PARABLE: Proton beam therapy in patients with breast cancer: evaluating early and late effects

PROTOCOL

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This protocol describes the PARABLE trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of patients outside of this trial.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
Version 1.2 07/02/2022	Original approved version
Version 1.3 15/07/2022	• Addition of recording adjuvant treatment administered at 60 months • Update to administration contacts • Typographical corrections and clarifications
Version 1.4 26/01/2023	• Addition of ability to provide written informed consent as eligibility criterion (section 5.3) • Clarification of help available for travel costs (section 9.2) • Addition that baseline diagnostic tissue and/or surgical tissue is requested, in line with other trial documents (section 10.1) • Clarification in sample size justification for co-primary endpoints (section 14.1) • Correction of typographical error under 'cancer disease outcomes' in the secondary endpoints section (section 14.3.2.6) • Addition of heading 'Analysis sets and subgroup analyses' under 'Statistical Analysis Plan' (section 14.4) • Correction of typographical error under 'Public and Patient Involvement' (section 18.2)
Version 2.0 14/09/2023	• Update to Trial Manager details in the Administration section • Addition of receipt of allocated intervention as a secondary endpoint in section 4.2 (with further details of definition and analysis in sections 14.3 and 14.4 respectively) for the purpose of ongoing monitoring of acceptability of PBT to patients (beyond the internal pilot) • Statement regarding eligibility of patients with a pacemaker/implantable defibrillator in section 5. • Addition that travel expenses for patients and/or carers staying in the provided accommodation for the proton centres will be reimbursed from a grant from Breast Cancer Now in section 9.2. • Clarification around the timing of the principal analysis of co-primary endpoints in section 14.4 • Replacement of patient reported early toxicity SWAT with PBT trial recruitment SWAT in section 21.2 and trial summary. • Further information on the definition of Heart Failure added to appendix A1
Version 3.0 14/11/2023	• Update to trial coordination details in the Administration section • Amendment of inclusion criterion 2 to include that in the case of an occult breast primary, axillary surgery only is permissible (section 5.3) • Amendment of inclusion criterion 3 in line with the previously defined trial population (section 5.3) • Addition of axillary surgery only to information required at randomisation (section 8) and balancing factors (section 14.2) • Clarification that information required at randomisation includes requirement for tumour bed boost irradiation (section 8) • Addition of simultaneous integrated boost to IMN, where indicated, to radiotherapy planning and treatment (section 11.2), trial design (section 3) and trial summary • Clarification that long-line DVTs count as a cardiac risk factor, but pregnancy-related DVTs do not (appendix A1)

Version 4.0 22/02/2024	• Update to trial coordination details in the Administration section • Update to timeframe for reporting treatment machine unavailability (section 11.3) • Update to mean heart dose thresholds and explanation of changes added (appendix A1)

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PARABLE TRIAL SUMMARY

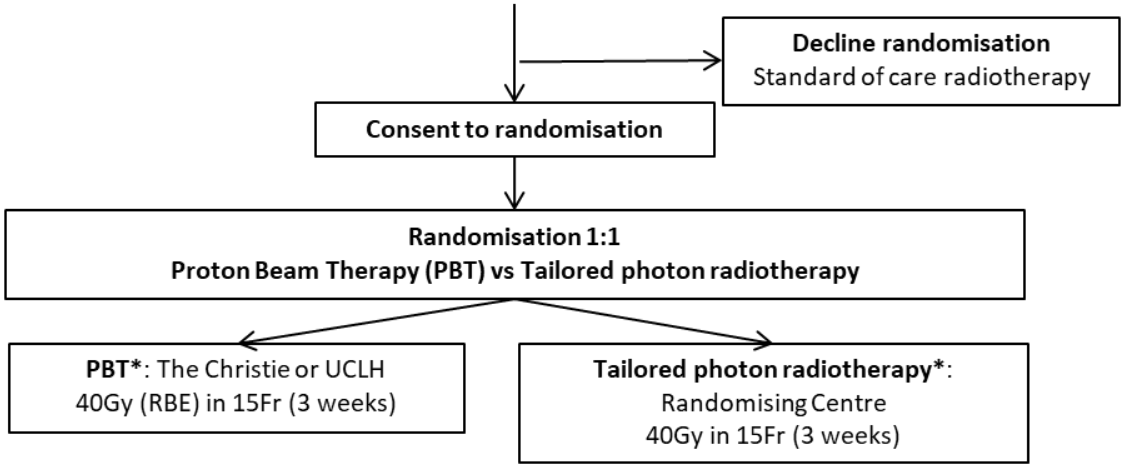
PROTOCOL TITLE	**PARABLE – Proton beam therapy in patients with breast cancer: evaluating early and late effects**
TARGET DISEASE	Breast cancer
TRIAL OBJECTIVES	I. To test whether proton beam therapy (PBT) a) Can reduce mean heart dose to <1Gy in patients who would have incurred a mean heart dose of typically >3Gy from photon radiotherapy thereby contributing to around 2% or higher estimated absolute lifetime risk of radiation-induced late major cardiac event and b) Is non-inferior to tailored photon radiotherapy (RT) (ideally intensity-modulated arc therapy (IMAT) delivered in breath-hold) in terms of 2-year patient-reported breast symptoms (<10-point clinically significant difference in breast symptoms score). II. To compare PBT vs tailored photon RT in terms of a) Early (<6 months post RT) effects including skin, lung and oesophageal toxicity, and fatigue and b) 2 and 5-year skin, breast/ chest wall/ reconstructed breast, rib and shoulder toxicity. III. To assess patients' acceptance of randomisation to PBT versus tailored photon RT.
TRIAL DESIGN	Phase III multi-centre randomised controlled trial with internal pilot.
TRIAL POPULATION	Patients undergoing adjuvant radiotherapy for breast cancer with around 2% or higher estimated absolute lifetime risk of radiation-induced late major cardiac event based on anticipated mean heart dose (estimated using wide-tangent field placement in breath-hold) together with cardiac risk factors. Eligible patients will predominantly be those requiring RT to the internal mammary nodes (IMN) and will also include patients with unusual anatomy (e.g. pectus excavatum).
RECRUITMENT TARGET	192 patients (1:1 allocation) provide 91% power overall to show a difference in mean heart dose of >1Gy and non-inferiority of PBT in 2-year patient-reported breast symptoms (<10-point clinically significant difference).
TRIAL TREATMENT	Patients will be randomised in a 1:1 ratio to the following: **Experimental intervention:** PBT 40 Gy (relative biological effectiveness, RBE) in 15 fractions over 3 weeks. **Control:** Tailored photon RT (intensity-modulated arc therapy ideally delivered in deep-inspiratory breath-hold) 40 Gy in 15 fractions over 3 weeks. Treatment allocation will be by minimisation using the following balancing factors: IMN RT, randomising centre, type of primary surgery, breast reconstruction and need for tumour bed boost. Tailored photon RT will ideally be delivered at patients' local RT centre, and PBT in either Manchester or London depending on proximity and availability of treatment slots within the required

	timeframe. A simultaneous integrated boost to the tumour bed and/or IMN will be given where indicated in both groups.
CO-PRIMARY ENDPOINTS	Mean heart dose; patient-reported normal tissue toxicity in the breast (EORTC QLQ-BR23 breast symptoms score) at 2 years.
SECONDARY ENDPOINTS	Dose to organs at risk and normal tissues, early and late toxicity, health-related quality of life, health economic consequences, receipt of allocated intervention, changes to planned RT pathway (including delays and re-planning), second primary cancers, recurrence and survival, major cardiac events.
MECHANISTIC SUB-STUDY	Aims to test internationally developed models of relative biological effectiveness (RBE) for PBT by comparing calculated normal tissue doses with outcomes i.e. post-treatment changes in lung and rib density on CT. Will also compare planned and accumulated doses to the heart and target volume for PBT versus photons. Mechanistic outcomes: change in median lung Hounsfield Units per Gy on CT from baseline to 2 years; differences in planned versus accumulated mean heart dose for PBT versus standard RT; in patients randomised to PBT, correlation of RBE-weighted dose maps for the RBE models with radiological changes in lungs and ribs.
PBT TRIALS RECRUITMENT STUDY	An embedded 'Study within a Trial' (SWAT) will utilise a questionnaire to identify barriers to recruitment for PBT trials, assess the accessibility of PBT for the target population, and assess the generalisability of results from PBT trials to the target population.
FOLLOW UP	Clinical follow-up to 5 years after randomisation will be at patients' local RT centre for both PBT and RT groups.

TRIAL SCHEMA

PARABLE (Proton beAm theRapy in patients with Breast cancer: evaluating early and Late Effects)

Patients undergoing adjuvant radiotherapy for breast cancer with around 2% or higher estimated absolute lifetime risk of radiation-induced late major cardiac event based on anticipated mean heart dose (estimated using wide-tangent field placement in breath-hold) together with cardiac risk factors



*Simultaneous Integrated Boost to tumour bed allowed in either arm: declared prior to randomisation

Baseline assessments (at local RT centre)

- Patient-reported outcomes (PRO) of health-related quality of life (QoL) including EORTC QLQ-C30 & QLQ-BR23, Body Image Scale, protocol-specific items, EQ-5D-5L; healthcare resource use
- Baseline signs & symptoms (CTCAE v5.0, RTOG)
- Medical history
- Weight & height
- Biological sample collection (optional)

On-treatment assessments (Weeks 1-3)

- Early skin & oesophageal toxicity (CTCAE v5.0) & adverse events
- PRO of early toxicity & QoL including skin, breast pain & swelling, fatigue, insomnia, mouth/throat sores, cough & breathlessness, emotional, cognitive, sexual & social function

Post-treatment assessments

2 weeks' post treatment and then weekly until acute local symptoms ≤1 (clinician reported)

- Early skin & oesophageal toxicity (CTCAE v5.0) & adverse events

Weekly (from week 4) until week 12

- PRO of early toxicity & QoL including skin, breast pain & swelling, fatigue, insomnia, mouth /throat sores, cough & breathlessness, emotional, cognitive, sexual & social function (& EQ-5D-5L, healthcare resource use at 3 months)

Follow-up assessments (post-treatment assessments at local RT centre for all patients)

- **3, 6 and 12 months post-treatment**
- Cough & breathlessness (RTOG)
- **6, 12, 24 and 60 months post-treatment**
- PRO of late toxicity & QoL including EORTC QLQ-C30, QLQ-BR23, Body Image Scale, protocol-specific items, EQ-5D-5L; healthcare resource use
- **24 months post-treatment**
- Chest CT scan (non-contrast enhanced)
- Biochemistry profile (thyroid function test)
- **12, 24, 36, 48 and 60 months post-treatment**
- Clinician-reported late toxicity
- Assessment for recurrence & survival

1. INTRODUCTION

1.1. Background and study rationale

1.1.1. Why is this research needed?

There is a small but important group of patients with breast cancer whose overall health is underserved by current standard-of-care radiotherapy (RT) due to unacceptable levels of cardiac risk. In the UK, this population is around 500 new patients per year.

Proton beam therapy (PBT) provides a solution to tackle the unmet need for this patient group. The UK has 2 NHS PBT facilities, providing a unique opportunity to investigate the potential benefit of PBT compared with RT within small, well-defined patient groups.

The PARABLE trial has been designed with a primary outcome analysis at 2 years' follow-up, and therefore has potential to change practice early for these patients in the UK and internationally. The mechanistic study will provide added value for the wider cancer population requiring PBT (not just breast cancer) by increasing understanding and application of biological models to refine PBT planning and delivery. A 'Study Within A Trial' will be embedded within PARABLE enabling better reporting of outcomes for future breast cancer RT trials.

1.1.2. What is the nature of this unmet health need?

Breast cancer is the commonest cancer in women and is heterogeneous in terms of molecular subtype and stage of presentation, each conferring very different risks of relapse for individual patients. RT is essential to the often curative pathway for around two-thirds of patients with breast cancer. Modern breast RT reduces the relapse risk by half across all breast cancer groups where it is indicated and can improve survival with few lasting side effects for the majority of patients (1-4). The absolute benefit of RT is dependent on absolute risk thus is greater in patients at higher risk of relapse. Breast RT consists of irradiation of breast/chest wall for all patients, but a subgroup also receive axillary nodal RT with a smaller subgroup of higher risk patients also receiving RT to internal mammary nodes (IMN)(5).

Three landmark studies showed that IMN RT provides benefit to women with higher risk breast cancer (6-8). These comprised eligible patient groups with quite different risks of relapse, with the Danish study recruiting higher risk node positive patients that are closely aligned to UK indications for IMN RT (9). The Danish study demonstrated a 3.7% absolute overall survival improvement at a median follow-up of 8.9 years, which increased to around 10% for the subgroup of patients with $\geq$4 positive axillary lymph nodes (7). This shows a remarkable potential absolute survival benefit with IMN RT and compares very favourably with the gains achieved using expensive systemic therapies.

The benefit of IMN RT can however come with an increased risk of side effects. In particular, the IMN is close to the heart and it can be difficult to avoid cardiac exposure completely when irradiating it. Any RT dose to the heart can result in an increased risk of symptomatic heart damage many years later (10), thereby potentially offsetting the survival advantage, especially in younger patients and those with co-morbidities. With modern RT, the benefit of IMN RT far outweighs the small increased risk of cardiac mortality for most patients. Of note, all 3 IMN RT studies showed no excess cardiac morbidity. However, with a median follow up of 9-10 years, relatively modest numbers and the patient population comprising women largely fit aside from their breast cancer, it would be unlikely to detect a difference in major clinical cardiac events that typically occur decades after RT.

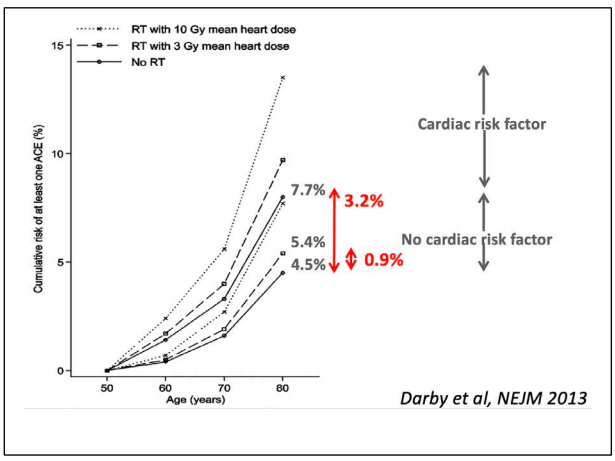
What is not evident from simply reviewing overall trial results is that for an important subgroup of patients with unusual chest wall shape and/or underlying cardiovascular risk factors standard RT techniques struggle to treat the IMN without significantly increasing patients' heart doses. For these patients, compromised RT could reduce the chance of cure and/or increase risk of serious heart damage many years later. Therefore, the balance of risks and benefits are less favourable with standard RT in this important group of patients.

Heart damage is still an important issue with modern breast cancer RT techniques

The literature review was carried out by Dr Carolyn Taylor who has specialist knowledge in this area (11). The risk of major coronary events in patients irradiated for breast cancer increases by 7.4% per Gray mean dose to the whole heart (10), with no evidence of a threshold below which there is no risk, suggesting that any dose to the heart confers some RT risk. An international case-control study with 963 events from a population of around 35,000 women who received breast RT demonstrated that mean heart dose predicts for late major cardiac events. In addition, a cross-sectional study of cardiac segment injury after breast cancer RT has shown that both myocardial and coronary arterial structures are sensitive to RT (12). This suggests that heart dose should be minimised as much as is feasible without compromising target coverage. In the UK, cardiac sparing techniques are widely used. For example, the heart may be shielded using multi-leaf collimation (13), or drawn away from the treatment fields using breath-hold (14). The absolute 30-year risks of RT-induced heart disease for most patients treated with these modern cardiac sparing regimens are likely to be less than 2% (15).

Nonetheless, for some patients the risks are higher than this, particularly where IMN RT is recommended. RT regimens for treating IMN include 3D-conformal wide tangents with deep inspiration breath hold and rotational intensity modulated RT. The average heart doses received from these modern IMN RT techniques range between 2 and 5 Gy (16, 17), with some patients receiving higher doses (>5 Gy)(18). Many of these patients would have a risk of RT-related heart disease exceeding 2%.

Risks of major coronary events can be estimated from the relative heart dose-response relationship of 7.4% per Gray, applied to European population data (10). The RT-related risks are higher for women with cardiac risk factors before their RT because radiation multiplies a woman's pre-existing cardiac risk. For example, for women treated with RT at age 50 years with none or ≥1 cardiac risk factors who receive mean heart doses of 2 to 4 Gy, their estimated absolute risks range from 0.6 to 2.2% and for women receiving mean heart doses of 4 to 6 Gy, risks range from 1.3 to 3.3% ((10) and Figure 2 (adapted below)).



Adapted from Darby et al NEJM, 2013 with permission from Dr Carolyn Taylor. Risks by age 80 of RT at age 50 years: results are shown for a woman 50 years old at the time of breast cancer diagnosis who received either no RT or RT with a mean dose to the heart of 3Gy or 10Gy. Results are shown for women with no cardiac risk factors and for those with one or more cardiac risk factors. Acute coronary events (ACE) are nonfatal or fatal major coronary events or unstable angina.

Recent evidence suggests that radiation risks may actually be higher than this for some women. Two population-based studies have suggested that chemotherapy (commonly required in patients for whom IMN RT is indicated) increases the slope of the radiation-dose response relationship (19, 20). A recent study of 2 million women treated for breast cancer (19) suggests that the slope of the heart radiation dose-response relationship is more than twice as steep for women who receive their RT when aged less than 40 years, hence the estimated absolute lifetime RT risks for these young women may actually be much higher than those shown above.

1.1.3. What is the size of the problem and how was this derived?

In the UK, around 33,000 patients/year receive breast RT of whom around 4,000 are eligible for nodal IMN RT (5). Estimates are based on a study led by Dr Carolyn Taylor (Nuffield Department of Population Health, University of Oxford) and Dr Frances Duane (Dublin), in which RCR 2016 UK Breast RT Consensus (9) recommendations for IMN RT were applied to patient and tumour variables for 111,729 patients receiving breast RT in England between 2012 and 2016. An "in silico" RT planning study of 179 patients treated with loco-regional RT in 18 European departments (21) estimated that more than 20% of plans would fail internationally agreed RT dose tolerance levels. Given that only 2/3 patients in this study were planned with UK standard of care RT techniques (i.e. deep inspiratory breath-hold), a conservative estimate is that around 10% of patients' UK standard RT plans would fail these dose tolerance levels (i.e. around 400 women per year in the UK). By also including women with unusual chest wall shapes such as pectus excavatum (depressed sternum) in whom the majority of patients will fail heart constraints (18, 22), there are around 500 women per year in the UK who are underserved by current RT techniques. Given the rarity of male breast cancer, it is impossible to predict the unmet need for men in the same way. However, it is likely that a small proportion of men requiring breast radiotherapy will also fail the internationally agreed RT dose tolerance levels.

1.1.4. Risks and benefits of proton beam therapy for this patient group

A possible solution to the problem for this patient group emerges with the technical developments afforded by PBT. The physical properties of PBT allow a sharp fall-off in radiation dose between the chest wall/breast/lymph nodal regions (where we want dose) and heart, lungs, contralateral breast (where we do not want dose). Several PBT in silico "planning studies" have demonstrated that the planned PBT mean heart dose is considerably lower than with photon RT (17, 23-25). Proof of concept has been shown in small, non-randomised series, mainly from US, suggesting that a 5-week course of PBT to breast/chest wall and regional lymph nodes is safe, can reduce heart dose and has comparable short to medium toxicity compared with 5-week RT with low rates of local and distant relapse (23, 24, 26-35). As PBT enables full dose to the breast and nodes whilst aiming to reduce mean heart dose, it can be concluded that cancer outcomes with breast PBT will be maintained or even improved due to better dose coverage of breast and nodes. Given the extremely low event rates for local breast cancer relapse, it would be infeasible to test this endpoint within a randomised comparison of PBT versus photon RT.

There is a higher risk of a second primary breast cancer in young women (< 40 years) following RT if mean dose to a quadrant of the contralateral breast exceeds 1Gy (36). In the patient group eligible for PARABLE this is often exceeded as coverage to target and minimisation of heart dose may be prioritised. Use of PBT could decrease the risk of an upper inner quadrant contralateral breast cancer six fold (37). PBT may also reduce dose to lungs and oesophagus reducing the risk of late radiation-induced lung and oesophageal cancers (25). However, unlike risk of major cardiac events and heart dose, there are as yet no validated models to estimate these risks.

Despite these potential advantages of PBT there has nevertheless been some evidence from non-randomised studies of increased adverse effects in patients receiving PBT for breast cancer, including skin reactions (28, 29) and rib fractures (38, 39). PARABLE will enable randomised comparisons of early and late toxicities to assess non-inferiority and superiority of PBT versus photon RT.

1.1.5. Understanding the biological effects of PBT

It is known that lower *physical* radiation doses to normal tissues are achievable using PBT, but there is still more to be learnt about the complex *biological* effect of PBT compared with photon RT (known as relative biological effectiveness or RBE). Current clinical PBT planning systems assume that the biological effect of PBT is uniformly 10% higher than for RT, expressed as an RBE of 1.1. However, on-going research suggests that RBE is *variable* throughout the PBT path and is dependent on a number of factors. A report from the American Association of Physicists in Medicine (40) suggest that taking account of these factors using variable RBE algorithms could help "fine-tune" PBT planning to optimise tumour control whilst minimising side effects, but mechanistic studies are required before standard-of-care use.

A retrospective analysis of CT scans in breast cancer patients previously treated with PBT (41) has shown that, by quantifying asymptomatic lung changes, these CTs will provide a highly informative experimental model for testing different variable RBE algorithms. Furthermore, a retrospective study (39) correlating rib fracture location after PBT with dose predicted by different RBE algorithms suggests that a variable RBE model (the McMahon Linear Energy Transfer (LET) model (42)) is better able to predict rib toxicity than the clinically-used fixed RBE algorithm.

PARABLE includes an embedded mechanistic study that aims to improve understanding of the biological effects of PBT, with potential benefit to a wider cancer patient group. Radiological findings from the above retrospective studies will be validated in the trial using serial CT scans acquired pre- and post PBT/RT as part of clinical care. Variable RBE models broadly-speaking cluster into three groups based on the underlying assumptions of the model. At least one model from each of these clusters will be assessed: 1) McMahon LET model (42), 2) McNamara model (43) and 3) Microdosimetric-Kinetic model (44). By evaluating one model from each group, it is likely that differences in biological dose distribution predicted by the three models will be large enough to be assessed against CT changes in rib and lung. It is anticipated that the results will inform optimisation of future PBT planning for breast and other cancers where PBT is indicated and therefore improve patient care for a broader population (45).

A second aspect of the mechanistic study is to better understand and account for the impact of daily position and shape changes on PBT delivery. For photon RT, daily changes in patient position and shape are accounted for by adding a "safety" margin of a few mm around the breast and nodal regions. This approach is not applicable to PBT due to the nature of how the dose distribution changes with patient position. Instead plans are recalculated under a number of uncertainty scenarios (including position shifts of a few mm). Additionally, PBT plans are more sensitive to changes in anatomy, and it is anticipated that re-planning during the treatment schedule will be necessary in around 30% of cases. The study aims to better understand the effects of changes in patient shape/position to minimise re-planning and reduce inconvenience for patients and NHS cost.

1.1.6. Understanding the patient impact of early toxicity from breast RT/PBT

Acute side effects from breast RT may have a major impact on patients' quality of life. Traditionally, early RT side effects have been inconsistently reported due to (i) a lack of a validated scale for patient-reported breast RT early toxicity (ii) under-reporting of side effects when relying on clinician reports alone (46), and (iii) limited follow up within 3 months of completion of breast RT. Patient diaries during and shortly after RT were used in an acute toxicity sub-study within the FAST-Forward trial, but this was limited to skin toxicity (47).

Patient advocates have highlighted the importance of a wider range of early side effects that can impact significantly on patients' lives at a very vulnerable time, including: (i) sore throat affecting eating (more common in patients receiving regional lymph node irradiation), (ii) fatigue, which may affect ability to work, exercise and carry out their normal activities and (iii) self-confidence and self-esteem.

A 'Study Within A Trial' embedded within PARABLE will explore user acceptability, completeness, quality and consistency of different data ascertainment methods for capturing early RT toxicity, including preliminary testing of electronic patient-reported outcomes (ePRO). This will be incorporated into PARABLE in a future protocol amendment.

2. TRIAL AIMS AND OBJECTIVES

2.1. Trial Aim and Hypothesis

PARABLE aims to compare PBT with tailored photon RT (intensity-modulated arc therapy ideally in deep-inspiratory breath-hold) for an important breast cancer subgroup currently underserved with RT. It hypothesises that PBT will reduce mean heart dose – an early predictor for serious RT-induced heart toxicity many years later – without increasing shorter-term side effects.

2.2. Trial Objectives

I. To test whether proton beam therapy (PBT) a) Can reduce mean heart dose to <1Gy in patients who would have incurred a mean heart dose of typically >3Gy from photon radiotherapy thereby contributing to around 2% or higher estimated absolute lifetime risk of radiation-induced late major cardiac event and b) Is non-inferior to tailored photon radiotherapy (RT) (ideally intensity-modulated arc therapy (IMAT) delivered in breath-hold) in terms of 2-year patient-reported breast symptoms (<10-point clinically significant difference in breast symptoms score).

II. To compare PBT vs tailored photon RT in terms of a) Early (<6 months post RT) effects including skin, lung and oesophageal toxicity, and fatigue and b) late (≥6 months) skin, breast/ chest wall/ reconstructed breast, rib and shoulder toxicity.

III. To assess patients' acceptance of randomisation to PBT versus tailored photon RT.

2.3. Secondary Objectives

To compare PBT vs tailored photon RT in terms of:

- Doses to specified organs at risk
- Acute and late normal tissue toxicity
- Changes to planned RT pathway
- Cancer outcome measures

- Health economic consequences

2.4. Mechanistic Study Aims and Objectives

Embedded mechanistic research will test internationally developed models of relative biological effectiveness (RBE) for PBT by comparing calculated normal tissue doses with outcomes i.e. post-treatment changes in lung and rib density on CT.

It is hypothesised that 1a) asymptomatic radiological changes in lung density at a given dose will be higher for PBT versus photon RT, validating findings from retrospective data series suggesting that end of range RBE>1.1, and 1b) variable RBE models will better predict radiological changes in lung and ribcage than standard RBE models of 1.1.

A second aspect of the mechanistic research will compare planned and accumulated doses for PBT versus photons. It is hypothesised that, using uncertainty scenarios(48) in the PBT planning pathway, accumulated dose to the heart and to the target volume will correlate as closely with planned dose as accumulated and planned doses do for standard RT.

3. TRIAL DESIGN

PARABLE is a phase III multi-centre parallel group randomised controlled trial comparing PBT vs tailored photon RT (each delivered in 15 fractions over 3 weeks). The trial includes an internal pilot to assess overall recruitment and acceptance of allocated treatment, an embedded mechanistic study and a study-within-a-trial (SWAT) exploring possible barriers to recruitment for PBT trials.

Eligible patients will be those undergoing adjuvant radiotherapy for breast cancer with around 2% or higher estimated absolute lifetime risk of radiation-induced late major cardiac event based on anticipated mean heart dose from a field-based placement in breath-hold together with cardiac risk factors. Eligible patients will predominantly be those requiring IMN RT and will also include patients with unusual anatomy (e.g. pectus excavatum).

Patients will be randomised in a 1:1 ratio to the following: **Experimental intervention:** PBT RBE-weighted dose of 40 Gy in 15 fractions over 3 weeks. **Control:** Tailored photon RT (deep-inspiratory breath-hold and rotational intensity modulated RT) 40 Gy in 15 fractions over 3 weeks. Treatment allocation will be by minimisation using the following balancing factors: IMN RT, randomising centre, type of primary surgery, breast reconstruction and need for tumour bed boost.

Tailored photon RT will be delivered at patients' local RT centres and PBT in either Manchester or London depending on proximity and availability of treatment slots within the required timeframe. A simultaneous integrated boost to the tumour bed and/or IMN will be given where indicated in both groups.

Clinical follow-up to 5 years after randomisation will be at patients' local RT centres for both PBT and RT groups.

4. STUDY ENDPOINTS

4.1. Co-primary Endpoints

- Mean heart dose
- Patient-reported normal tissue toxicity in the breast (EORTC QLQ-BR23 breast symptoms score) at 2 years

4.2. Secondary Endpoints

- Dose to organs at risk and normal tissues
- Early and late toxicity
- Health-related quality of life
- Health economic consequences
- Receipt of allocated intervention (at least one fraction)
- Changes to planned RT pathway (including delays and re-planning)
- Second primary cancers (including contralateral breast, lung and oesophagus)
- Recurrence and survival
- Major cardiac events will be recorded, although are expected to be rare within the 5-year follow-up period

4.3. Mechanistic Endpoints

- Change in median lung Hounsfield Units per Gy on CT from baseline to 2 years for PBT versus photon RT
- In patients randomised to PBT, correlation of RBE-weighted dose maps for the 3 selected variable and standard RBE 1.1 models with radiological changes in lungs and ribs
- Differences in planned versus accumulated mean heart dose for PBT versus photon RT

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit 192 participants; 96 into each group of the study.

5.2. Source of Participants

Participants will be recruited from approximately 22 participating sites in the UK. Potential participants will be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

5.3. Inclusion Criteria

1) Age ≥18 years, female or male
2) Histologically proven invasive breast carcinoma treated with:
   a) Breast conservation surgery with axillary surgery (biopsy or dissection)
   OR
   b) Mastectomy with axillary surgery (biopsy or dissection)
   OR
   c) In the case of an occult breast primary, axillary surgery (biopsy or dissection) only is permissible
3) Recommended to undergo RT to the breast/chest wall +/- axilla +/- IMN

4) Estimated lifetime risk of radiation-induced late cardiac toxicity around 2% or higher*
   * Calculated from tables of mean heart dose, age and cardiovascular risk factors (pre-existing cardiac disease, other circulatory diseases, diabetes, chronic obstructive pulmonary disease, smoking, body mass index >30 kg/m^2)(10).
   N.B. Mean heart dose is estimated using wide-tangent field placement in deep inspiration breath hold (DIBH)) as this is the commonest technique for IMN RT in the UK and can be carried out quickly to ensure an efficient patient pathway.
5. Ability to provide written informed consent to participate in PARABLE

5.4. Exclusion Criteria

1) Definitive clinical or radiological evidence of metastatic disease.
2) Prior RT to the ipsilateral chest wall, breast and thorax.
3) Connective tissue disorders requiring active medical therapy. (Patients with a history of connective tissue disorders in whom a multidisciplinary team has agreed that the benefits of radiotherapy outweigh the risks may be included. Methotrexate and/or other immune therapies must be stopped during RT or PBT).
4) Concomitant TDM1 or capecitabine is not permitted. Refer to Section 11.5 for further details.
5) Breast tissue expander implants with integrated metallic injection ports are contraindicated and not permitted within PARABLE.

The eligibility of patients with a pacemaker/implantable defibrillator will be discussed on a case by case basis, as there are additional risks associated with proton beam therapy (e.g. neutron production) which must be accounted for. Not all device types/locations will be eligible for treatment with protons.

6. SCREENING

6.1. Screening Log

All participating sites will be required to keep a log of all patients recommended to undergo radiotherapy to the breast/chest wall with/without internal mammary node radiotherapy that are potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable)

This information will be used by the TMG to monitor recruitment activity. No patient identifiable data should be sent to ICR-CTSU at this stage.

6.2. Procedure for Obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current ethics approved PARABLE patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial, and the opportunity to ask any further questions.

No protocol-required assessments should be conducted until the PARABLE consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

6.3. Participation in other Clinical Trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in PARABLE even if they have participated in other clinical trials prior to recruitment.

Patients who have consented to participation in PARABLE may also wish to participate in other studies and this should be supported where possible. Participation in other research whilst patients are being treated and followed up within PARABLE will be considered on a study-by-study basis by the PARABLE Trial Management Group (TMG). In addition to the patient's wishes, the TMG's key concern will be whether such participation would compromise ascertainment of the PARABLE co-primary endpoints at the 2-year post treatment primary time point of interest.

7. PATIENT PATHWAY PRIOR TO RANDOMISATION

- Suitable patients can be identified in the local MDT, oncology clinics or at the time of radiotherapy planning as part of their standard of care.
- Patients recommended IMN RT and/or with unusual anatomy will be provided with an introductory information sheet prior to radiotherapy planning. This will provide further details of the PARABLE trial and information regarding the calculation of mean heart dose and potential trial suitability.
- Eligibility is determined using (i) mean heart dose estimated using wide-tangent field placement (in DIBH assuming the patient can manage it) as this is the commonest technique for IMN RT in the UK and can be undertaken relatively quickly to ensure an efficient patient pathway (ii) presence of absence of cardiovascular risk factors* and iii) patient age. Patients whose mean heart doses exceed the values in the table in appendix A1 will be those with a lifetime risk of radiation-induced late cardiac toxicity of around 2% or higher and will be eligible for PARABLE *

* Cardiovascular risk factors: pre-existing cardiovascular disease, diabetes, chronic obstructive pulmonary disease, active smoker, body mass index >30 kg/m^2(10)

- Following assessment of eligibility, the trial should be further discussed and the main PARABLE trial patient information sheet provided to the patient in the oncology clinic. <u>All patients</u> should be offered the additional generic information regarding travel and accommodation for proton beam therapy.
- Patients should be given at least 24 hours to consider participation in the trial, and typically be contacted the following day for their decision
- Patients should provide written informed consent to participate in the trial
- Trial specific pre-screening assessments should be completed to confirm eligibility for the trial
- Baseline assessments (i.e. PRO booklets) should be completed after consent but before randomisation.

8. RANDOMISATION

Patients must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

After RT planning at the local RT centre, sites will contact ICR-CTSU to obtain treatment allocation for a consented patient.

Patients should be randomised by emailing the ICR-CTSU randomisation service at:
randomisation-icrctsu@icr.ac.uk
09.00-17.00 (UK time) Monday to Friday

Randomisation should take place as close to the planned start date of treatment as possible. An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for trial and for any sub-studies;
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number
- IMN RT (yes/no), randomising centre, type of surgery (breast conserving surgery with axillary surgery / mastectomy with axillary surgery / axillary surgery only), breast reconstruction (none/autologous/non-autologous) and requirement for tumour bed boost irradiation (yes/no).
- Calculated lifetime risk of radiation-induced heart disease based on wide-tangent plan

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation.

ICR-CTSU will send confirmation to the data management contact at the recruiting site to confirm a patient's entry into the trial.

9. PROTON BEAM THERAPY: ACCOMMODATION AND TRAVEL

9.1. Accommodation

Patients allocated to PBT will need to visit one of the two national NHS proton centres for treatment planning and the treatment itself. The proton centres are located at The Christie NHS Foundation Trust in Manchester and University College London Hospitals NHS Foundation Trust in London. Patients do not have to stay in the provided accommodation if they prefer to return home every day following their treatment. The NHS will provide accommodation for the pre-assessment visit and duration of radiotherapy for one patient plus one partner or carer. The accommodation arrangements will be made by the key worker from the proton centre and only accommodation suggested by the proton centre will be funded by the NHS. Further details about the accommodation should be provided to the patient at the time of consent.

9.2. Travel

Patients will need to make their own travel arrangements. The assigned key worker should discuss the travel arrangements with the patient and answer any questions that the patient may have.

Economy travel expenses for patients and/or carers staying in the provided accommodation for the proton centres will be reimbursed by the ICR-CTSU from a grant from Breast Cancer Now in accordance with specific terms and conditions detailed in the 'Guidance on the Reimbursement of Travel Expenses for the PARABLE Study'. The guidance will be provided to participating centres by ICR-CTSU and should be given to all patients prior to consent.

Help with travel costs for those with a low income in both the proton and photon treatment groups not staying in the provided accommodation for the proton centres may be available e.g. from the NHS Healthcare Travel Costs Scheme.

10. TRIAL ASSESSMENTS

10.1. Baseline Assessments (Pre-randomisation)

The following assessments should be conducted prior to randomisation

- Medical history (including specific risk factors for cardiovascular disease and RT toxicity)
- Weight and height
- Baseline signs and symptoms (CTCAE v5.0, RTOG)
- Patient-reported outcomes (PRO) of health-related quality of life (QoL) including EORTC QLQ-C30 and QLQ-BR23, Body Image Scale, protocol-specific questions relating to breast changes resulting from cancer treatments, PRO-CTCAE items, EQ-5D-5L, healthcare resource use to be collected prior to patient being aware of treatment allocation.
- Biological sample collection (tumour tissue collected from the diagnostic biopsy and/or surgery when requested and research bloods) for those patients providing optional consent

10.2. On-treatment Assessments

The following assessments should be conducted in weeks 1-3 on treatment

- Early skin and oesophageal toxicity (CTCAE v5.0) and adverse events (clinician reported)
- PRO of early toxicity and QoL including skin, breast pain and swelling, fatigue, insomnia, mouth /throat sores, cough and breathlessness, emotional functioning, cognitive functioning, sexual functioning, social functioning, EQ-5D-5L

10.3. Post-Treatment Assessments

The following assessments should be conducted 2 weeks' post-treatment (5 weeks from date treatment commenced) and then weekly until acute local symptoms ≤1

- Early skin and oesophageal toxicity (CTCAE v5.0) and adverse events (clinician reported). Assessments can be conducted remotely (i.e. via telephone) where patient attendance at clinic is not required.

The following assessments should be conducted weekly (from week 4) until week 12

- PRO of early toxicity and QoL including skin, breast pain and swelling, fatigue, insomnia, mouth /throat sores, cough and breathlessness, emotional functioning, cognitive functioning, sexual functioning, and social functioning, with the addition of EQ-5D-5L and healthcare resource use at the 12 week time point

On-treatment PRO/QoL booklets will be provided at participating centres for patients to complete in clinic. Post-treatment, patients will receive a questionnaire booklet to take home to complete from week 4 (from date treatment commenced) onwards (to 12 weeks). From the 6-month post-treatment follow-up assessment booklets will be sent to participants' homes directly by ICR-CTSU.

Where assessments are conducted remotely, any medical and/or psychological concerns identified should be followed by appropriate local clinical review. Patients completing questionnaire booklets are instructed to contact the local clinical team should they experience any distress or concerns resulting from the questions asked.

10.4. Post-treatment Follow-up

After treatment, clinical follow up should follow local guidelines. The study requires the following assessments to be conducted, timed from commencement of treatment:

3, 6 and 12 months post-treatment

- Cough and breathlessness assessment (RTOG). NB A 12-month assessment will only be required if the patient experienced symptoms at 3 and/or 6 months. Patients with confirmed pneumonitis will be followed up as per local protocol, with status documented at 12 months

6, 12, 24 and 60 months post-treatment

- PRO of late toxicity and QoL, including EORTC QLQ-C30, QLQ-BR23, Body Image Scale, protocol-specific questions relating to breast changes resulting from cancer treatments, EQ-5D-5L; healthcare resource use

24 months post-treatment

- Chest CT scan (non-contrast) for comparison with RT planning CT for mechanistic study to compare changes in ribs and lungs between PBT and tailored RT
- Biochemistry profile (thyroid function test)

12, 24, 36, 48 and 60 months post-treatment

- Clinician-reported late toxicity
- Assessment for recurrence and survival
- Recording adjuvant treatment administered (60 months)

10.5. Long term follow-up

Over the course of the study, the study team aim to transfer the provision of long term follow-up data (including data to determine recurrence outcomes) from research sites to routine data sources, providing the patient has given consent to do so and the required information can be accessed from routine sources. This is intended to relieve the burden of long term follow-up on research sites, and as a move towards this, data collection in the eCRF is minimal for patients in whom no disease event has occurred.

10.6. Procedure at disease recurrence/relapse or diagnosis of new primary cancer

If a patient has a local or distant relapse, new primary cancer (including contralateral breast, lung and oesophagus) the following procedures should be followed:

- Routine clinical, histological and imaging information should be collected on the disease relapse and entered into the relevant PARABLE eCRF
- Tumour tissue collected from the diagnostic biopsy and/or any applicable surgical procedures should be provided to the study central laboratory where requested and patient consent has been provided
- The patient should be treated according to local protocol for relapse/new primary cancer.

10.7. Discontinuation from Treatment

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression or recurrence
- Unacceptable toxicity
- Pregnancy

Participants who discontinue treatment should continue to be followed-up.

10.8. Discontinuation from Follow-up

If a patient no longer wishes to attend follow-up visits:
If a patient chooses to withdraw from further follow-up, centre personnel should confirm whether the patient simply no longer wishes to attend trial follow up visits but is happy for the information to be collected from other sources, or whether the patient has withdrawn consent for any further information to be sent to the ICR-CTSU. ICR-CTSU should be informed via completion of the relevant forms in the eCRF.

If a patient no longer wants their data to be sent to ICR-CTSU:
In the very rare event that a patient requests that the ICR-CTSU can no longer collect information on them from routine data sources, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing.

Schedule of Assessments

Visit/Assessment	Baseline Assessments (Pre-randomisation)	On-treatment			Post-treatment			Follow up							
		Time from start of radiotherapy													
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 12	6 months	12 months	2 years	3 years	4 years	5 years	Long term follow-up
Informed consent	x														
Randomisation checklist	x														
Baseline PRO/QoL measures, health resource usage	x														
Medical history	x														
Weight and height measurement	x														
Baseline signs & symptoms (CTCAE v5.0, RTOG)	x														
Early skin & oesophageal toxicity (CTCAE v5.0) and adverse events		x	x	x		x	x[a]								
PRO - Early toxicity		x	x	x	x	x	x[b]	x							
Cough & breathlessness assessment (RTOG)								x	x	x[c]					
PRO – Late toxicity									x	x	x			x	
Non-contrast chest CT scan											x				
Biochemistry profile											x				
Clinician-reported late toxicity										x	x	x	x	x	
Assessment for recurrence and survival										x	x	x	x	x	x
Recording adjuvant treatment administered														x	
Biological sample collection (blood, diagnostic/relapse tumour tissue)[d]	x														

Footnotes

[a] Collected week 2 post treatment (week 5) and then weekly until acute reaction ≤1

[b] Collected week 1 post treatment (week 4) until week 12

[c] Only if patient symptomatic at 3 and/or 6 months

[d] Blood samples will be requested at baseline from all consenting patients (optional); where applicable and consent has been obtained, tumour tissue (diagnostic and relapse) may be requested.

11. TRIAL TREATMENT

11.1. Treatment Timelines

Radiotherapy should commence as soon as possible and ideally within 4 weeks of randomisation.

11.2. Radiotherapy Planning and Treatment

Patients entered in the PARABLE trial are randomised to receive either proton beam therapy (PBT) at The Christie (Manchester) or UCLH (London), or intensity modulated arc radiotherapy (IMAT) ideally in DIBH at their local radiotherapy centre. Radiotherapy imaging, positioning, outlining, planning and treatment (including verification) should be carried out in accordance with the guidelines in the current version of the radiotherapy planning document, available on request from ICR-CTSU (parable-icrctsu@icr.ac.uk).

For PBT and IMAT, the treatment prescription is:

- 40 Gy (RBE-weighted dose for PBT) in 15 fractions (2.67 Gy (RBE-weighted dose for PBT) per fraction) over 3 weeks
- Where indicated, a simultaneous integrated boost to tumour bed of 48 Gy (RBE-weighted dose for PBT) in 15 fractions (3.2 Gy (RBE-weighted dose for PBT) per fraction) over 3 weeks and/or simultaneous integrated boost to IMN of 48 Gy (RBE-weighted dose for PBT) in 15 fractions (3.2 Gy (RBE-weighted dose for PBT) per fraction) over 3 weeks

11.3. Treatment Scheduling and Gaps

Treatment can start on any day of the week. Patients should not have a break in treatment where possible. Where interruptions are due to breakdown or unavailability of the treatment machine, patients should be transferred to a matched treatment machine in the first instance.

Where this is not possible, a gap of up to 5 consecutive days is acceptable in the event of machine service or breakdown. If the treatment machine is unavailable for more than 48 hours, please contact the QA team (enh-tr.parableqa@nhs.net) and notify the PARABLE trial manager at parable-icrctsu@icr.ac.uk

11.4. Concomitant Therapy

Due to increased risk of pneumonitis with TDM-1, it is recommended that patients treated in PARABLE should not receive concomitant TDM-1 alongside IMAT or PBT. Concomitant capecitabine is also not permitted. Concomitant endocrine therapy, trastuzumab and pertuzumab *are* permitted. Please contact the ICR-CTSU if any clarification around new drugs required.

Otherwise, all medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. All concomitant medications must be recorded in the patient's notes.

11.5. Non-permissible Medications/Therapies

As above, concomitant Trastuzumab emtansine (TDM-1) and/or capecitabine are not permitted alongside IMAT or PBT.

12. Radiotherapy Quality Assurance (QA)

The radiotherapy quality assurance (RT QA) programme for the PARABLE trial has been designed and will be implemented by the National Radiotherapy Trials QA (RTTQA) Group. The components of the PARABLE QA programme are described in the PARABLE Radiotherapy Planning and Delivery guidelines ("Quality Assurance (QA) pack").

The full details of the programme are available on the RTTQA group website (www.rttrialsqa.org.uk).

13. Safety Reporting

13.1. Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the first study intervention and within 30 days of the last treatment administration and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Progression of the indicated disease, death due to progression of the indicated disease and planned hospital admissions (e.g. for surgery) are not considered SAEs and do not need to be reported as such but should be reported on the appropriate eCRF as required.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the trial treatment, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial treatment
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Related **Unexpected Serious Adverse** Event
An adverse event that meets the definition of serious and is assessed by the CI or nominative representative as:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event that is not considered to be an expected occurrence by the Chief Investigator

13.2. Reporting Adverse Events to ICR-CTSU

Any toxicity, sign or symptom that occurs after commencement of radiotherapy treatment and within 12 weeks of the last administration of radiotherapy treatment, which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant eCRF and submitted to ICR-CTSU.

The severity of AEs should be graded according to the NCIC-CTC criteria version 5. For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

13.3. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs after the commencement of radiotherapy treatment and up to 30 days following the last administration of radiotherapy treatment must be reported.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the PARABLE SAE form and emailing to:

The ICR-CTSU safety desk
sae-icr@icr.ac.uk
For the attention of the PARABLE Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.

13.4. Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.)

SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 11.5).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

13.5. Expedited Reporting of Related Unexpected SAEs

If an SAE is identified as being related and unexpected by the Chief Investigator it will be reported by ICR-CTSU to the main REC, the Sponsor and all other interested parties within 15 days of being notified of the event.

The Principal Investigators at all actively recruiting sites will be informed of any related unexpected SAEs occurring within the trial at appropriate intervals.

13.6. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator or designee becomes aware of the outcome.

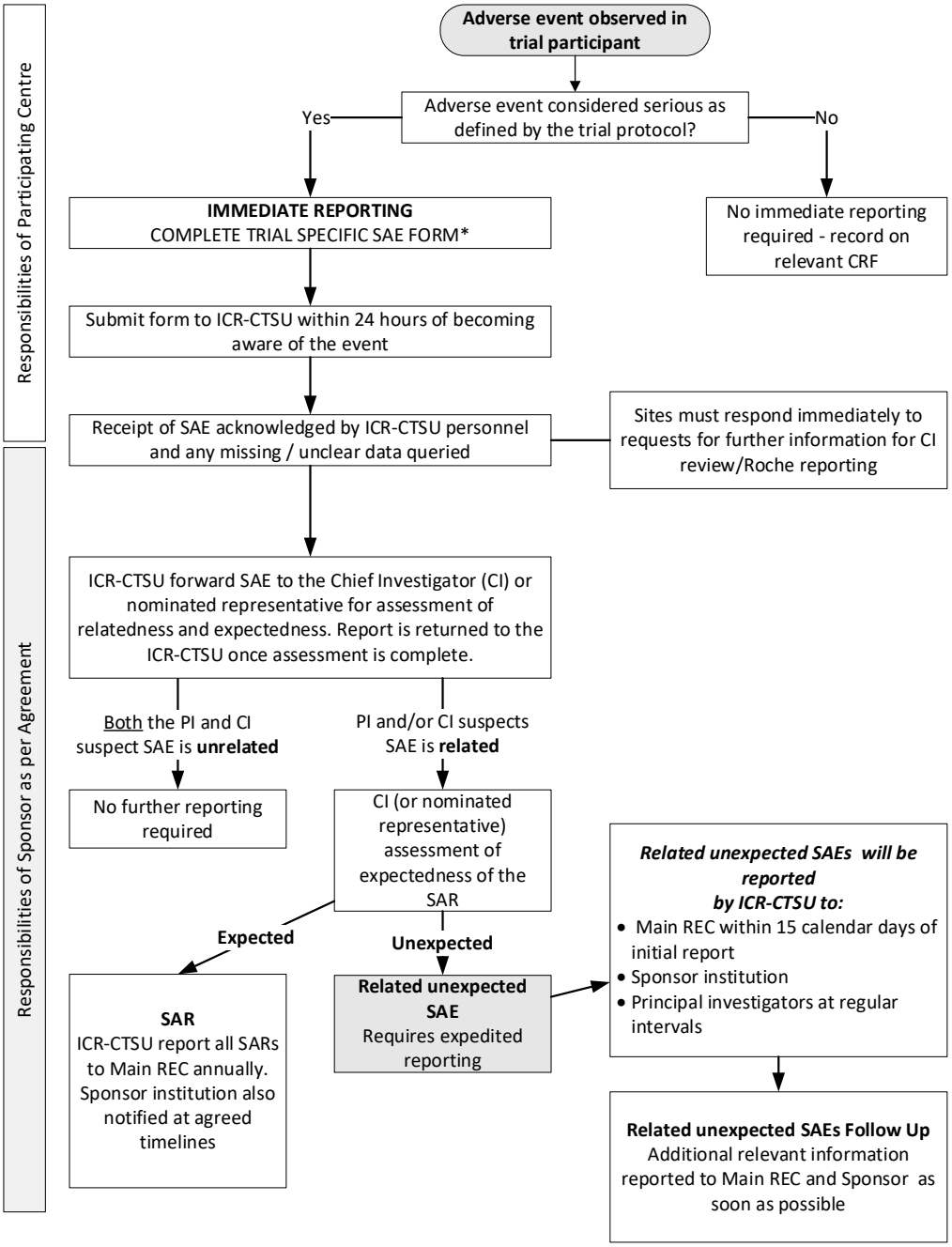
13.7. Annual Safety Reporting

An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor at the end of the reporting year. This will include data about related unexpected SAEs and whether any safety concerns have arisen during the reporting period.

13.8. Reporting Pregnancies

If any trial participant becomes pregnant while receiving trial treatment or up to 90 days after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 1: Flow diagram for SAE reporting, and action following report



All SAEs should be followed up until resolution.

14. STATISTICAL CONSIDERATIONS

14.1. Statistical Design and Sample Size Justification

Sample size justification for co-primary outcomes

The sample size requirements are driven by the co-primary outcome of patient-reported 2-year breast symptoms, hence this is considered first. A total of 192 patients (96 in each randomised group) would provide 92% power to exclude a 2-year mean breast symptoms subscale score (from EORTC QLQ-BR23) at least 10 points higher for PBT compared with tailored RT (assuming standard deviation (SD) =19 and 1-sided α=0.025 as testing for non-inferiority). Non-inferiority of PBT will be concluded if the upper 95% confidence limit for the difference between mean breast symptoms scores is <10. The sample size allows for 10% unevaluable for patient-reported outcome at 2 years, from experience with previous breast RT trials. A 10-point difference is usually considered a minimally important difference for EORTC quality of life scores.

A sample size of 192 patients provides ~99% power to detect a difference in mean heart dose of at least 1 Gy between PBT and tailored RT (assuming SD =1 Gy and 2-sided α=0.05); 1 Gy reduction in mean heart dose for PBT corresponds to an estimated 7.4% reduction in rate of major coronary events(10). The effect of PBT versus tailored RT should be shown for both co-primary outcomes in order to establish clinical benefit; the conjunctive power for this overall assessment is 91% (100 x 0.92 x 0.99).

Sample size justification for mechanistic outcomes

Sample size calculations for the mechanistic study are primarily based on validating published findings suggesting end of range RBE>1.1(41). This study compared pre- to post-treatment radiological lung changes in Hounsfield Units (HU) per Gray (HU/Gy) (RBE) between PBT and photons (N=10 in each group), with estimated mean difference of -1.08 (for PBT vs RT) and SD =1.1 (standardised effect size 0.98). Compared with Underwood's retrospective study, PARABLE's harmonised, prospective imaging will provide a far improved methodology for detecting post-treatment HU changes, hence it is possible that anticipated effect sizes in PARABLE may be larger than those in Underwood's study. Allowing for 10% unevaluable at 2 years, 96 patients per group (192 total) provides 90% power to detect standardised effect sizes >0.5 (mean difference >0.55 HU/Gy, SD 1.1) in terms of radiological lung changes from pre- to post-treatment, comparing PBT and tailored RT (2-sided α=0.05).

Sample size justification for the other mechanistic hypotheses is as follows:
96 patients in the PBT group will provide >90% power to detect standardised effect sizes >0.4 in terms of mean differences in radiological changes in lung and ribcage(39) between each of the 3 alternative RBE models versus 1.1 RBE model (PBT patients only). This assumes use of a paired t-test with 2-sided α=0.017 to account for the 3 pairwise comparisons, and allows for 10% unevaluable at 2 years.

A total of 192 patients (96 per group) provides 94% power to test non-inferiority of PBT compared with RT in terms of relative difference between planned and accumulated mean heart dose assuming 9% for tailored RT and aiming to exclude >10% for PBT, allowing for 10% unevaluable at 2 years (SD = 2% and 1-sided α=0.05).

14.2. Treatment Allocation

Patients will be allocated to PBT (in Manchester or London) versus tailored RT at local centre in a 1:1 ratio. Treatment allocation will use a minimisation algorithm with a random element, to ensure balanced distributions of clinically important factors (balancing factors) between treatment groups. Balancing factors will include IMN RT (yes/no), randomising centre, type of surgery (breast conserving surgery with axillary surgery / mastectomy with axillary surgery / axillary surgery only), breast reconstruction (none/autologous/non-autologous), and need for tumour bed boost.

14.3. Endpoint Definitions

14.3.1. Co-Primary endpoints

• Mean heart dose from treatment plan (PBT or VMAT)
• Patient-reported normal tissue toxicity in the breast (EORTC QLQ-BR23 breast symptoms score) at 2 years

Mean heart dose is a predictor for late major coronary events, with an estimated increase in risk of major coronary events in patients irradiated for breast cancer of 7.4% per Gray mean dose to the whole heart and no evidence of a threshold below which there is no risk.

The EORTC QLQ-BR23 is a validated quality of life tool widely used in breast cancer patients across disease stages and treatment modalities, comprising 4 symptom scales (breast symptoms, arm symptoms, systemic therapy side effects, upset by hair loss) and 4 functional scales (body image, sexual functioning, sexual enjoyment, future perspective). Each scale ranges from 0-100, with higher scores indicating worse symptoms and better functioning respectively. The breast symptoms scale is a composite score encompassing breast pain, breast swelling, breast oversensitivity and skin problems on affected breast. Previous breast RT trials have shown 2-year toxicity to be a good marker for late toxicity, with relative differences between RT treatments changing little after 2 years although absolute rates increase for many years following RT.

14.3.2. Secondary endpoints

14.3.2.1 Dose to organs at risk and normal tissues

Mean lung and contralateral breast doses measured from the treatment plan (PBT or VMAT) will be reported.

14.3.2.2 Early toxicity and health-related quality of life

Early skin and oesophageal toxicity assessed by clinician-recorded CTCAE v 5.0 weekly on treatment, 2 weeks post-RT then weekly until acute reaction graded as 0 (none) or 1 (mild). Severe toxicity is defined as grade 3 or worse.

Patient-assessed early toxicity including skin, breast pain and swelling, fatigue, insomnia, cough and breathlessness, sore mouth/throat will be assessed using items from the PRO-CTCAE, EORTC QLQ-C30 and QLQ-BR23. Health-related quality of life will be assessed using items from the EORTC QLQ-C30 including cognitive functioning, emotional functioning, sexual functioning and social functioning. PRO

for early toxicity and health-related quality of life will be collected weekly on treatment and then weekly until week 12.
Scores from the EORTC questionnaires will be calculated according to established guidelines. The proportion of patients with moderate/marked effects for individual items from the questionnaires will be calculated. PRO-CTCAE has separate endpoints for each toxicity measuring severity of symptoms and interference with usual or daily activities, and uses the CTCAE grading scale, with severe effects defined as grade 3 or worse.

14.3.2.3 Late toxicity and health-related quality of life
Cough and breathlessness will be assessed by clinician-recorded RTOG at 3, 6 and 12 months. RTOG uses a similar scale to CTCAE, ranging from 0 (no symptoms) to 5 (death directly related to radiation effects); severe effects are defined as grade 3 or worse.

Late toxicity and health-related quality of life will be assessed by patients using PRO including EORTC QLQ-C30, QLQ-BR23, Body Image Scale and items capturing breast changes resulting from cancer treatments (established in previous trials). Questionnaires will be administered at baseline, 6, 12, 24, 60 months. Scores for the EORTC questionnaires and Body Image Scale will be calculated according to the relevant scoring manuals. The proportion of patients with moderate/marked effects for individual items from the questionnaires will be calculated.

Skin, breast / chest wall / reconstructed breast, rib and shoulder late toxicity will be assessed by clinicians using methodology established in previous trials at annual follow-up to 5 years. Effects are scored on a 4-point scale (none, mild, moderate, marked). The proportion of patients with moderate/marked effects for individual endpoints will be calculated.

The incidence of major cardiac events will be reported, defined as proportion of patients with atherosclerotic coronary heart disease or other heart disease death, myocardial infarction, coronary revascularisation, or hospitalisation for major cardiovascular event (heart failure, valvular disease, arrhythmia, or unstable angina). International Classification of Diseases (10th revision, I-20 to I-25 and I-30 to I-152)

14.3.2.4 Health economic consequences
Analysis will utilise the Healthcare resource use questionnaire developed for the trial and the EuroQol five-dimensional questionnaire (EQ-5D-5L). These will be collected at baseline, 3, 6, 12, 24 and 60 months.

14.3.2.5 Receipt of allocated intervention, delays and re-planning
The number and proportion of patients receiving their allocated intervention (at least one fraction of photon RT or PBT) will be considered for each trial arm, along with reasons, as a means of assessing acceptability of PBT to patients. The proportion of patients with a delay to photon RT or PBT exceeding 4 weeks' overall treatment time, and the proportion requiring re-planning will be presented.

14.3.2.6 Cancer disease outcomes
Incidence of second primary cancers (including contralateral breast, lung and oesophagus) will be defined as proportion of patients.

Loco-regional tumour control is defined as time from randomisation to loco-regional recurrence i.e. recurrence (or new primary) in ipsilateral breast or regional lymph nodes. Patients will be censored at time of death prior to loco-regional recurrence. Location of loco-regional tumour recurrence will also be of interest.

Disease-free survival is defined as time from randomisation to any recurrence (local, regional or distant), contralateral breast cancer or death from breast cancer. Patients will be censored at time of non-breast cancer death prior to recurrence or contralateral breast cancer.

Overall survival is defined as time from randomisation to death from any cause.

14.3.3. Mechanistic endpoints

14.3.3.1 Change in median lung Hounsfield Units per Gy on CT from baseline to 2 years

Lung density will be measured on baseline versus 2-year CTs and quantified using linear regression adjusting for mean lung dose using the methodology of Underwood[46].

14.3.3.2 Correlation of RBE-weighted dose maps with radiological changes in lungs and ribs

In patients randomised to PBT, doses to lungs and ribs on RBE-weighted dose maps for the 3 selected variable and standard RBE 1.1 models will be compared with radiological changes in lungs (lung fibrosis) and ribs (rib fractures and/or increased rib density). Candidate RBE models have been selected representing a phenomenological approach (McNamara model(43)), LET-weighted dose (McMahon(42)) and a mechanistic approach (Microdosimetric-Kinetic (44)).

14.3.3.3 Mean planned versus accumulated doses to heart and target tissues

For all patients treated in PARABLE, accumulated (i.e. delivered) dose will be calculated using deformable image registration and compared with dose from the planning CT in order to calculate percentage difference in dose.

14.4. Statistical Analysis Plan

<u>Statistical analysis plan for co-primary outcomes</u>

Analysis of the co-primary outcomes will take place once all patients have reached the 2-year follow-up time point (or are known to have ceased follow-up). Mean heart dose and mean 2-year breast symptoms scores will each be compared between PBT and tailored photon RT using a 2-sample t-test, and 2-sided 95% confidence intervals for the mean differences calculated. Non-inferiority of PBT for patient-reported breast symptoms at 2 years will be concluded if the upper 95% confidence limit for the difference between mean breast symptoms scores is <10; a superiority test will be carried out if

non-inferiority is shown. Although the primary analysis of the co-primary outcomes will be non-stratified, consideration will also be given in the statistical analysis plan to sensitivity analyses including adjustment for balancing and other prognostic factors. Mean heart dose data should be available for all trial participants, as this will be obtained from the RT treatment plans. Missing data for the patient questionnaires can occur in terms of missing responses to individual items or entire questionnaires not returned. The EORTC quality of life scoring manual specifies approaches for dealing with missing data. If a significant proportion of patients are not evaluable for 2-year patient-reported breast symptoms, missing data patterns will be assessed, e.g. by comparing characteristics of patients with and without 2-year questionnaires. If there appear to be differences between evaluable/non-evaluable patients, a sensitivity analysis for the co-primary patient-reported outcome assuming different missing data patterns may be performed.

Statistical analysis plan for secondary outcomes

Analyses of dosimetry outcomes (mean heart, lung and contralateral breast doses) will be done once all patients have completed their RT/PBT treatment. Analysis of mean lung and contralateral breast doses will use the same methods as described for mean heart dose.

Acute toxicity data will be analysed once all patients have reached 6 months after RT/PBT. Key time points for analysis of the other secondary outcomes including late toxicities and disease-related outcomes will be at 2 and 5 years.

Analyses of toxicity data will follow methods established in previous breast RT trials. Frequencies of early and late toxicities will be summarised at each time point and compared between treatment groups at specific time points using chi-squared test or Fisher's exact test as appropriate. Longitudinal models (e.g. generalised estimating equations) including all assessments over follow-up, and survival analyses of time to first moderate/marked adverse effect will be carried out with comparisons between treatment groups, and adjusting for balancing and other prognostic factors where appropriate. Event rates at key time points will be reported, with 95% confidence intervals.

Analyses of compliance (receipt of allocated intervention, delays and re-plans) will be largely descriptive, with proportions presented according to trial arm, along with 95% confidence intervals where appropriate.

Analyses of disease-related recurrence and survival outcomes will also be primarily descriptive due to rarity of events, which would likely preclude formal statistical comparisons.

Statistical analysis plan for mechanistic outcomes

Mechanistic outcomes will be analysed once all evaluable patients have reached 2 years' follow-up. Pre and post treatment median lung Hounsfield Units per Gy on CT will be compared between PBT and RT using the methodology of Underwood(41) and quantified using linear regression adjusting for mean lung dose. Candidate RBE models have been selected representing phenomenological approaches (McNamara model(43)) as well as different mechanistic approaches (McMahon(42) and Microdosimetric-Kinetic model(44)). Dose distributions incorporating each of the proposed RBE models will be calculated and associations with lung fibrosis and rib fractures assessed using multivariable logistic regression as per standard dose-volume/outcome modelling methodology. For

the comparison of planned and delivered dose to target and normal tissues, delivered dose will be calculated using deformable image registration and compared with dose from the planning CT in order to calculate percentage difference in dose. Non-inferiority of PBT compared with RT in terms of percentage difference between planned and accumulated dose will be tested using a t-test.

Analysis sets and subgroup analyses

All analyses will be on an intention to treat basis, including patients in the group to which they were randomised. Since protocol deviations may bias tests of non-inferiority hypotheses a sensitivity analysis of the co-primary patient-reported outcome will be done using the per protocol population excluding major treatment deviations; non-compliance will be carefully monitored during the trial.

The trial is not powered for formal subgroup analyses. However exploratory analyses will investigate differences between the treatment groups according to clinical groups including the balancing factors. Descriptive analyses will check for any differences between RT centres in terms of patient or treatment characteristics, or outcomes.

Full details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

14.5. Interim Analyses and Stopping Rules

There will be no formal interim analyses of outcomes; accumulating data will be reviewed at least annually by the Independent Data Monitoring Committee (IDMC). There will be no stopping rule as it is unlikely that there will be sufficient data for formal comparison.

14.6. Internal pilot

The internal pilot will assess trial progress at end of month 15 (9 months after accrual opens). Trial progress will be assessed by:

- Overall recruitment (total patients/month from expected 11 centres): red <2; amber 2-3; green >3
- Acceptance of randomised allocation: red <80%, amber 80-90%, green >90%

The internal pilot will be considered successful and the trial will continue as planned if both sets of criteria are “green”. Where both recruitment and acceptance of allocated treatment are red, discussions will be held with the funder and trial oversight committees to establish where amendments could be put in place to address these issues. Where recruitment or acceptance is amber or red, screening logs will be reviewed and centres surveyed to understand and address reasons behind this, and findings discussed with funder and trial oversight committees. If either remains red by month 21, the trial will be considered unfeasible. Where either remains amber, recruitment and/or acceptance will be reviewed 3-monthly until green.

15. TRIAL MANAGEMENT

15.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Clinical Trials Programme Manager and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

15.2. Trial Steering Committee (TSC)

The ICR-CTSU Breast RT Trials Steering Committee will provide strategic oversight of the study on behalf of the funder and sponsor. The TSC will meet at regular intervals, and at least annually. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

15.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a Chair and at least two further members with clinical or statistical expertise (at least one member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC.

The IDMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16. RESEARCH GOVERNANCE

16.1. Sponsor Responsibilities

The Sponsor of this clinical trial is the Institute of Cancer Research (ICR).

16.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site. The Principal Investigator is responsible for the trial team and trial conduct at the participating site.

17. TRIAL ADMINISTRATION & LOGISTICS

17.1. Site Activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity that takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

17.2. Investigator Training

Each centre should complete the comprehensive pre-trial section of the radiotherapy quality assurance programme prior to commencing recruitment, as detailed in the PARABLE Radiotherapy Planning and Delivery guidelines ("Radiotherapy Quality Assurance (RTQA) Pack"). In addition to this, again prior to commencing recruitment, centres will need to complete QA training in contouring and planning according to the schedule described in the RTQA pack.

17.3. Data Acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

Patient Reported Outcomes will be collected using paper questionnaires following current Standard Operating Procedures within ICR-CTSU. However, it may be possible to utilise electronic data collection systems in future when available. An embedded Study Within a Trial will explore options for collecting acute toxicity assessments from patients.

Radiotherapy treatment DICOM data will also be collected. Guidelines on DICOM data submission will be given in the PARABLE RTQA pack

17.4. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be

found, queries will be raised for resolution by the site. Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

17.5. On-Site and Remote Monitoring

On-site monitoring visits or remote monitoring sessions may be conducted by ICR-CTSU in order to review essential documentation and carry out source data verification to confirm compliance with the protocol, in accordance with the study monitoring plan. If an on-site monitoring visit/remote monitoring session is required, ICR-CTSU will contact the site to make the necessary arrangements Once a date has been confirmed, the site should ensure that full patient notes of participants, including electronic notes, selected for source data verification are available for monitoring. If any problems are detected during the course of monitoring activities, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

17.6. Completion of the Study and Definition of Study End Date

The study end date is deemed to be the date of last data capture.

17.7. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

18. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

18.1. Risk Assessment and Approval

This trial has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research.

18.2. Public and Patient Involvement

Patient advocates were involved in all aspects of the trial including study design/methodology, sample collection, patient information and consent forms and are represented on the TMG.

18.3. Ethics Approvals

The trial will not commence at any participating site until the required approvals are in place. ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee (REC) for multi-centre trials, HRA approval and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

18.4. Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with the UK Policy Framework for Health and Social Care and the principles of GCP.

18.5. Informed Consent

The Principal Investigator retains overall responsibility for the conduct of research at their site; this includes the taking of informed consent of participants. The PI must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to do so in accordance with the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki.

Patients should be asked to sign the current ethics approved PARABLE consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved PARABLE patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

18.6. Patient Confidentiality

Patients will be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU will require access to participants' hospital records for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

18.7. Data Protection

All investigators and trials staff must comply with applicable data protection laws at all times.

18.8. Liability

Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements.

19. FINANCIAL MATTERS

This trial is investigator designed and led. ICR has received funding from National Institute for Health Research (NIHR) for the central coordination of the trial. The trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio by virtue of its funding by the NIHR and for similar networks in the three devolved UK nations. NIHR CRN (and their equivalents in the devolved UK nations) resources should therefore be made available for the trial to cover UK specific research costs

20. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies. Authorship of all publication will usually be in accordance with ICMJE guidance.

No investigator may present or attempt to publish data relating to the PARABLE trial without prior permission from the TMG.

21. ASSOCIATED STUDIES

21.1. Translational Study

Subject to patients' written informed consent, baseline blood samples will collected for future translational sub-studies, which will be defined separately.

Subject to patients' written informed consent, archival tissue samples (FFPE blocks) of primary tumour collected at the time of diagnosis or any other applicable surgical procedures (including subsequent disease relapses or new primary cancers) will be requested. Associated information, including imaging scans carried out at the time of any relapse as part of standard care will also be requested.

Tissue samples are prospectively collected for use in future translational sub-studies which will be defined separately.

21.2. Study within a Trial (SWAT): PBT Trials Recruitment Study

PARABLE, along with other trials involving PBT, provides an opportunity to explore possible barriers to recruitment for PBT trials and to inform future trial design and development. An embedded 'Study within a Trial' (SWAT) will utilise a questionnaire to identify barriers to recruitment for PBT trials, assess the accessibility of PBT for the target population, and assess the generalisability of results from PBT trials to the target population.

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23. APPENDICES

A1 AGE AND RISK ADJUSTED TABLE FOR ASSESSMENT OF ELIGIBILITY

The table below shows Mean Heart Dose (MHD) Thresholds on the standard radiotherapy plan that confer around 2% or higher absolute risk of **radiation-related disease**: major cardiac event - MCE (including fatal) or unstable angina by age 80 years, adapted from Darby *et al* Appendix Table S13(10). Table S13 modelled the risks of receiving breast radiotherapy at age 40, 50, 60 and 70 years. The age groupings by decade in this table reflect these ages at the mid-point and include women <40 and >70 years.

Update to MHD thresholds in protocol v4.0
The PARABLE trial has been recruiting steadily using mean heart dose eligibility thresholds determined using data from Darby et al (2013). These were rounded up to the nearest 0.5Gray at the outset of the trial for simplicity. However, it has been noted that several patients just miss eligibility thresholds, as a result of the rounding, meaning that patients who could potentially benefit from PBT are unable to participate. In addition, the contribution of the breast tumour bed boost dose to the mean heart dose is not currently considered as it was felt, prior to the trial opening, that this was likely to be negligible. However, it has become apparent that some patients narrowly miss out on randomisation due to the combination of rounding down and omitting the small, but not insignificant, contribution of the breast tumour bed boost dose to the mean heart dose. A revised table has therefore been prepared with estimated mean heart dose thresholds to the nearest 0.1Gy and which takes account of the contribution of the breast tumour bed boost to mean heart dose. These changes should enable more women in the appropriate cardiac risk category to be included in the trial. There will be no impact on the statistical design of the trial.

Age (years) at study registration	**Mean heart dose (Gy) needed for around 2% or higher risk of radiation-related heart disease by aged 80 years**			
	No Cardiac Risk Factor		**At Least One Cardiac Risk Factor***	
	No boost[$]	Boost[$]	No boost[$]	Boost[$]
≤44[¶]	≥4 Gy	≥3.7 Gy	≥2.4 Gy	≥2.1 Gy
45-54	≥6 Gy[#]	≥6 Gy[#]	≥3.6 Gy	≥3.3 Gy
55-64	≥6 Gy[#]	≥6 Gy[#]	≥4.3 Gy	≥4.0 Gy
65+	≥6 Gy[#]	≥6 Gy[#]	≥5.3 Gy	≥5.0 Gy

[¶] Incorporating data for women <40 years (Henson et al)[(19)].
[#] Represents clinically acceptable threshold for mean heart dose based on RCR UK consensus[(9)].
[$] Represents boost to breast tumour bed only (ie does not refer to nodal boosts)

***Cardiac Risk Factors include:**

Pre-existing cardiac disease:
Myocardial infarction or coronary revascularisation procedure

Pericarditis, endocarditis, myocarditis
Cardiac valve disorders
Cardiomyopathy
Cardiac arrhythmia or conduction disorders
Heart Failure, including

- Confirmed diagnosis of heart failure in medical notes. This usually covers symptomatic patients with heart failure at any level of LVEF: heart failure with reduced ejection fraction (<40%), heart failure with mild reduced EF (40-49%) and heart failure with preserved ejection fraction (>50%). This is whether caused by cancer treatment or pre-existing prior to cancer therapy.
- Moderate or severe asymptomatic cancer therapy-related cardiac dysfunction. This includes patients who have asymptomatic LV dysfunction detected on surveillance and where their LVEF has fallen to <50% (40-49% = moderate, <40% = severe). They can be included if any history of CTRCD, even if recovered with cardiac treatment. These cases could all be classified as 'asymptomatic heart failure' and in the US would be Stage B heart failure(49).

Other Circulatory Diseases:
Hypertension
Cerebrovascular disease
Peripheral vascular disease
Pulmonary Embolism or Deep Vein Thrombosis (Long-line DVTs count as a cardiac risk factor, but pregnancy-related DVTs do not)

Other:
Diabetes
Chronic obstructive pulmonary disease
Body Mass Index >30 kg/m^2
Smoking: defined as long term continuous smoking in the year prior to study registration.

This list summarises the codes from International Classification of Diseases (10^{th} revision, I-00 to I-15 and I-20 to I-99) and risk factors used in model by Darby et al.

A2. MECHANISTIC SUB-STUDY

A2.1 PARABLE RBE Modelling

While PBT offers more conformal physical doses than conventional RT, the complex difference in the biological effect of a given dose of PBT vs RT (known as the Relative Biological Effectiveness, RBE) is less well known. Current clinical PBT practice assumes a fixed RBE of 1.1 for PBT. However, it is known that RBE depends on both the dose delivered and the Linear Energy Transfer (LET) of the protons that deliver the dose. Proton LET increases with decreasing particle energy: lower energy protons towards the end of their range have higher LETs and thus RBEs.

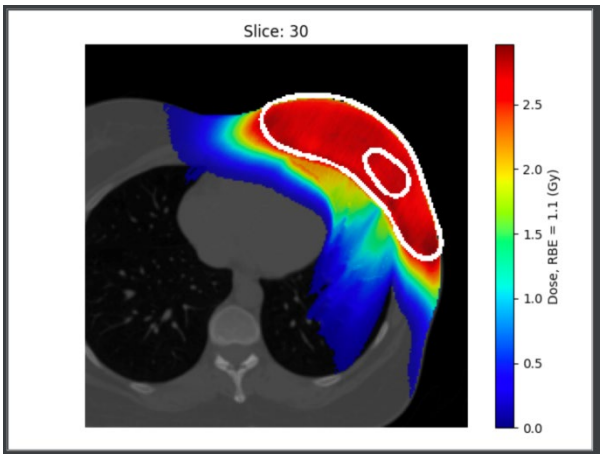
These effects are potentially significant because many protons reach end-of-range in normal tissues, and elevated RBEs in these tissues may impact significantly on side-effects. Variable RBE algorithms considering this could help fine-tune PBT planning, but these have seen limited clinical testing (30).

Recent prospective single cohort studies (31, 32) suggest that end of range increases in RBE may not be significant for breast patients. However, post-radiotherapy CT scans in breast patients can be used to quantify asymptomatic lung changes, providing a highly informative experimental model for measuring end-of-range RBE and testing variable RBE algorithms (33).

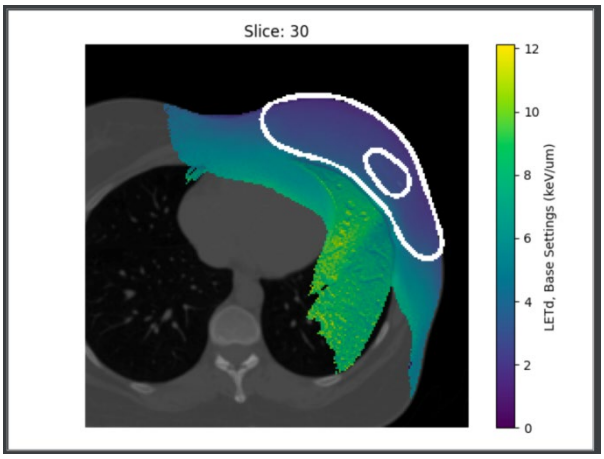
The PARABLE cohort offers a unique opportunity to address this mechanistic challenge, **to test internationally developed RBE models for PBT by comparing calculated doses with serial changes in lung density**. This will be achieved through a series of steps:

1. Apply validated Monte Carlo radiotherapy models to determine patient LET distributions

LET is not calculated as part of current PBT planning. To provide necessary information for subsequent analyses, we have already set up a framework for Monte Carlo simulations to be performed for optimised treatment plans (50). Our simulations enable us to generate both dose and associated LET maps, as shown in the figure below. These maps will be used to evaluate the range of LET values present in the lung from end-of-range protons, a key driver of subsequent RBE effects.



Dose to water



LET to water

Figure: Dose and LET maps calculated for a PARABLE treatment plan using our Monte Carlo simulation framework (based on GATE/GEANT4). Maps thresholded at 2% of the prescription dose. The contours in white show the PTV_{low} + PTV_{high} regions. The right figure shows that 50% of the total left lung volume receives an LET greater than 7 keV/µm.

2. Validate elevated RBE of end-of-range protons for radiographic lung changes

It was recently demonstrated in a small, retrospective study (33) that end-of-range protons led to greater radiographic changes in the lung than photons at similar dose levels. As a first step, we will replicate this analysis in this larger, prospective dataset. We will quantify radiographic changes in the lung as a function of dose in proton and photon therapy patients, and test if there is a statistically significant difference between these two treatment modalities above and beyond the clinically-accepted value of 1.1. This will represent the first validation of a variable proton RBE in a prospective clinical trial, and provide an essential starting point for future analysis.

3. Establish uncertainty bounds for proton RBE as a function of dose and LET

With evidence of an elevated proton RBE, we will then seek to parameterise the possible values of proton RBE in a model-independent fashion. As a first step, we will parameterise radiographic changes as a function of dose in the low-LET photon cohort. This will then be used to calculate RBEs for lung changes in our proton treatment plans, as a function of both dose and LET. By mapping out the variation of RBE with these parameters, we will be able to establish confidence bounds that must be satisfied by any model applied to these systems, potentially significantly restricting the parameter space for some models and possible forms for the dose-LET-RBE relationship.

4. Test predictive power of published models to predict serial lung changes

Finally, using these datasets showing the relationship between dose, LET and lung changes, we will seek to test a range of published RBE models to determine if they effectively predict the relationship between these parameters, and provide estimates of the uncertainty range on parameters of these models.

A range of proton RBE models have been published. These include purely phenomenological models which parameters linear quadratic model parameters as a function of LET (43, 51, 52), recently reviewed by Rorvik et al(53). There are also a range of other mechanistic models including the Local Effect Model, the Microdosimetric Kinetic Model, the Monte Carlo Damage Simulation, MEDRAS, and the Manchester Model. Significantly, while these models often differ in assumptions or fitting data, many show very similar dependencies between dose and LET which would be tested in this model.

To evaluate the applicability of these models for radiographic lung changes, we will generate RBE-weighted dose maps for a set of models. Although they are built on different assumptions and datasets, almost all phenomenological models show a linear dependence of RBE on LET at typical proton LETs, and so as an exemplar of this class of model, we will apply the McNamara model. Other mechanistic models include a range of different dependencies on LET. To evaluate a reflective sample of these, we will also generate RBE-weighted dose maps for the MKM, MEDRAS, and the Manchester model.

For all of these models, we will evaluate the correlation between the model predicted and observed RBEs, determining which offer superior predictive power. This information will be used to stratify models in terms of their accuracy, and identify areas where further data may help refine these models and translate them towards clinical practice.

A3. PATIENT-REPORTED OUTCOMES

Rationale for PRO measurement

PARABLE aims to test whether PBT reduces risk of serious RT-induced heart toxicity many years after RT without increasing shorter-term adverse effects compared with tailored photon RT. To this end, co-primary endpoints have been selected to address each of these aspects. Patient-reported breast symptoms at 2 years is a co-primary endpoint in PARABLE, selected to test whether PBT is non-inferior to tailored RT in terms of breast adverse effects in the shorter-term.

PRO evaluations in PARABLE are based on standardised measures that will provide data and allow comparison with other relevant trials. The scales selected include specific measures for evaluating breast cancer therapies, body image, protocol-specific post RT symptoms, a general cancer health related quality of life scale and a generic quality of life scale widely used in health economic evaluations. These measures have been used in the START, IMPORT and FAST-Forward breast radiotherapy trials. Assessment will be carried out over at least 5 years of follow-up. Timings of assessments are in line with those used in the START, IMPORT and FAST-Forward radiotherapy trials.

The PRO early toxicity assessments in PARABLE build on the FAST-Forward acute toxicity sub-study and include additional endpoints proposed during patient focus group discussions informing design of the PARABLE trial. An embedded 'Study Within A Trial' will refine the acute toxicity PRO study.

Measures

EORTC QLQ-C30 is a 30-item cancer quality of life-specific instrument, which comprises 5 functional sub-scales, 2 symptom subscales and additional symptom items and questions about global health and global quality of life (54).

EORTC QLQ-BR23 breast cancer module is a 23-item scale designed for use in breast cancer treatment [4]. It consists of 6 subscales: breast symptoms, arm symptoms, body image, systemic side effects, sexual functioning, sexual enjoyment and items on hair loss and future perspective (55).

10-item Body Image Scale (BIS) (of which 4 items are already incorporated in the BR23) was designed for use with cancer patients and has been widely used in national breast cancer treatment trials (56).

Protocol-specific items as used in previous breast RT trials: 6 items specific to post-treatment effects evaluating change in skin appearance, change in overall appearance of the breast, breast shrinkage and hardening, position of the nipple and difficulty getting a bra to fit. An additional item measures shoulder stiffness. Also items relating to acute breast and skin changes during and immediately after radiotherapy, as used in the FAST-Forward acute toxicity study.

PRO-CTCAE items relating to acute toxicities including skin darkening, mouth or throat sores, cough (57).

EQ-5D-5L is a generic measure of health-related quality of life comprising 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale that assesses health state (58).

Timing of data collection

Participants will be asked to complete questionnaire booklets in clinic weekly for the 3 weeks of radiotherapy treatment; subsequent acute toxicity questionnaires will be sent to participants' homes by ICR-CTSU, with subsequent questionnaires being sent to participants' homes by ICR-CTSU at 6, 12, 24 and 60 months from commencing treatment.

A4. GLOSSARY

CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTRad	Clinical and Translational Radiotherapy Research Working Group
CTU	Clinical trials unit
DIBH	Deep inspiration breath hold
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic patient-reported outcomes
EQ-5D-5L	EuroQol 5-dimension 5-level
Gy	Gray, unit of radiation dose
HRA	Health Research Authority
HU	Hounsfield Units
ICR-CTSU	The Institute of Cancer Research Clinical Trial and Statistics Unit
IDMC	Independent data monitoring committee
IMN	Internal mammary nodes
IMRT	Intensity modulated radiotherapy
ISRCTN	International Standard Randomised Controlled Trial Number
NCRI	National Cancer Research Institute
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PBT	Proton beam therapy
PPI	Patient and Public Involvement
PRO	Patient-reported outcomes
QLQ-BR23	Quality of Life of Cancer Patients – breast cancer module
QLQ-C30	Quality of Life of Cancer Patients – core questionnaire
RBE	Relative biological effectiveness
RCR	Royal College of Radiologists
RCT	Randomised controlled trial
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RTTQA	Radiotherapy Trials Quality Assurance
SWAT	Study within a trial
TMG	Trial management group
TSC	Trial steering committee
UCLH	University College London Hospital

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