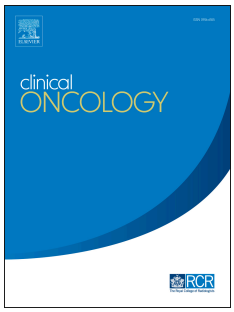

Hitting the Target: Developing High-quality Evidence for Proton Beam Therapy Through Randomised Controlled Trials

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Hitting the target: developing high quality evidence for proton beam therapy through randomised controlled trials

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3. literature research: all authors
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5. experimental studies / data analysis: EMH
6. statistical analysis: N/A
7. manuscript preparation: EMH, FS, KB
8. manuscript editing: all authors

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Abstract

The National Health Service strategy for the delivery of proton beam therapy (PBT) in the UK provides a unique opportunity to deliver high quality evidence for PBT through Randomised Controlled Trials (RCTs). We present a summary of three UK PBT RCTs in progress, including consideration of their key design characteristics and outcome assessments, to inform and support future PBT trial development.

The first three UK multicentre phase III PBT RCTs (TORPEdO, PARABLE and APPROACH), will compare PBT with photon radiotherapy for oropharyngeal squamous cell carcinoma, breast cancer and oligodendroglioma, respectively. All three studies were designed by multidisciplinary teams, which combined expertise from clinicians, clinical trialists and scientists with strong patient advocacy and guidance from national radiotherapy research networks and international collaborators.

Consistent across all three studies is a focus on reduction of long-term radiotherapy-related toxicities and evaluation of patient-reported outcomes and health-related quality of life, which will address key uncertainties regarding the clinical benefits of PBT. Innovative translational components will provide insights into mechanisms of toxicity and help to frame the key future research questions regarding PBT.

The UK radiotherapy research community is developing and delivering an internationally impactful PBT research portfolio. The combination of data from RCTs with prospectively collected data from a national PBT outcomes registry will provide an innovative, high-quality repository for PBT research and the platform to design and deliver future trials of PBT.

Key words

- Radiotherapy
- Proton Beam Therapy
- Randomised controlled trials
- Clinical Trial Design
- Research Networks

Overview

Hitting the Target: Developing High-quality Evidence for Proton Beam Therapy Through Randomised Controlled Trials

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Abstract
The National Health Service strategy for the delivery of proton beam therapy (PBT) in the UK provides a unique opportunity to deliver high-quality evidence for PBT through randomised controlled trials (RCTs). We present a summary of three UK PBT RCTs in progress, including consideration of their key design characteristics and outcome assessments, to inform and support future PBT trial development. The first three UK multicentre phase III PBT RCTs (TORPEdO, PARABLE and APPROACH), will compare PBT with photon radiotherapy for oropharyngeal squamous cell carcinoma, breast cancer and oligodendroglioma, respectively. All three studies were designed by multidisciplinary teams, which combined expertise from clinicians, clinical trialists and scientists with strong patient advocacy and guidance from national radiotherapy research networks and international collaborators. Consistent across all three studies is a focus on the reduction of long-term radiotherapy-related toxicities and an evaluation of patient-reported outcomes and health-related quality of life, which will address key uncertainties regarding the clinical benefits of PBT. Innovative translational components will provide insights into mechanisms of toxicity and help to frame the key future research questions regarding PBT. The UK radiotherapy research community is developing and delivering an internationally impactful PBT research portfolio. The combination of data from RCTs with prospectively collected data from a national PBT outcomes registry will provide an innovative, high-quality repository for PBT research and the platform to design and deliver future trials of PBT.

Key words: Clinical trial design; proton beam therapy; radiotherapy; randomised controlled trials; research networks

Introduction (A head)

Proton beam therapy (PBT) involves the delivery of high-energy protons and requires modern computing techniques and treatment delivery systems. There is considerable interest in PBT because of its ability to produce highly conformal dose distributions and minimise dose to normal tissues. It is hypothesised that this will reduce long-term toxicities [1]. However, aside from paediatric cancers and tumours of the skull base, the clinically meaningful benefits of PBT in comparison with photon radiotherapy remain uncertain [1–3]. There are a limited number of randomised controlled trials (RCTs) and high-quality evidence to support the use of PBT, especially in an era of highly conformal photon radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) [4]. PBT is also considerably more expensive than photon radiotherapy, and requires considerable capital investment [1,2]. Despite a lack of evidence of clinical benefit for the treatment of adults, the use of PBT rapidly expanded internationally, but in recent years this situation has been questioned by policy makers and healthcare funders [2]. The recent investment into two National Health Service (NHS) England PBT centres located at University College London Hospitals NHS Foundation Trust (UCLH) and The Christie NHS Foundation Trust in Manchester provides an important opportunity to undertake RCTs of PBT in comparison with photon radiotherapy. This will provide internationally impactful high-quality evidence regarding PBT that is urgently required to justify its use.

UK Strategy for Proton Beam Therapy Research (A head)

The UK has taken considerable steps to develop a robust and effective framework for PBT research. The UK PBT programme received a £250 million capital investment for the two centres, with a combined capacity to treat up to 1500 patients per year [5]. This incorporates research capacity with a substantial commitment to clinical trials and commissioning studies to establish the evidence base in adult patients [3,6].

A PBT Clinical Trials Strategy Group was formed within the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group (CTRad) to develop a strategic PBT portfolio and accelerate study development, bringing together expertise, promoting national collaboration and avoiding competing research [7]. PBT research was also supported through the Advanced Radiotherapy Technologies Network (ART-NET), funded by a 5-year £4.3 million Cancer Research UK Network Accelerator award. The network brought together leading radiotherapy clinical and academic institutes, including The Institute of Cancer Research (ICR)/Royal Marsden Hospital, University of Leeds, Manchester Cancer Research Centre, Oxford and University College London. ART-NET provided a mechanism for synergic collaboration to develop and solve the complexities of implementing advanced radiotherapy techniques, including PBT [8].

The CTRad PBT Strategy Group recognised the importance of recording and evaluating patient outcomes after receiving PBT, regardless of whether patients are treated within a clinical trial [7]. Each of the PBT centres has a dedicated team funded to capture, analyse and publish outcome data for all PBT-treated patients [9]. The Proton Clinical Outcomes Unit (PCOU) is the dedicated team for the Christie and has developed a core outcome dataset, to be collected for all proton patients, in addition to outcomes tailored to each indication [9]. All outcomes after treatment will be collected from data recorded at patients' local radiotherapy centres. The UCLH outcomes unit will mirror the set-up of the PCOU.

The significant financial investments, national commitment to research and an ensemble of multidisciplinary research groups provide UK radiation oncology researchers with a unique opportunity to design and develop exemplar and complementary studies that will define the future standard of care. This collaboration has facilitated the exchange of expertise and knowledge in treatment practices and clinical trial design. Here we describe the development and design of the first wave of UK PBT trials in detail, providing a framework for future PBT trials to build from.

Rationale for Current UK-funded Trials (A head)

Three multicentre phase III RCTs comparing PBT with photon radiotherapy have been developed and are at different stages, with one recently completing recruitment, one currently open to recruitment and one in the final stages of site set-up. These three trials represent the first wave of RCTs in the UK and will be the focus of this paper. A further four trials have been developed and funded, evaluating the use of PBT in mesothelioma, sinonasal carcinoma, oesophageal adenocarcinoma and hepatocellular carcinoma.

TORPEdO (B head)

The first trial is TORPEdO (TOxicity Reduction using PBT for Oropharyngeal cancer), funded by Cancer Research UK, with funding also received from The Taylor Family Foundation. TORPEdO is sponsored by the ICR and led by the ICR Clinical Trials and Statistics Unit (ICR-CTSU). The trial opened in February 2020 and completed recruitment with 205 patients ahead of schedule in June 2023.

The standard care for locally advanced oropharyngeal squamous cell carcinoma is concurrent chemoradiotherapy using IMRT [10]. Despite improved tissue sparing with IMRT, over 60% of patients experience severe acute toxicities that may require hospital admission and lead to treatment gaps and poor chemotherapy compliance [11]. Acute toxicities can be a precursor to late effects, including oral dryness, swallow dysfunction and gastrostomy dependence, which can have a significant impact on long-term quality of life [6,12,13]. The TORPEdO trial [14] will investigate whether PBT can reduce long-term treatment-related toxicities.

PARABLE (B head)

The second trial is PARABLE (Proton beAm theRApy in patients with Breast cancer), evaluating early and late effects, funded through the Efficacy and Mechanism Evaluation (EME) Programme funded by the National Institute for Health Research (NIHR) and the Medical Research Council. PARABLE is also sponsored by the ICR and led by ICR-CTSU. The first PARABLE patient was recruited in August 2022.

After breast cancer surgery, radiotherapy is often recommended to the breast/chest wall ± regional nodes to optimise long-term local control and survival [15,16]. Modern photon radiotherapy for breast cancer, including IMRT and deep-inspiratory breath-hold, can provide satisfactory target volume coverage with minimal dose to surrounding normal tissues, which minimises risks of long-term cardiac and pulmonary toxicities. In a small subset of patients, however, there is a greater risk of long-term cardiac side-effects due to young age, cardiac risk factors or higher mean heart dose (MHD) [17]. MHD is a predictor of long-term cardiac

toxicity and can be increased by factors such as variation in individual chest wall shape, especially if this is combined with treatment of internal mammary chain lymph nodes. Clinically acceptable thresholds for MHD depend on the patient's age and cardiac risk factors. PBT can potentially reduce these risks by facilitating coverage of target tissues while minimising dose to the heart. PARABLE will compare PBT to optimal photon therapy in patients with at least a 2% increased risk of radiotherapy-induced late cardiac toxicity [18].

APPROACH (B head)

The third trial is APPROACH (Analysis of Proton vs. Photon Radiotherapy in Oligodendroglioma and Assessment of Cognitive Health), which is in site set-up and due to open to recruitment in 2023. APPROACH is also funded by the NIHR EME programme. The trial is sponsored by the University of Leeds and led by the Leeds Clinical Trials Research Unit.

Oligodendroglioma is a rare, good-prognosis glioma, with adults diagnosed at a mean age of 45 years [19] and a median survival of over 10 years [20,21]. Although photon radiotherapy is an important component of treatment, it can cause long-term neurocognitive dysfunction, which can impact quality of life and daily activities. This is particularly relevant for oligodendroglioma patients, given their young age and prolonged survival. PBT is an approved treatment for paediatric and young adult oligodendroglioma patients in the UK [22]. The APPROACH trial aims to investigate whether PBT can reduce long-term neurocognitive dysfunction compared with photon radiotherapy in a wider adult population.

UK Proton Beam Therapy Trial Development Framework (A head)

The Cancer Research UK-funded Clinical Trials Units (CTUs) at the ICR-CTSU and the University of Leeds have extensive experience in the design, development and delivery of multidisciplinary practice-changing clinical trials. Their expertise played a crucial role in shaping the PBT trials. Experiences from TORPEdO informed the PARABLE and APPROACH studies through shared learning within and across CTUs, facilitated by the trial teams and CTRad research network.

Patient and public involvement (PPI) co-development has been central to each trial. The use of focus groups with patient representatives helped to understand and address concerns regarding feasibility and inclusivity. PPI played a pivotal role in defining and shaping the research questions to ensure outcomes were relevant to patients [23,24]. The acceptability of travel for PBT and associated challenges were identified at PPI events as key issues to be addressed during trial development. Each of the three studies included a PPI contributor as a co-applicant, providing a patient voice throughout the development process. PPI members are also included on the trial management groups and oversight committees to ensure all key decisions have PPI input.

Each of the studies were presented in dedicated CTRad PBT trial development workshops. These workshops provided opportunities for structured review by clinical and methodological experts and input from patient advocates, regarding the research questions, study endpoints and trial design. Attendees represented diverse disease groups, fostering valuable cross-discussion and a collaborative problem-solving approach across different disease sites. Key methodologists involved in the development of the three PBT trials were members of the CRUK ART-NET clinical trial workstream, providing expert leadership and efficient knowledge sharing between the trial development teams [8]. To further the legacy of

the ART-NET award, CTUs involved in the design, analysis and management of PBT RCTs have established a PBT trial buddy group to provide peer support and share lessons learnt and solutions to the challenges of delivering PBT trials in the UK.

The prospective involvement of the national Radiotherapy Quality Assurance (RTTQA) group has been integral to the development of the PBT trials. This enables iterative learning experiences to be applied to subsequent studies, ensuring efficiencies in the processes for credentialling and quality assurance of PBT and photon radiotherapy contouring and treatment planning [25].

International Collaboration with Proton Beam Therapy Trial Teams (A head)

International collaborations to optimise radiotherapy quality assurance programmes have been a major component of PBT trial design and delivery. In TORPEdO, quality assurance processes include prospective review of all contouring benchmark cases and the first plan from each centre, with retrospective review of all other treatment plans [14]. This process is supported by a collaboration with an independent international proton centre and is funded by the NIHR. For PARABLE, the investigators collaborated with RTTQA and a multidisciplinary team of colleagues from centres in Denmark, the Netherlands and the USA to develop the radiotherapy and quality assurance guidelines [18]. PBT credentialling and on trial case review is also supported by colleagues from Denmark.

The UK PBT trial teams have also collaborated with international researchers to ensure global relevance and comparability between trials, and to strengthen the global evidence base for PBT. These international networks will also provide opportunities for further research. In collaboration with researchers in the Netherlands, TORPEdO data will help validate the normal tissue complication probability model for head and neck cancer patient selection in the Netherlands. Protocols for PARABLE and APPROACH have been harmonised with the Danish Breast Cooperative Group and NRG-BN005 US glioma (NCT03180502) PBT studies, respectively, for potential future meta-analyses.

Trial Design (A head)

The three trials have comparable design features, collectively providing a framework for future trials to build on. Table 1 presents the key aspects of the trial designs and their respective primary endpoints. Table 2 presents the secondary outcomes collected and Table 3 presents the timing of outcome collection.

Tables 1-3 here

Recruitment (B head)

The trial sample sizes range between 192 and 246, each formally powered to meet their respective primary endpoint(s) while ensuring deliverability within a reasonable timeframe. The planned recruitment periods are between 2.5 and 3.5 years, with participating radiotherapy centres distributed across the UK, to maximise geographical access where possible.

Internal Pilot (B head)

Both PARABLE and APPROACH include an internal pilot assessment, exploring the feasibility of recruitment and acceptability of randomisation [18]. Predefined traffic light criteria will aid decision making regarding trial continuation. NHS England supports accommodation costs for patients allocated to PBT but not travel costs. Where possible, travel costs have been sought through charitable funders. Further studies will explore in greater depth the factors associated with patient participation in the three PBT trials, including the impact of the unique requirement to travel or temporarily relocate for treatment if randomised to PBT [26].

Primary Endpoints (B head)

Each of the three trials represents a stage 3 study within the R-ideal framework for clinical evaluation of radiation oncology technologies [27], comparable with phase III in the conventional clinical trial classification. All the studies have a primary endpoint focused on the reduction of toxicities or improved functioning when compared with photon radiotherapy, each tailored to the specific cancer site and patient population. The overall trial outcomes are potentially practice changing for standard of care in the UK within the corresponding patient populations.

The TORPEdO co-primary outcomes combine patient-reported outcome measures (PROMs) and clinician-recorded toxicities, both assessed at 12 months. The trial is designed such that a positive result in either of the primary outcomes would lead to a recommendation of PBT for the standard of care treatment of oropharyngeal cancer.

PARABLE also has co-primary endpoints, investigating the superiority of PBT for the MHD, as an early predictor for serious radiotherapy-induced late heart toxicity [17], while also investigating non-inferiority of PBT for patient-reported breast symptoms at 2 years. A 2-year endpoint for late breast toxicity was selected because data indicate that differences in toxicity observed between radiotherapy dose fractionation schedule/techniques at 2 years are indicative of differences at later timepoints [28].

The APPROACH study will assess a single primary outcome of 5-year neurocognitive function measured by the European Organization for Research and Treatment of Cancer (EORTC) Clinical Trial Battery Composite (CTB COMP) [29], a core set of neurocognitive tests recommended for use in clinical trials. Current literature suggests the differences in neurocognition between PBT and photons are likely to increase beyond 5 years [30], therefore establishing differences at 5 years as the earliest timepoint will be indicative of longer-term patient benefits, without requiring extensive, costly further follow-up.

Patient-reported Outcome Measures and Health-related Quality of Life (B head)

A key strength of all the trials is a central role for PROM-assessed toxicity and health-related quality of life, which has been lacking in prospective PBT studies to date [4]. The trials collect PROMs related to general cancer outcomes and disease-specific modules capturing tailored symptoms (Table 2). The complementary collection of EORTC QLQ-C30 health-related quality of life data will enable cross-study comparison of the general effects of PBT.

Clinical Secondary Endpoints (B head)

Toxicities will be clinically assessed in all studies using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. PARABLE will also assess cough and breathlessness using the Radiation Therapy Oncology Group scale, as key adverse events associated with breast treatment delivery. Definitions of acute and late toxicities are similar between studies (acute = adverse events occurring up to 3 months, late = after 3 months evaluated up to 5 years).

Standard cancer clinical outcomes are included as secondary endpoints, including overall survival, progression and tumour response. Disease-specific functioning measures, capturing established side-effects of photon radiotherapy, have been included with patient and clinician focus.

Health Economic Data (B Head)

To inform future use of PBT in these patient groups, a cost-effectiveness assessment is essential. However, decisions regarding the collection and analysis of health economic data were influenced by funding constraints. Although the studies lack a full detailed cost-effectiveness analysis, all incorporate instruments to provide some level of health economic assessment. TORPEdO includes a health economics secondary endpoint, assessed by the Use of Healthcare Resources questionnaire (a bespoke tool designed specifically for each study) and the Work Productivity and Activity Impairment (WPAI) and EQ-5D-5L questionnaires, all analysed in collaboration with the Health Economics Research Centre, University of Oxford. Both PARABLE and APPROACH will collect EQ-5D-5L and Use of Healthcare Resources questionnaire, while APPROACH will also use [AQ1]WPAI. The use of complementary questionnaires will facilitate future collaborations for general evaluation of the cost-effectiveness of PBT.

Follow-up (B head)

The trials will collect outcomes up to 5 years, which will address a need for long-term outcomes after PBT [4]. This highlights the importance of collecting data concerning long-term late effects and PROMs as a priority for funders. Some radiotherapy-related toxicities, such as neurocognitive dysfunction, and the potential benefits of PBT over photon radiotherapy in reducing this, could become apparent beyond 5 years [30]. Although the funding envelopes for trial data collection beyond 5 years remain a challenge, PARABLE will continue to obtain data on cardiac toxicity, disease recurrence and survival using routine data sources beyond 5 years, linking with the PCOU. This approach could also be utilised for the other PBT studies. This combination of data from trials, PCOU (see below) and routine data sources offers a powerful and potentially cost-effective approach for assessment of the long-term effects of PBT.

Timing of Data Collection (B head)

The timing of the collection of outcomes is principally designed around standard clinical visits, aimed to reduce patient and clinician burden, with considerations for cost implications. Naturally, there is some variation in the timings of collection, but key similarities remain.

Wider Research (A head)

Proton Clinical Outcomes Unit Data Collection (B head)

The PCOU will collect 'real-world' data regarding disease outcomes, clinician-assessed toxicity and PROMs from patients treated using PBT regardless of whether they are participating in a research study or not. These data are collected at baseline, during and after treatment, with more intensive collection of post-treatment data initially, phasing to annually then every 5 years. To avoid duplication of data and to minimise the burden from its collection, the CTUs will share relevant trial data with the PBT units. The PCOU will enable the development of a unique body of knowledge about PBT, help drive improvements in treatment and support future research [9].

Translational Research (B head)

Each of the studies includes a strong focus on translational and/or mechanistic research relating to the biological mechanisms that underpin PBT. TORPEdO will collect PBT and photon treatment plans. The combination of radiotherapy dosimetric data and toxicity outcomes from the main study will improve normal tissue complication probability models and provide greater insights into optimum constraints for organs at risk [14]. In addition, evaluation of on-treatment cone beam computed tomography scans will aid the development of adaptive radiotherapy strategies for PBT. In PARABLE, an additional computed tomography scan at 2 years will be carried out, which will enable the assessment of changes in lung and rib density when compared with the planning computed tomography scan [18]. This work will enable the evaluation of models of relative biological effectiveness for PBT. PARABLE will also undertake an assessment of delivered versus planned dose to the heart, which will provide greater insight into the relationship between accumulated dose to the heart and the development of cardiac toxicity. In APPROACH, voxel-based lesion symptom mapping will be used to explore relationships between radiotherapy dose and its location within the brain and the development of neurocognitive dysfunction.

Additional sub-studies are also planned for TORPEdO, which will inform the development of future biomarker-driven trials based on tumour and normal tissue genomics and help to identify which patients are most likely to benefit from PBT [14]. These sub-studies will explore relationships between treatment response and toxicity outcomes from PBT and photon radiotherapy and predictive/prognostic genomic signatures, including markers of DNA damage response, radiosensitivity and immune response.

Further Proton Beam Therapy Trials (B head)

Since the initial three RCTs, additional UK PBT studies have been developed and funded [3]. PROTIS is a phase III study that will compare PBT to IMRT for sinonasal carcinomas with a disease-free survival primary endpoint. HIT-MESO is a phase III study that will evaluate overall survival with the addition of PBT to standard of care versus standard of care alone for mesothelioma. RaTIO is a phase II study in patients with hepatocellular carcinoma that will compare a radiotherapy–immunotherapy combination against immunotherapy alone, with a further randomisation between PBT and photon radiotherapy in the combination arm. Finally, PROTIEUS is a phase II study comparing PBT versus IMRT for neoadjuvant treatment of oesophageal adenocarcinoma.

Conclusion (A head)

The UK success thus far in the development and delivery of multiple PBT RCTs reflects the strong multidisciplinary collaborations between clinicians, methodologists, scientists, PPI representatives and research advisory groups. The expertise gained and knowledge shared across TORPEdO, PARABLE and APPROACH have established a framework for the design and funding of future PBT trials. Opportunities within the UK for translational research, international collaborations and integration of clinical trial outcomes with real-world datasets will provide a substantial contribution to the global evidence base for PBT. Leveraging the established track record and national capacity to conduct high-quality clinical trials, the UK is well-positioned to be at the forefront of international PBT research.

Conflicts of interest

The TORPEdO (DJT, EH) trial team reports that financial support was provided by Cancer Research UK. PARABLE (AK, JH, KB) and APPROACH (LM, SB, EMH) trial teams report that financial support was provided by NIHR EME. FS reports that financial support was provided by Cancer Research UK.

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Author contributions
EMH is the guarantor of integrity of the entire study. EMH, KB, EH, SB, JH, LM and DSM were responsible for study concepts and design. All authors carried out the literature research. EMH was responsible for experimental studies/data analysis. EMH, FS and KB prepared the manuscript. All authors edited the manuscript.

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Table 1
Trial design information and primary endpoint(s) for TORPEdO, PARABLE and APPROACH

		TORPEdO	PARABLE	APPROACH
General trial information	Design	Parallel superiority	Parallel superiority/non-inferiority *	Parallel superiority
	Phase/R-IDEAL stage	Phase III/stage 3	Phase III/stage 3	Phase III/stage 3
	Principal funder	CRUK	NIHR EME	NIHR EME
	Cancer site	Head and neck	Breast	Brain
	Disease	Oropharyngeal	Early breast	Oligodendroglioma
	Sample size	201	192	246
	Allocation ratio	2:1 (IMPT:IMRT)	1:1 (IMPT:IMRT)	1:1 (PBT:IMRT)
	Treatment	Therapeutic dose 70 Gy (RBE equivalent) in 33 fractions and elective dose 56 Gy (RBE equivalent) in 33 fractions Both over 6.5 weeks	40 Gy (RBE equivalent) in 15 fractions over 3 weeks	54 Gy (RBE equivalent) in 30 fractions/59.4 Gy (RBE equivalent) in 33 fractions over 6.5 weeks
	Planned no. recruiting centres	15	23	18
	Planned recruitment period	3.5 years	2.5 years	3.5 years
	Length of follow-up	5 years	5 years	5 years
	Trial status as of February 2023	Recruitment	Recruitment	Site set-up
	CTU involvement	ICR-CTSU	ICR-CTSU	Leeds CTRU
Primary endpoint(s)	Primary research question	To assess whether IMPT compared with IMRT reduces treatment-related toxicities in patients with locally advanced oropharyngeal squamous cell carcinoma.	Compared with standard radiotherapy for women with breast cancer, does PBT reduce mean heart dose (predictor of serious heart toxicity many years later) without increasing shorter-term side-effects?	Does PBT offer neurocognitive benefits when compared with photon radiotherapy in adult patients with oligodendroglioma?
	Outcome(s)	Co-primary: • UW-QoL physical composite score; and • gastrostomy dependence or CTCAE grade 3 weight loss	Co-primary: • Planned mean heart dose • Patient-reported normal tissue toxicity in breast/chest wall via QLQ-BR23	Primary: Neurocognitive function assessed via EORTC CTB COMP
	Time point	12 months after the end of treatment	2 years after the end of radiotherapy treatment	5 years after the end of radiotherapy treatment

CRUK, Cancer Research UK; CTCAE, Common Terminology Criteria for Adverse Events; CTRU, Clinical Trials Research Unit; CTU, Clinical Trials Unit; EORTC CTB COMP, European Organization for Research and Treatment of Cancer Clinical Trial Battery Composite; ICR-CTSU, The Institute of Cancer Research Clinical Trials and Statistics Unit;
IMPT

IMRT, intensity-modulated radiotherapy; PBT, proton beam therapy; RBE, relative biological effectiveness; NIHR EME, National Institute for Health Research Efficacy and Mechanism Evaluation programme; UW-QoL, University of Washington Quality of Life.

*Co-primary endpoint planned mean heart dose is superiority, other co-primary endpoint patient-reported normal tissue toxicity is non-inferiority.

Table 2
Outcome collection for trials and the Proton Clinical Outcomes Unit

			TORPEdO	PARABLE	APPROACH
General cancer outcomes	Performance	Overall survival	✓	✓	✓
		Tumour response	✓	✓	✓
		Resection rates	✓		
	Toxicities	Acute	✓	✓	✓
		Late	✓	✓	✓
	PRO HRQoL	EORTC QLQ-C30	✓	✓	✓
	Health economic data	EQ-5D-5L	✓	✓	✓
		Healthcare resource use	✓	✓	✓
		WPAI questionnaire	✓		✓
	Treatment	Treatment compliance		✓	✓
Cancer site specific	PRO HRQoL	EORTC QLQ-H&N43	✓		
		MDADI	✓		
		UW-QoL	✓		
		EORTC QLQ-BR23		✓	
		Trial-specific acute toxicity		✓	
		EORTC QLQ-BN20			✓
		HADS			✓
		MFI			✓
		30-item Caregiver Needs Screen			✓
	Functioning	Hearing loss	✓		
		PSS-HN	✓		
		Swallowing	✓		
		Trismus	✓		
		Tube feeding status	✓		
		Endocrinopathy			✓
		Neurocognition			✓

EORTC, European Organization for Research and Treatment of Cancer; HADS, Hospital and Anxiety Depression Scale; MDADI, M. D. Anderson Dysphagia Inventory; MFI, Multi-dimensional Fatigue Inventory; PRO HRQoL, patient-reported outcome health-related quality of life; PSS-HN, Performance Status Scale for Head and Neck Cancer; QLQ-BN20, Quality of Life Questionnaire – Brain Neoplasm 20-item questionnaire; QLQ-BR23, Quality of Life Questionnaire - Breast Cancer 23-item questionnaire; QLQ-C30, Quality of Life Questionnaire – Core 30-item questionnaire; QLQ-H&N43, Quality of Life Questionnaire – Head & Neck Cancer 43-item questionnaire; UW-QoL, University of Washington Quality of Life; WPAI, Work Productivity and Activity Impairment.

Table 3
Timing of outcome collection type

			Study	Baseline	During radiotherapy	End of radiotherapy	1 month	6 weeks	3 months	6 months	12 months	18 months	2 years	3 years	4 years	5 years	5+ years
Secondary outcomes	Cancer general outcomes	Overall survival	TOR	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	
			PAR	✓							✓		✓	✓	✓	✓	
			APP	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓
		Tumour response/recurrence evaluation	TOR	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	
			PAR	✓							✓		✓	✓	✓	✓	✓
			APP	✓					✓	✓	✓		✓	✓	✓	✓	
		Resection rates	TOR	✓	✓	✓			✓	✓	✓		✓				
			PAR*														
			APP*														
		Acute and late Toxicities	TOR	✓	✓	✓			✓	✓	✓	✓	✓				
			PAR	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
			APP	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	
		PRO HRQoL	TOR	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
			PAR	✓	✓	✓				✓	✓		✓			✓	
			APP	✓		✓	✓		✓	✓	✓		✓	✓	✓	✓	
		Health economic data	TOR	✓		✓		✓	✓	✓	✓	✓	✓				
			PAR	✓						✓	✓		✓			✓	
			APP	✓		✓	✓		✓	✓	✓		✓	✓	✓	✓	

*Resection rates not applicable for PARABLE or APPROACH.

APP, APPROACH; PAR, PARABLE; PRO HRQoL, patient-reported outcome health-related quality of life; TOR, TORPEdO.

Author queries

Original references [7] and [9] were the same. Therefore [9] was removed, text citations changed to [7] and subsequent references renumbered

[22] web address has been inserted. Please confirm that it is correct

AQ1 WAPI has been changed to WPAI. Is that OK?

Table 1: please clarify IMPT in footnote

Table 1 - Trial design information and primary endpoint(s) for TORPEdO PARABLE and APPROACH (RBE: relative biological effectiveness)

		TORPEdO	PARABLE	APPROACH
General Trial info	Design	Parallel superiority	Parallel superiority/non-inferiority *	Parallel superiority
	Phase/ R-IDEAL Stage	Phase III/ Stage 3	Phase III/ Stage 3	Phase III/ Stage 3
	Principal funder	CRUK	NIHR EME	NIHR EME
	Cancer site	Head and Neck	Breast	Brain
	Disease	Oropharyngeal	Early breast	Oligodendroglioma
	Sample size	201	192	246
	Allocation ratio	2:1 (IMPT:IMRT)	1:1 (IMPT:IMRT)	1:1 (PBT:IMRT)
	Treatment	Therapeutic dose 70Gy (RBE equivalent) in 33 fractions and elective dose 56Gy (RBE equivalent) in 33 fractions Both over 6.5 weeks	40 Gy (RBE equivalent) in 15 fractions, Over 3 weeks	54Gy (RBE equivalent) in 30 fractions / 59.4Gy (RBE equivalent) in 33 fractions, Over 6.5 weeks
	Planned no. recruiting centres	15	23	18
	Planned recruitment period	3.5 years	2.5 years	3.5 years
	Length of follow-up	5 years	5 years	5 years
	Trial status as of Feb 2023	Recruitment	Recruitment	Site set-up
	CTU involvement	ICR-CTSU	ICR-CTSU	Leeds CTRU
Primary endpoint(s)	Primary research question	*To assess whether IMPT compared with IMRT reduces treatment-related toxicities in patients with locally advanced oropharyngeal squamous cell carcinoma.*	*Compared with standard radiotherapy for women with breast cancer, does PBT reduce mean heart dose (predictor of serious heart toxicity many years later) without increasing shorter-term side effects?*	Does PBT offer neurocognitive benefits when compared with photon radiotherapy in adult patients with Oligodendroglioma?
	Outcome(s)	**Co-primary**: • UW-QoL physical composite score; and • gastrostomy dependence or CTCAE grade 3 weight loss	**Co-primary**: • Planned mean heart dose • Patient-reported normal tissue toxicity in breast/ chest wall via QLQ-BR23	**Primary**: Neurocognitive function assessed via EORTC CTB COMP
	Time point	12 months post end of treatment	2 years post end of radiotherapy treatment	5 years post end of radiotherapy RT treatment

**Co-primary endpoint planned mean heart dose is superiority, other co-primary endpoint patient reported normal tissue toxicity is non-inferiority*

Table 2 - Outcome collection for trials and PCOU

			TORPEdO	PARABLE	APPROACH
General Cancer outcomes	Performance	Overall survival	✓	✓	✓
		Tumour response	✓	✓	✓
		Resection rates	✓		
	Toxicities	Acute	✓	✓	✓
		Late	✓	✓	✓
	PRO HRQoL	EORTC QLQ-C30	✓	✓	✓
	Health economic data	EQ-5D-5L	✓	✓	✓
		Healthcare resource-use	✓	✓	✓
		Work Productivity and Activity Impairment (WPAI) questionnaire	✓		✓
	Treatment	Treatment compliance		✓	✓
Cancer site specific	PRO HRQoL	EORTC QLQ-H&N43	✓		
		MDADI	✓		
		UW-QoL	✓		
		EORTC QLQ-BR23		✓	
		Trial-specific acute toxicity		✓	
		EORTC QLQ-BN20			✓
		HADS			✓
		MFI			✓
		30-item Caregiver Needs Screen			✓
	Functioning	Hearing loss	✓		
		PSS-HN	✓		
		Swallowing	✓		
		Trismus	✓		
		Tube feeding status	✓		
		Endocrinopathy			✓
		Neurocognition			✓

EORTC *European Organisation for Research and Treatment of Cancer*
QLQ-C30 *Quality of life questionnaire – Core 30 item questionnaire [27]*
EQ-5D-5L *EuroQoL EQ-5D-5L [28]*
PSS-HN *Performance Status Scale for Head and Neck Cancer [29]*
WPAI *Work Productivity and Activity Impairment [30]*
QLQ-BN20 Quality of Life Questionnaire – Brain Neoplasm 20 item questionnaire [31]
QLQ-BR23 Quality of life Questionnaire - Breast cancer 23 item questionnaire [32]
QLQ-H&N43 *Quality of Life Questionnaire – Head & Neck Cancer 43 item questionnaire [33]*
HADS *Hospital and Anxiety Depression Scale [34]*
MDADI *M. D. Anderson Dysphagia Inventory [35]*
MFI *Multi-dimensional Fatigue Inventory [36]*
UW-QoL *University of Washington QoL [37]*

Table 3 - Timing of outcome collection type

			Study	Baseline	During RT	End of RT	1m	6w	3m	6m	12m	18m	2y	3y	4y	5y	5y+
Secondary outcomes	Cancer General outcomes	Overall survival	TOR	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	
			PAR	✓							✓		✓	✓	✓	✓	
			APP	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓
		Tumour Response/ Recurrence evaluation	TOR	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	
			PAR	✓							✓		✓	✓	✓	✓	✓
			APP	✓					✓	✓	✓		✓	✓	✓	✓	
		Resection rates	TOR	✓	✓	✓			✓	✓	✓		✓				
			PAR*														
			APP*														
		Acute and late toxicities	TOR	✓	✓	✓			✓	✓	✓	✓	✓				
			PAR	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
			APP	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	
		PRO HRQoL	TOR	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
			PAR	✓	✓	✓				✓	✓		✓			✓	
			APP	✓		✓	✓		✓	✓	✓		✓	✓	✓	✓	
		Health economic data	TOR	✓		✓		✓	✓	✓	✓	✓	✓				
			PAR	✓						✓	✓		✓			✓	
			APP	✓		✓	✓		✓	✓	✓		✓	✓	✓	✓	

**Resection rates N/A for PARABLE or APPROACH*

TOR = TORPEdO

APP = APPROACH

PAR = PARABLE

PRO HRQoL = Patient Reported Outcome Health Related Quality of Life

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

TORPEdO (DJT, EH) trial team reports financial support was provided by Cancer Research UK. PARABLE (AK, JH, KB) and APPROACH (LM, SB, EMH) trial teams reports financial support was provided by NIHR EME. FS reports financial support was provided by Cancer Research UK.