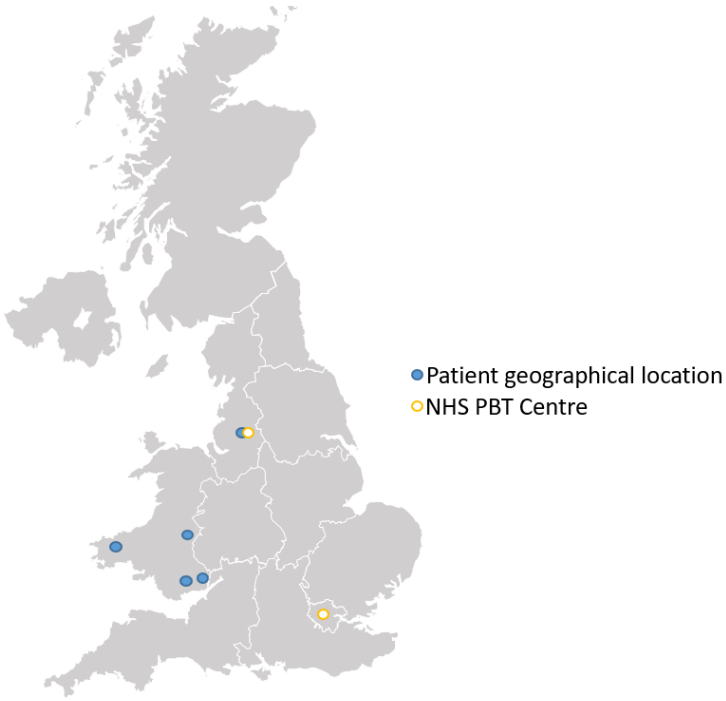

Figure 2: UK map showing patient home location and NHS PBT centres

Perception of proton beam therapy

Participants reported PBT was generally perceived to be a superior treatment to photon beam therapy and felt it would contribute to reduced toxicity and better cure rates making the trial very attractive to patients.

Patient acceptability on travelling for PBT

All participants reported that they would be willing to travel for PBT. However, participants felt that a significant proportion of patients would not travel due to the additional burden on family as well as a potential loss of earnings due to time off work. All participants felt very strongly that travel and accommodation expenses should be covered to ensure all UK patients had equal access to PBT and so no one would be unjustly penalised for living a long distance away from a PBT centre.

Patients agreed that dietician and physiotherapy support would be essential. Some patients suggested additional 'pre-habilitation' facilities be made available with others suggesting additional 'hospitality packs' considering the amount of free time when not undergoing treatment.

Patient pathway and trial Design

Trial name and pathway

Most contributors felt that the ProtOeus trial name was acceptable and explained the trial. The treatment pathway was acceptable to all participants but emphasised that delays had to be avoided so that time to surgery would not be jeopardised.

Randomisation

Participants all accepted that randomisation was an essential component of good clinical trials. Interestingly, most participants reported that the 1:1 randomisation was preferable to the 2:1 randomisation as this reflected clinical equipoise.

Fractionation Schedules

Several fractionation schedules were proposed (see figure 1). Most participants favoured the shorter, moderately hypofractionated schedule as this meant patients would spend less time away from home at the PBT centre, lessening the impact on family life and income. Participants were very positive about receiving fewer cycles of chemotherapy as this was perceived to be a main cause of toxicity.

Trial endpoints

Different trial endpoints were presented to patients. (see appendix 1) Participants all felt that toxicity reduction was a more important endpoint compared to clinical equivalence. Several participants had had previous nCRT followed by surgery and felt that despite being cancer-free and several years from surgery, the treatment still had a debilitating impact on their quality of life.

Patient information

Although most participants felt that written information with a section for FAQs was adequate with no need for additional media content, some felt additional video content would be beneficial. It was highlighted that patient information must be written simply and concisely, avoiding any complex medical terminology. Several PPI representatives volunteered to contribute to the writing of patient information sheets.

Clinical scenarios

Participants did not raise any concerns regarding clinical scenarios including transfer to an acute hospital local to the PBT centre should the clinical need arise. The participants highlighted the importance of good lines of communication between referring hospital and the PBT centre, suggesting weekly email updates and teleconferences with their usual oncologist if required.

Table 2 summarises refinements to trial design following input from PPI contributors.

Aspect of trial Design	**Initial Proposed Design**	**Modifications following PPI**

Provision of support	Specialist supportive care (dieticians, physiotherapy etc.) Cover accommodation for patients plus one (e.g. spouse, carer) Travel expenses not covered	Cover travel expenses for all patients plus one (e.g. spouse, carer) Consider provision of pre-habilitation services and 'hospitality pack'.
Randomisation	2:1 randomisation or 1:1 randomisation	1:1 randomisation
Fractionation Schedule	41.4Gy/23# with 5 cycles of Carboplatin/Paclitaxel or 40Gy/15# with 3 cycles of Carboplatin/Paclitaxel or 45Gy/25# with 5 cycles of Carboplatin/Paclitaxel	40Gy/15# with 3 cycles of Carboplatin/Paclitaxel
Trial Endpoints	Toxicity Reduction and pCR (pathological complete response) and R0 (clear resection margin) rate are co-primary endpoints	Toxicity Reduction is the primary endpoint pCR and R0 rate becomes a secondary endpoint
Patient information	Written information Consideration of other media (videos, apps etc.)	Written information will be provided Additional video content favourable but not necessary Patient-facing materials will be reviewed by PPI contributors
Clinical Scenarios and Communication	Referral to acute hospital in cases of emergencies (e.g. MI, Stroke)	Regular communication with referring centre with weekly email updates or teleconferencing

Table 2: Trial Design modifications following consultations with patient contributors

Discussion

Our focus groups had good representation from different geographical areas of the UK with many living a long distance from PBT centres. Our work suggests that while many patients are willing to travel for PBT treatment, a significant minority would find the disruption to daily living an unsurmountable barrier to trial entry. In order to minimise inequity of access, there was clear consensus that travel and accommodation must be provided to adequately facilitate trial participation. This is analogous to feedback received in previous PPI work for another UK PBT trial, TORPEdO. [13] It is becoming increasingly clear that investigators in PBT trials will need to take deliberate steps to ensure equity of access to trial participation for all patients. This will need to be taken into consideration by any future PBT trial proposals and their potential funders.

Participants placed a strong emphasis on toxicity reduction and minimising the impact of treatment. Patients were also very clear in their support for a moderately shortened (hypofractionated) treatment schedule to minimise disruption to patient's lives. Most participants chose toxicity reduction over efficacy endpoints as the primary endpoint of the study. This echoes the findings of recent work by Lorgelly et al. that cancer patients value toxicity reduction just as much as survival outcomes. [23] Substantial changes were made to trial design based on patient feedback, making this, we believe, an epitome of co-produced research. To ensure ongoing co-production of research throughout the research cycle, two PPI representatives have formally joined the trial management group. Further PPI work will be required to select patient- facing materials including selecting appropriate patient reported outcome measures (PROMs) questionnaires.

We believe that the challenges in this trial will be mirrored in many research groups across Europe who are developing PBT trials. The format of holding focus groups required minimal costs and technological infrastructure and is easily reproducible for researchers across Europe, thus providing a cost-effective strategy of incorporating patient perspectives into clinical research. In the current pandemic, widely available video-conferencing tools may be the preferred method of carrying out similar work.

This work provided a patient's perspective on our study with this work showing direct and tangible impact into final trial design. We believe the incorporation of patient's views into trial design are invaluable and will improve patient enrolment, trial feasibility and overall impact; augmenting the likelihood of a successful PBT trial.

Appendix

Co-Primary Endpoint	Toxicity reduction by 1/3 - 90 days morbidity (cardiac and lung) Non-inferiority to standard nCRT - pCR rate, R0 rate
Secondary Endpoints	Progression Free Survival Overall Survival Rate of G4 Lymphopenia Patient reported outcome measures (PROMs) Health Economic Analyses 6 month toxicity endpoints – incl. leak rates Translational work

Table 3: Proposed primary and secondary endpoints for the ProtOeus trial. Primary endpoint in ORANGE selected to final trial design following PPI feedback. Non-inferiority efficacy endpoints becomes a secondary endpoint.

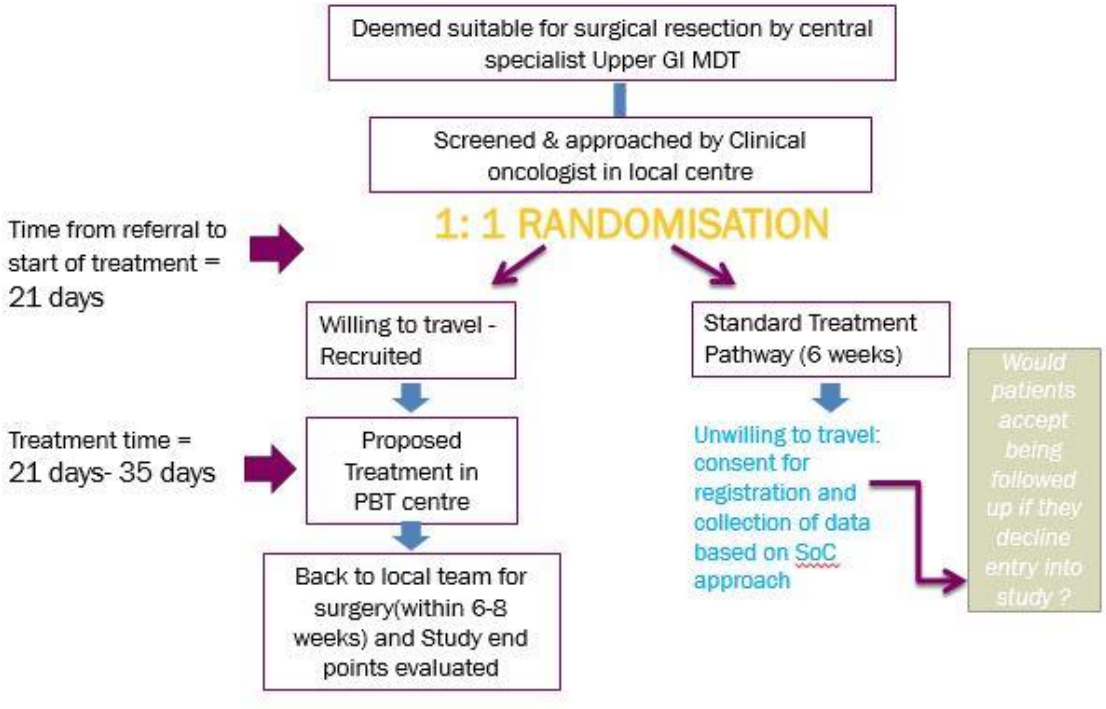

Figure 3: Proposed Patient pathway for the ProtOeus trial

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