Support, Positioning and Organ Stabilisation during Breast Cancer Radiation Therapy: The SuPPORT 4 All bra.

Study Protocol Version 4 01/08/2018

Funder: National Institute for Health Research (NIHR) Invention for Innovation Programme (programme grant number: II-LA-0214-20001).

Sponsor: Sheffield Hallam University

Protocol Development Group

- Professor Heidi Probst -Chief Investigator
- Kirsty Bryan-Jones- physics planning
- Dr Caroline Lee- Lead Breast Oncologist Weston Park Hospital.
- Janet Johnson- Superintendent Radiographer Weston Park Hospital
- Dr Anil Gumber- Health Economics lead
- Professor Stephen Walters- Statistical lead
- Keeley Rosbottom- Research Assistant
- Heath Reed- Product designer
- Professor Karen Collins- Patient and Public Involvement lead
- Dr Helen Crank- patient representative

Table of Contents

Trial Summary

Title	Support, Positioning and Organ Stabilisation during Breast Cancer Radiation Therapy: The SuPPORT 4 All bra.
Aim	This feasibility trial is an essential preliminary to a definitive Randomised Controlled Trial (RCT). The purpose of this feasibility trial is to ensure the design and methods of that future trial are sound, practicable and feasible. The aims of the feasibility trial are: 1. To test the feasibility, practicality, and acceptability of the study design and protocol; 2. To resolve practical issues for the conduct of the future RCT such as the reproducibility of the outcome measures, and recruitment and attrition rates; 3. To investigate the acceptability of the care pathway to patients and Clinicians and to refine it prior to the full RCT; 4. To inform the sample size calculation for the full trial.
Eligibility Criteria	All of the following criteria need to be met for inclusion in the study: • Age ≥18 years • Have undergone conservative surgery leaving an intact breast. • Invasive carcinoma of the breast • pT1-3, pN0-1, M0 disease • Referred for whole breast radiotherapy only • Able to give written informed consent. • A bra cup size that fits in the S4A bra size 3 and above (ie 28F/30E/32DD/34D/36C and above). All standard systemic therapies are allowed except those prescribed concurrent chemotherapy. **Exclusion Criteria** • Previous ipsilateral or contralateral breast cancer (including DCIS). • Concurrent cytotoxic chemotherapy, (sequential adjuvant chemotherapy is allowed). • Radiotherapy to regional lymph nodes. • Requires a radiotherapy boost to the site of the primary tumour bed.
Study Design	This is a prospective randomised feasibility trial.
Endpoints	**Primary feasibility endpoint** Recruitment of 50 participants recruited in a 6-month recruitment window at 1 centre

	Secondary feasibility endpoints • Recruitment and attrition rates (CONSORT data): number of patients assessed for eligibility; reasons for exclusion, numbers discontinuing intervention (with reasons), numbers analysed and excluded from the analysis. • Number of missing values/incomplete cases: Acceptable rates of missing values for all the questionnaires prospectively defined as 0.5% in line with industry standards for phase I-III clinical trials. • Intervention adherence: Defined objectively as the number of radiotherapy fractions where the bra is used (for the intervention group) divided by the number of fractions prescribed. • Ease of radiation planning using the bra and ease (or difficulty) of producing an acceptable plan using the bra compared with no bra. • Intervention fidelity: During the study period site observations will be undertaken of treatment set-up for patients in both the control and intervention arms to ensure the support bra is used and positioned correctly and technique protocols are used in a standard manner across intervention and control groups. A checklist of criteria that reflects the protocol for using the support bra will be used to monitor intervention fidelity. • Feasibility of recruiting future participating centres. • Decision on primary endpoint for main trial. **Primary Efficacy Endpoint** Treatment accuracy and reproducibility will be collected as part of this feasibility trial. We would expect the S4A bra to either maintain or improve on existing levels of accuracy (where approximately 73.3% of cases had mean systematic errors <3mm and approximately 75% of cases had mean random errors <3mm for central lung depth on treatment verification images. Results will be viewed in relation to improvements in the dose to organs at risk (mean lung and mean heart dose where applicable). **Secondary efficacy Endpoints** • Skin reactions. • Dose to organs at risk. • Breast oedema. • Patient comfort. • Patient modesty. • Patient empowerment. • Participant views on acceptability of the intervention. • Therapist views on the acceptability of the intervention. • Body Image.
Sample Size	A sample size of 40 patients allows a standard deviation, for a continuous outcome such as accuracy of radiotherapy (measured in mm), to be estimated to within a precision of approximately ±23% of its true underlying value with 95% confidence. Therefore, allowing for a 20% attrition or loss to follow-up we propose to recruit and randomise 25 patients per group (50 in total). This SD estimate will be synthesised with standard deviations observed in other published studies and on going trials to provide a robust estimate for use in the sample size calculation for the full trial.

Outcomes	• Random and systematic treatment errors, using on-treatment portal images. • Skin reactions using the Radiation Therapy and Oncology Group skin scoring assessment (RTOG)(1) both staff scored and patient self – reported using a new lay reporting skin assessment tool (developed jointly by our patient group and health care practitioner group). • Dose to organs at risk, including mean ipsilateral lung dose, combined total lung dose, and mean heart dose (for those treated for a left breast cancer). • Incidence of dry/moist desquamation in the inframammary fold. • Breast oedema measured via a new self reporting tool (SELF- SizE, Look, Feel, tool). • Patient comfort measured by a new comfort questionnaire developed from interviews with healthy volunteers that have tried the support bra • Patient modesty and experience measured by a storyboard incorporating questions from the patient modesty scale(2). • Patient empowerment using the 15-item patient empowerment scale for cancer patients(3) • Participant views on acceptability of the intervention using a specially designed Technology Acceptance questionnaire based on the Technology Acceptance Model(4). • Therapist views on the intervention using a specially designed Technology Acceptance questionnaire(4). • Body Image using the 10-item body image scale(5)

1.0 Background

Breast cancer affects a substantial proportion of the population(6); with over 1.67 million women diagnosed globally in 2012(7). For many of these women the primary treatment is local excision (LE) followed by external beam radiotherapy to the whole breast. Traditionally this has been given using basic tangential radiotherapy beams. New technology employing complex approaches such as 3D conformal and Intensity Modulated Radiotherapy (IMRT) provide the opportunity to spare sensitive structures that lie close to the breast; these require greater accuracy in patient alignment. Set up inaccuracies (anterior-posterior and superior-inferior systematic displacements) have dosimetric consequences that vary depending on breast gradient, standard or IMRT based techniques and magnitude of error(8) and may increase the risk of a loco-regional recurrence(9) or a poorer cosmetic outcome (10). Added to this in the majority of radiotherapy centres worldwide women lie for breast irradiation, bare from the waist upwards, with up to four therapy radiographers (including men) adjusting and manipulating their thorax and breast in preparation for treatment. Most radiotherapy centres rely on the use of permanent tattoos marked on the patient and laser systems aligned to the machine. However, accuracy using this approach can be problematic(11) and the use of permanent tattoos is of concern to many patients(12). In addition, women with large (above a D bra cup size) or pendulous breasts can be difficult to position. Specifically, overhang of the breast inferiorly produces a self-bolusing effect that leads to an increased skin dose in the lower part of the breast and on the chest wall underneath the tissue overhang. The use of a support bra would lift the breast tissue away from the chest wall, reduce the skin reaction at the inferior aspect, making the potential cosmetic outcome and treatment experience for women with larger breasts more comparable to that experienced by women with smaller breasts

Currently no immobilisation device is available for use with supine positioning that can accurately stabilise the breast while also maintaining patient dignity(13). We have developed a support bra and determined proof of concept of the design through experimental testing.

2.1. Why is this research important -

Survival rates following LE and radiotherapy are good (79-98% at 4-5 years). With local recurrence generally low (0.3-10%)(14-18) more women are living with the side effects of therapy with survival projected to reach 1.7 million by 2040(19).

The long-term effects of incidental cardiac irradiation during breast radiotherapy are a concern. First highlighted in the Early Breast Cancer Trialists Collaborative Group (EBCTCG)(20) report in 1995, more recent studies have indicated that while modern radiotherapy techniques do not increase mortality from cardiac irradiation, the impact of cardiac morbidity on breast cancer survivors is a worry(21). Review of doses received by the heart in patients treated between 1958 and 2001 in Sweden and Denmark(22, 23) indicated a 7.4% increase in the rate of major coronary events for each increase of 1Gray (Gy) in the mean radiation dose delivered to the heart (95% CI, 2.9 to 14.5, $p<0.001$). In order to reduce the dose to the heart many centres are employing cardiac avoidance techniques including voluntary deep inspiration breath hold (vDIBH)(24) which has been shown to reduce mean heart dose by approximately 50%(24). However, using vDIBH techniques adds further opportunity for patient movement during the beam on time and requires imaging (adding additional radiation dose to the patient) to ensure accuracy especially in the caudo-cephalic direction where mean systematic error in heart position of 0.5cm have been

reported(25).

In our early testing of the first prototype we were able to demonstrate that using the support bra on a large breast phantom reduced the mean heart dose from 5.1Gy (no bra) to 3.7Gy (with the prototype support bra) p=0.036.Thus allowing the opportunity to reduce long-term sequela that require costly interventions and reduce patient quality of life.

Additionally, clinical trials are testing partial organ techniques compared with whole breast irradiation (eg IMPORT low trial) in cases where there is low risk of tumour recurrence. The principle is to spare sensitive tissues by reducing the volume of breast tissue irradiated (26) but partial organ techniques require accurate positioning if favourable cosmetic outcomes and local control are to be achieved(10). Interim data from some Phase III partial breast clinical trials raised concerns over lower than anticipated cosmetic outcomes(27, 28). It is possible this was influenced by poor breast stabilisation. Many centres are employing image-guided radiotherapy (IGRT) as a way of confirming radiotherapy field placement prior to treatment exposure. IGRT incorporates kilovoltage imaging on the treatment set, this additional imaging increases the total body dose of radiation received by the patient, for younger women there is concern that the life time additional risk from this extra exposure to the contra-lateral breast could increase the likelihood of a second cancer(29). If there was greater confidence in the immobilisation method used to stabilise the breast this could reduce the frequency of on-treatment imaging.

Our support bra has the potential to stabilise the breast (increasing treatment accuracy) and reduce the dose to organs at risk such as the heart (for women treated for a left breast tumour) while providing modesty during treatment delivery.

3.0 Study Aim and Research Questions.

This feasibility trial is an essential preliminary to a definitive Randomised Controlled Trial (RCT). The aim of the definitive RCT is to assess the effectiveness and cost-effectiveness of a support bra for immobilising breast tissue during breast irradiation for women that have been diagnosed with breast cancer (and have undergone removal of the tumour leaving an intact breast i.e have undergone conservative surgery) compared to current practice of no immobilisation. The purpose of this feasibility trial is to ensure the design and methods of that future trial are sound, practicable and feasible. The aims of the feasibility trial are:

1. To test the feasibility, practicality, and acceptability of the study design and protocol;
2. To resolve practical issues for the conduct of the future RCT such as the reproducibility of the outcome measures, and recruitment and attrition rates;
3. To investigate the acceptability of the care pathway to patients and Clinicians and to refine it prior to the full RCT;
4. To inform the sample size calculation for the full trial.

This feasibility trial proposes to answer the following research questions in relation to the prototype support bra:

<u>Research questions-bra functionality</u>

- Is the design and current functionality of the bra able to fit with current set-up procedures without too much process adaptation?
- Does the inflation bladder retain consistency across the treatment course?

<u>Research questions-bra accuracy</u>

- What are the random and systematic errors in breast positioning with the immobilisation support bra compared with a control group with standard immobilisation (no bra)? (specifically the proportion of set ups achieved with ≤3mm set-up error(30))

- Is accuracy of positioning using the support bra the same across all breast sizes?

Research questions- Improvements in care
- What are the differences in the dose to organs at risk when the support bra is used compared with no support bra?
- Does the support bra reduce the incidence of moist desquamation in the inframmary fold (grade 2 using the Radiation Therapy Oncology Group acute morbidity scoring system)?(30)

Research questions-patient experience
- Is the current inflation bra design appropriate for patients' aesthetic, and comfort needs?
- Does the support bra provide measureable changes in patient modesty? and
- Does the support bra allow measurable changes in feelings of empowerment compared with the standard no immobilisation process?

Research questions- Health Economics
- Are there any treatment related cost savings from using the support bra?

The primary endpoint is a support bra that is technically acceptable to health-care professionals (HCPs) and aesthetically acceptable to patients.

3.1. Success or stop go criteria for this feasibility trial

Table 1 Stop/Go Criteria for the Feasibility Trial.

Criteria to be assessed and potential outcome	Proposed Action at end of feasibility trial
Random and systematic errors > 3mm for CLD in more than 30% of cases using the bra.	Review bra fit comments across sample and review training and bra use instructions. Further experimental testing (use of healthy volunteers and 3D surface imaging to measure improvements in accuracy and reproducibility, recommended before definitive RCT.
Mean lung dose, no improvement in mean lung doses over control arm.	Review inflation levels used in the study and recommend changes to inflation levels used, further experimental testing recommended before definitive RCT.
Mean heart dose (left sided cases only), no improvement in mean heart doses over control arm.	Review inflation levels used in the study and recommend changes to inflation levels used, further experimental testing recommended before definitive RCT.
Recruitment to sample size (n=50) takes longer than 6-months.	Review recruitment process and devise strategy to enhance recruitment to the definitive RCT.

Retention in study < 80%	Review attrition reasons and identify strategies to remedy ahead of full RCT.
Intervention adherence < 84%	Review comfort questionnaire responses and consider strategies to enhance patient comfort.
RTOG score in the intervention arm ≥3 in one or more cases.	Review of bra fit, inflation levels and dosimetry for affected cases, recommend bra refinement. If a grade 3 (or above) reaction occurs **during** the course of radiotherapy, treatment will be reviewed by the patient's Oncologist immediately. Treatment may continue without the bra following re-planning at the discretion of the treating Oncologist

3.1.1 Primary efficacy outcome data to be collected.

This study is a feasibility study but the data will inform the sample size needed for a future larger randomised controlled trial. In order to calculate the sample size needed for the follow on study, data on treatment accuracy and reproducibility will be collected as part of this feasibility trial. In a previous audit of reproducibility at the Host Institution without any immobilisation (n=30 women) 73.3% of cases had mean systematic errors <3mm and 75% of cases had mean random errors <3mm for central lung depth on treatment verification images. We would expect the S4A bra to either maintain or improve on this reproducibility. However, reproducibility achievements must be viewed in relation to improvements in the dose to organs at risk (mean lung and mean heart dose where applicable). Hence the data from this feasibility trial will be viewed collectively in terms of reproducibility achievements and the ability to reduce the dose to organs at risk.

3.1.2 Primary feasibility outcome

Feasibility of recruitment to main trial: defined as recruitment of 50 participants recruited in a 6-month recruitment window at 1 centre.

3.1.3 Secondary efficacy outcomes

This study will evaluate the usefulness of a number of efficacy outcome measures and their suitability for use in the main follow on trial. Efficacy outcomes that we will test in this feasibility trial are as follows:

- Skin reactions using the Radiation Therapy and Oncology Group skin scoring assessment (RTOG)(1) both staff scored and patient self –reported using a new lay reporting skin assessment tool (developed jointly by our patient group and health care practitioner group).
- Dose to organs at risk, including mean ipsilateral lung dose, combined total lung dose, and mean heart dose (for those treated for a left breast cancer).
- Incidence of moist desquamation in the inframammary fold.

- Breast oedema measured via a new self reporting tool (SELF- SizE, Look, Feel, tool).
- Patient comfort measured by a comfort questionnaire developed from interviews with healthy volunteers that have tried the support bra and adaptations of the Kolcaba patient comfort questionnaire for radiotherapy patients(31).
- Patient modesty measured by the patient modesty scale(2) and a newly developed story board of the radiotherapy journey to measure patient experiences of physical exposure.
- Patient empowerment using the 15-item patient empowerment scale for cancer patients(3)
- Participant views on acceptability of the intervention using a specially designed Technology Acceptance questionnaire based on the Technology Acceptance Model(4).
- Therapist views on the intervention using a specially designed Technology Acceptance questionnaire(4).
- Body Image using the 10-item body image scale(5)

3.1.4 Secondary feasibility outcomes

- Recruitment and attrition rates (CONSORT data): number of patients assessed for eligibility; reasons for exclusion, numbers discontinuing intervention (with reasons), numbers analysed and excluded from the analysis.
- Number of missing values/incomplete cases: Acceptable rates of missing values for all the questionnaires (see section 5.2) prospectively defined as 0.5% in line with industry standards for phase I-III clinical trials. Unacceptably high error rates will trigger staff re-training and, where refractory, consideration by Trial Steering Committee of exclusion of the instrument from the battery.
- Intervention adherence: Defined objectively as the number of radiotherapy fractions where the bra is used (for the intervention group) divided by the number of fractions prescribed.
- Intervention fidelity: During the study period site observations will be undertaken of treatment set-up for patients in both the control and intervention arms to ensure the support bra is used and positioned correctly and technique protocols are used in a standard manner across intervention and control groups. A checklist of criteria that reflects the protocol for using the support bra will be used to monitor intervention fidelity (see Appendix 4).
- Feasibility of recruiting future participating centres: target sites for the main study will be screened for suitability, by interviewing potential principal investigators.
- Decision on primary endpoint for main trial: descriptive assessment based on the above and sample size estimation

4.0 Trial Design

The SuPPORT 4 All (S4A) study is a single centre randomised feasibility trial. The safety of the product in terms of the radiation absorption properties have been fully tested through a series of physics tests performed on both a 6 and 10MV linear accelerators (see Appendix 1). The positional accuracy achievable using the S4A bra has been tested through a Healthy Volunteer Study using 3D surface scanning (stereophotogrammetry). Hence the purpose of this feasibility trial is to test the acceptability of the SuPPORT 4 All bra by patients (in terms of comfort, modesty and usability) and staff (in terms of ease of daily set-up) and to assess the appropriateness of a range of measurement tools that might be used in post implementation surveillance as part of the on-going update to the product technical file.

This study also proposes to assess the impact of the bra on the ability or ease of producing an acceptable radiation treatment plan. To achieve this those patients randomised to the intervention arm will undergo two planning CT scans (using a repeated measures design); one CT scan while

wearing the S4A bra and one scan as normal without the bra. Thus enabling a direct comparison between participants of dose homogeneity achievable with and without the bra.

The following parameters are standard tools or measures that will be adopted in the study (see section 7.0 for more details) some are validated tools others are being tested for the first time in this study:

- Skin reactions using a standard measuring tool Radiation Therapy and Oncology Group skin scoring assessment (RTOG)(1).
- Incidence of moist desquamation in the inframammary fold.
- Dose to organs at risk (mean lung and mean heart doses) taken from the patient's individual dosimetry plan (see section 7 for further details).
- Patient comfort measured via a new comfort questionnaires designed specifically for this study.
- Patient modesty measured by aspects of the patient modesty scale(2) within a newly developed story board of the radiotherapy journey to measure patient experiences.
- Patient empowerment using the 15-item patient empowerment scale for cancer patients(32)
- Technology acceptance from both healthcare practitioners and patients using an adapted Technology Acceptance Tool (based on the Technology Acceptance Model(4)).
- Body Image using the 10-item body image scale(5)

In addition, an ancillary patient self-reporting booklet will be used and this contains:

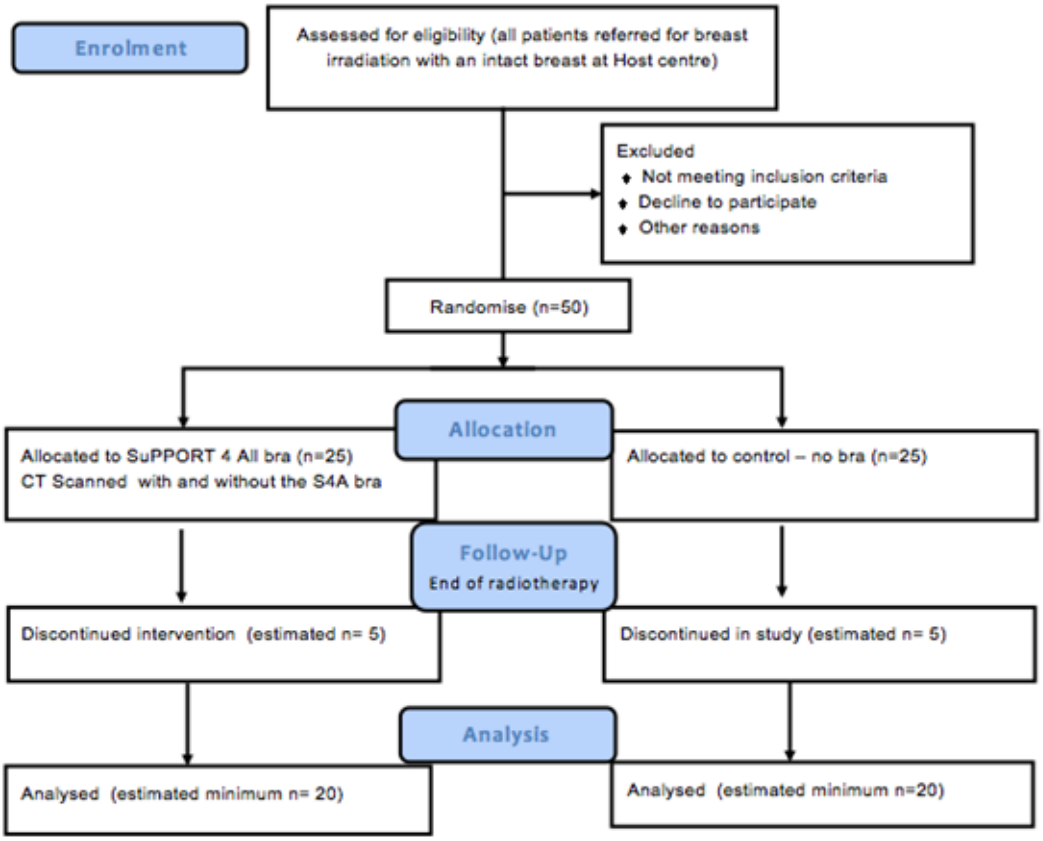
- Sections to record the size of the bra and all the fitting dimensions (strap positions and details about fit) for those in the intervention arm.
- A self-reporting skin scoring scale based on the RTOG system and
- A tool for measuring and monitoring changes in the breast the SELF tool (SizE, Look, Feel).

The self-reporting tools will also be assessed for acceptability and usability in this feasibility study. The purpose of the patient self-reporting booklets is to enhance patient input to their own treatment, provide some opportunity for patient control and for empowerment. To aid this a comparison of patient self-reporting of skin reactions will be assessed against reporting by the healthcare practitioners to measure comparability.

4.1. Trial Flow Chart

CONSORT
TRANSPARENT REPORTING of TRIALS

Figure 1. Trial Flow Diagram



5.0 Patient Selection and Eligibility

5.1. Patient selection

Women who have undergone conservative surgery for early breast cancer referred to the Host Institution for post-operative radiotherapy.

5.2. Number of patients

The sample size for a feasibility study should be adequate to estimate the uncertain critical parameters (SD for continuous outcomes; consent rates, event rates, attrition rates for binary outcomes) needed to inform the design of the full RCT with sufficient precision. A sample size of 40 patients allows a standard deviation, for a continuous outcome such as accuracy of radiotherapy (measured in mm), to be estimated to within a precision of approximately ±23% of its true underlying value with 95% confidence. Therefore, allowing for a 20% attrition or loss to follow-up we propose to recruit and randomise 25 patients per group (50 in total). This SD estimate will be synthesised with standard deviations observed in other published studies and on going trials to provide a robust estimate for use in the sample size calculation for the full trial. Preliminary estimates suggest the definitive RCT would need to have between 192 and 266 patients, in total, to detect a standardised effect sizes of between 0.50 to 0.40 at conventional levels of power (90%) and significance (5% two-sided).

For the parameters such as skin reaction measured by RTOG scoring system, a score of 3 or more on the 0 to 4 integer scale would be regarded as a negative event. With 20 randomised patients in the support bra group; then if none of these patients had a RTOG score of 3 or more; then we would be 95% confident that the true negative event rate would lie between 0 and 16.1%. Observing one or more patients with RTOG scores of 3 or more would suggest that the underlying negative event rate for the support bra, is between 1% and 24%, which is not adequate enough for the support bra in its present form to replace existing practice (ie no immobilisation) and requires further development and refinement.

5.3. Inclusion Criteria

All of the following criteria need to be met for inclusion in the study:

- Women
- Age ≥18 years
- Have undergone conservative surgery leaving an intact breast.
- Invasive carcinoma of the breast
- pT1-3, pN0-1, M0 disease
- Referred for whole breast radiotherapy only
- Able to give written informed consent.
- A bra cup size that fits in the S4A bra size 3 and above (ie 28F/30E/32DD/34D/36C and above) see Appendix 1.

All standard systemic therapies are allowed except those prescribed concurrent chemotherapy.

5.4 Exclusion Criteria

- Previous ipsilateral or contralateral breast cancer (including DCIS).
- Concurrent cytotoxic chemotherapy, (sequential adjuvant chemotherapy is allowed).

- Radiotherapy to regional lymph nodes.
- Requires a radiotherapy boost to the site of the primary tumour bed.

6.0 Randomisation

6.1. Randomisation procedure

Prior to randomisation an eligibility checklist should be completed and signed informed consent should be obtained. Allocation will be through block randomisation (with blocks an integer multiple of four); stratified by breast/bra cup size (S4A bra size 3-7 vs. S4A bra size 8-12). The trial statistician will generate a randomisation schedule using existing software. This will be held remotely by the study-co-ordinator (who will not be directly involved in recruiting patients to the study). At the point of randomisation, the recruiting clinician will contact (telephone) the study co-ordinator, give the patient's details and NHS number and receive a study number and treatment allocation in return. At the end of the trial, the complete remote schedule will be checked against the study dataset. Staffing the randomisation line will be straightforward, as randomisation will occur exclusively during office hours.

6.2. Treatment Allocation

Patients will be randomised 1:1 to receive the intervention (breast radiotherapy with S4A bra one tattoo) or the control (existing radiotherapy set-up with no immobilisation with tattoos).

7.0 Trial Evaluations

7.1. Accuracy and Reproducibility

Standard methods to calculate random and systematic errors will be used(33) taken from on-treatment imaging on days 1-3, then weekly until treatment completion. The random and systematic errors analysis will be reported with confidence intervals to allow estimation of the effect size for random and systematic errors (the probable primary endpoint for the definitive study) to check that the likely effect is within a clinically relevant range (as confirmation that it is worth progressing with the full trial). To check positioning patients in both arms of the study will have a single image taken at the start of the daily treatment exposure. This image will be used to confirm set up accuracy before the treated dose is delivered.

7.2 Plan acceptability

Patients randomised to receive the intervention (the S4A bra) will have two CT planning scans (one with and one without the S4A bra). Each scan will be planned as normal but patients will only be treated using the plan with the patient wearing the S4A bra. Both scans will be compared using the following parameters:

- Time taken to achieve an acceptable plan
- Beam energy required to achieve an acceptable plan
- Comparison of dose volume histograms for Planning Target Volume (PTV), lungs and heart (for women planned for a left sided breast cancer).
- Dose to organs at risk, lungs and heart mean doses (see section 7.5 for specific dose measurements to be recorded).

7.3. Skin Toxicity

Skin toxicity will be measured using validated skin assessment scoring systems as follows:

- The Radiation Therapy Oncology Group (RTOG) toxicity scoring scale for acute skin reactions(1).

- A lay RTOG scoring system for patient self reporting (developed within the co-design workshops with patients and healthcare practitioners). This tool has not been validated and ease of use and comparison of lay scoring with HCP scoring will be assessed within this study.

RTOG scores will be recorded at day 0 (at the CT planning visit) and once weekly until the end of treatment by a designated radiographer blind to the intervention group and self reported by the patient. The patient will also self-report skin reactions at four weeks post treatment. In addition, participants will be asked to complete a breast assessment, the SELF tool (SizE, Look, Feel)[1], designed for patients to monitor and document breast swelling that maybe indicative of breast oedema. User representatives and healthcare practitioners designed both these patient self-scoring tools in the product development phase of this study. The aim of introducing these tools in this feasibility study is to assess compliance, usefulness and ability for patients to score skin and breast changes themselves; constituting the first part of the validation process for these tools.

7.4. Patient comfort, Modesty, Empowerment

7.4.1. Assessing patient comfort

In order to assess patient comfort with and without the support bra a new comfort questionnaire has been designed based on interviews with healthy volunteers that have worn the support bra. Patients will be asked to complete the questionnaire after the first treatment session and once weekly until the end of the treatment course. As the patients' skin may become sore as treatment progresses it is important to ensure the support bra does not exacerbate skin discomfort.

7.4.2. Assessing patient modesty

A story-board documenting the radiotherapy journey has been developed to enable participants to define experiences of being naked and un-covered at different points in the radiotherapy pathway.

7.4.3. Assessing patient empowerment

Patients will be asked to complete the 15-item patient empowerment scale for cancer patients (32) at day 0 (Radiotherapy planning CT visit) and once weekly during treatment (ie week 1, week 2 and week 3).

7.5. Dose to Organs at Risk

Dose to organs at risk will be assessed at the planning stage for all trial patients the following parameters will be calculated for all patients:

- Mean ipsilateral lung dose
- V12- Volume of ipsilateral lung receiving more than 12Gy total dose.
- Combined lungs total mean lung dose.

For patients undergoing radiotherapy to the left breast the following additional parameters will be calculated:

- Mean heart dose
- Percentage of heart volume receiving >10Gy and 2Gy

[1] The Patient RTOG and SELF tool can be found in the supplementary files

Table 2 The Research Questions and the associated outcome measures proposed for this feasibility trial.

No	Research question	Proposed Assessment Method
1	Is the design and current functionality of the bra able to fit with current set-up procedures without too much process adaptation?	Interview of staff involved in the planning and treatment of patients using the bra.
2	Does the bra make it easier to produce an acceptable treatment plan?	Those in the intervention arm will undergo two planning CT scans one with and one without the S4A bra. Two radiotherapy treatment plans will be produced for each patient in the intervention arm; the patient will only be treated using the plan with the patient wearing the S4A bra. Plan evaluations will include measures of dose homogeneity across the planning target volume, time taken to plan, complexity of plan and beam energy required to produce the optimal plan.
3	What are the random and systematic errors in breast positioning with the immobilisation support bra compared with a control group with standard immobilisation (no bra)?	Accuracy derived from on-treatment images on days 1-3 and weekly until the end of treatment for five different parameters (see section 12.1).
4	Is accuracy of positioning using the support bra the same across all breast sizes?	Using individual mean random and systematic errors to correlate with breast volume taken from the radiotherapy plan.
5	What are the differences in the dose to organs at risk when the support bra is used compared with no support bra?	Mean lung and mean heart dose compared between bra and no bra cohorts.
6	Does the support bra reduce the	Skin assessments by health care

	incidence of dry/moist desquamation in the inframmary fold	practitioners taken at baseline and weekly during treatment with comments on the skin scoring (using RTOG) in the inframmary fold ie dry/moist desquamation yes/no and duration
7	Is the current inflation bra design appropriate for patients' aesthetic, and comfort needs?	Assessed with comfort assessment tool (using questions derived from Healthy Volunteer study questionnaire analysis and interviews).
8	Does the support bra provide measureable changes in patient modesty?	Modesty assessed with the Storyboard of the process with and without the bra – participants asked to choose responses that represent their experiences of physical exposure measured after day 1 and repeated in the final week of treatment. Patients in the control arm are given the storyboard without the bra and asked to rate their experience; patients in the intervention arm given the storyboard with the bra and asked to rate their experience. In the final week of treatment participants are given both storyboards and asked to choose their preference.
9	Does the support bra allow measurable changes in feelings of empowerment compared with the standard no immobilisation process?	Measured using the 15-item patient empowerment scale for cancer patients.
10	Are there any treatment related cost savings from using the support bra?	Assessed through the recording of: 1. Time taken for the CT radiotherapy planning session. 2. Time taken for the radiotherapy dosimetry planning. 3. Time taken for each treatment session. 4. The number of extra/repeated on-treatment imaging exposures. 5. The number of repeat plans required. 6. A measure of the grades of staff required undertaking CT planning, dosimetry planning and treatment set-up procedures.
11	Are the patient self-reporting tools easy to use and complete?	Compliance with completion, number of correctly completed booklets and comments made in the booklet by patients.

12	Do HCP RTOG scores correlate with the patient-self reporting scores?	Comparison of HCP recorded RTOG scales and patient scores recorded in the patient-held booklet.

8.0 Radiotherapy

8.1. Dose prescription

The dose prescription is 40 Gy in 15 fractions; treating each field daily. The dose is prescribed to the reference point to which the dose distribution is normalised.

9.0 Radiotherapy Target Volumes, Localisation and Outlining

The following borders are marked on the patient's skin prior to the Computerised Tomography (CT) planning scan:

Medial border:	Positioned about the midline, covering palpable breast tissue with a margin not less than 1cm.
Lateral border:	Positioned on the skin parallel to the medial field, approximately mid-axillary line, with a margin not less than 1cm from breast tissue keeping lung volume within tolerance.
Inferior border:	1 cm below inframammary fold or palpable breast tissue.
Superior border:	lower end of sternoclavicular joint or 1 cm above the superior edge of palpable breast tissue avoiding the axilla when an axillary clearance has been performed.

A planning CT scan is performed in the treatment position. Scans are acquired with contiguous 2.5 mm slices.

9.1 Target Volume Definition

The breast 3D PTV contour is field based with negative (inner) margins of:

- 1cm inside the superior and inferior field edges
- 0.5cm inside the patient surface
- 0.5cm from the lung/tissue interface
- 0.5cm inside the field back border -

9.2 Patient Position

Patients lie in a supine position, inclined on a breast board (usually with both arms abducted above the head and gripping poles and cup rests to support the raised arms). Additional devices such as footrests, knee rests, etc., may be used to ensure patient comfort and compliance with positioning. Positional aids marked on the patient (tattoos) or on the support bra are used to ensure patients are in a reproducible position longitudinally with minimal lateral rotation.

9.2.1. Support Bra Positioning and Modifications

Patients randomised to the support bra arm of the study will be measured and fitted for the support 4 all bra at the CT planning session. The bra fitting will only be undertaken by therapy radiographers trained to measure and fit the bra. HP and KR will undertake training with staff ahead of the study start date. Patients will be taught how to put the bra on themselves at the CT planning session and any modifications to the bra will be recorded in the patient support 4 all bra pack as well as on the patient's radiotherapy prescription data record, so both staff and patient have a record of bra fit, and bra settings. Subsequently, patients will put the bra on themselves at home before travelling for their radiotherapy treatment. Staff will check bra fitting and bra settings as the patient lies down on the linear accelerator treatment bed.

To fit the bra each patient should be measured when they attend for radiotherapy planning, usually at the CT planning visit. The patient will be first assessed in her own bra to gauge the approximate size of the Support 4 all bra required. This will be achieved by measuring the patient using a standard dressmaker tape measure, below her current bra to determine chest size and using the chart in appendix 1 along with a judgement about the fit of the patient's existing bra a support 4 all bra size (3-12) will be chosen. The patient will be fitted with the appropriate Support 4 All bra and adjustments made to the straps, and band while the patient is sitting or standing. The anterior straps will be readjusted once the patient is positioned semi-supine on the breast board if required.

The patient will be aligned on the breast board at CT planning using the scanner laser system to ensure the patient is straight. The ipsilateral breast cup will be inflated (point 9 in the diagram in Appendix 3) so the breast is lifted superiorly and anteriorly until the over hang of breast tissue at the inframmary fold, as near as possible, is eliminated.

A central positioning line, chosen mid way between the SSN and Xiphi-sternum should be marked on the anterior aspect of the bra in the midline, and also on the lateral bra wings using an indelible marker pen, a further vertical laser positioning mark will also be chosen (and marked) on right and left sides at this point. All of the bra settings (points 2 and 12 on the diagram in Appendix 3) are recorded on the patient radiotherapy data sheet and in the patient held Support 4 All pack (see Appendix 6). The inflation levels (ipsilateral and contralateral), and measurements from the SSN to the top of the bra, and the xiphi-sternum to the bottom edge of the bra should be recorded on the patient radiotherapy set up record held by the radiographers. The longitudinal position of the central laser in relation to the breast board scale should be recorded for the purpose of couch/breast board indexing. Following the planning scan the inflated bladders are released and the patient removed from the bed.

The patient may go home in the bra as it is now fitted and the patient should be instructed to avoid changing any of the bra settings when removing the bra at home. The bra can be taken off (and replaced for the first treatment) using the anterior/front fasteners. The patient should be given instructions to wear the bra for the first and subsequent radiotherapy procedures.

9.3 Acquisition of Outlines

A field-based target volume is to be used for treatment planning. (As such the target volume is not a PTV as defined by ICRU 50, but is treated as such for the purposes of dose reporting and referred to as the PTV henceforth.) In order to generate the initial fields on which the resultant target volume is based, the following borders of the palpable breast tissue are marked on the patient's skin prior to the CT planning scan:

Table 3 Fields marked at CT Planning session.

Field Border	Description
Medial	Positioned about the midline, covering palpable breast tissue with a margin not less than 1cm.
Lateral	Positioned on the skin parallel to the medial field, approximately mid-axillary line, with a margin not less than 1cm from breast tissue the lateral field border may be adjusted to remain within lung volume tolerance.
Inferior	1 cm below inframammary fold or palpable breast tissue.
Superior	Lower end of sternoclavicular joint or 1 cm above the superior edge of palpable breast tissue avoiding the axilla when an axillary clearance has been performed.

A planning CT scan is performed in the treatment position with a slice thickness of no more than 2.5 mm. The scan must extend to cover the entire ipsilateral lung, as well as a margin of 2 cm around the superior and inferior borders as defined above.

10.0 Radiotherapy Planning

10.1 Whole Breast

The final dose calculation must be performed with correction for tissue heterogeneity, using a Type B algorithm.

The PTV is planned using a pair of isocentric (SAD 100 cm) tangential fields with a non-divergent back edge. The isocentre can be placed on the slice that falls in the centre of the PTV and should be positioned approximately halfway between the posterior border and the anterior surface of the breast. The fields are angled to produce the non-divergent posterior border.

The fields are positioned to cover the PTV such that the maximum depth of lung in the field (defined as the perpendicular distance from the chest wall to the posterior field border) does not exceed 2cm and the maximum depth of heart in the fields (defined as the maximum distance between the posterior field border and the external contour of the heart) does not exceed 1cm.

Wedges are used where necessary to optimise the dose distribution (in some instances, a longitudinal wedge may be required). The use of multileaf collimators (MLC) and field-in-field (FiF) is permitted for further optimisation of distributions as deemed necessary.

Inverse-planned IMRT must not be used.

Planning should aim to produce a balanced distribution across the PTV in all three directions. Where uniform coverage cannot be achieved, coverage of the tumour bed by the 95% (38 Gy) isodose should be prioritised.

The treatment plan should be normalised to a clinically relevant reference point, usually the intersection of the fields, located centrally within the PTV.

10.2 Dose Constraints for Organs at Risk (OAR)

The Organs at Risk must be contoured prior to commencement of treatment planning.

Heart: The heart should be outlined using a heart outlining atlas guide(34)

Ipsilateral lung: The entire ipsilateral lung must be contoured, ensuring any major vessels and airways are excluded from the structure.

10.3 Beam Energy

Treatment plans are produced for treatment using photon energies according to local practice. This will normally be 4 – 6 MV, although higher energies (10-12 MV) may be used to provide dosimetric improvements (for example, in fields with a larger separation). The use of mixed energies within a plan should be avoided unless the dose requirements in sections 11.3 and 11.4 cannot be met using the techniques described above.

10.4 Bolus

No bolus should be applied to the skin.

10.5 Dose Limits

The PTV dose limits are defined in Table 4 below.

Table 4 Dose Limits

Parameter	Mandatory Dose limit	Optimal limits
Maximum point dose	< 44 Gy, D_{max}≤110% $V_{105\%}$≤ 7% $V_{107\%}$≤2%	V105%≤5%
Minimum dose	$V_{95\%}$ ≥90%	$V_{95\%}$≥95%

10.6 Dose Constraints for Organs at Risk

Treatment planning should aim to meet the OAR dose constraints defined in Table 5 below.

Table 5 Dose constraints to Organs at Risk

	OAR	Dose constraint Optimal	Mandatory
Radiotherapy to left or right breast	Ipsilateral lung	$V_{30\%}$≤ 15%	$V_{30\%}$≤17%
Radiotherapy to left breast only	Heart		$V_{25\%}$≤ 5% $V_{5\%}$≤ 30%

10.7 Radiotherapy Planning Data

Dose-volume histograms (DVHs) are generated for the PTV, ipsilateral lung and heart.

The parameters in Table 6 below should be recorded.

The parameters used to produce the optimum plan will be recorded for each participant (and for each plan produced comparing S4A bra and no bra scans for those women randomised to the intervention arm).

Table 6 Radiotherapy Planning data Recorded for each Patient.

	Structure	Parameter
Radiotherapy to left or right breast	PTV	Maximum point dose
		$V_{42.8\ Gy}$
		$V_{42\ Gy}$
		$V_{38\ Gy}$
	Ipsilateral lung	$V_{12\ Gy}$
		Mean dose
	Combined lungs	Total combined mean lung dose
Radiotherapy to left breast only	Heart	V_{10Gy}
		V_{2Gy}
		Mean dose
Planning information		
Beam energy required		
Number of fields required		
Time to achieve acceptable plan		
Ease/difficulty of planning score (1 to 3)	2=standard, 1=easier & 3=more difficult	

11.0 Treatment Scheduling

Patients should be treated daily Monday to Friday with no gaps (these patients are considered a category 2 patient), to deliver 40Gy in 15fractions to breast tissue.

12.0 Treatment Verification

Verification of the treatment fields is achieved using 2D megavoltage imaging in conjunction with radiographer assessment of the field coverage on the skin surface/bra surface in comparison with a 3D rendered image of the patient produced from the planning CT dataset. The megavoltage image is a pre-treatment beam portal image allowing assessment of central lung depth, lung symmetry and breast contour.

12.1 Treatment Set-up Verification Breast

The verification procedure outlined above is undertaken on fractions 1-3, then weekly, throughout the treatment course for the purposes of assessment of random and systematic error. All patients in the S4A study will have an image taken daily throughout the treatment course to reassure regarding breast positioning. The impact of the additional imaging is explained below:

- The effective dose from a single lateral portal image of 1 MU at 6MV is 0.6 mSv (Harrison et al BJR 2007 DOI: 10.1259/bjr/32814323). Where Sv represents Sievert (the SI unit for radiation absorption), 1Sv is roughly equivalent in biological effectiveness to 1Gy (1Gy is roughly equivalent to1000mSv). The maximum organ dose for 1 MU at 6MV is approximately 10 mGy.

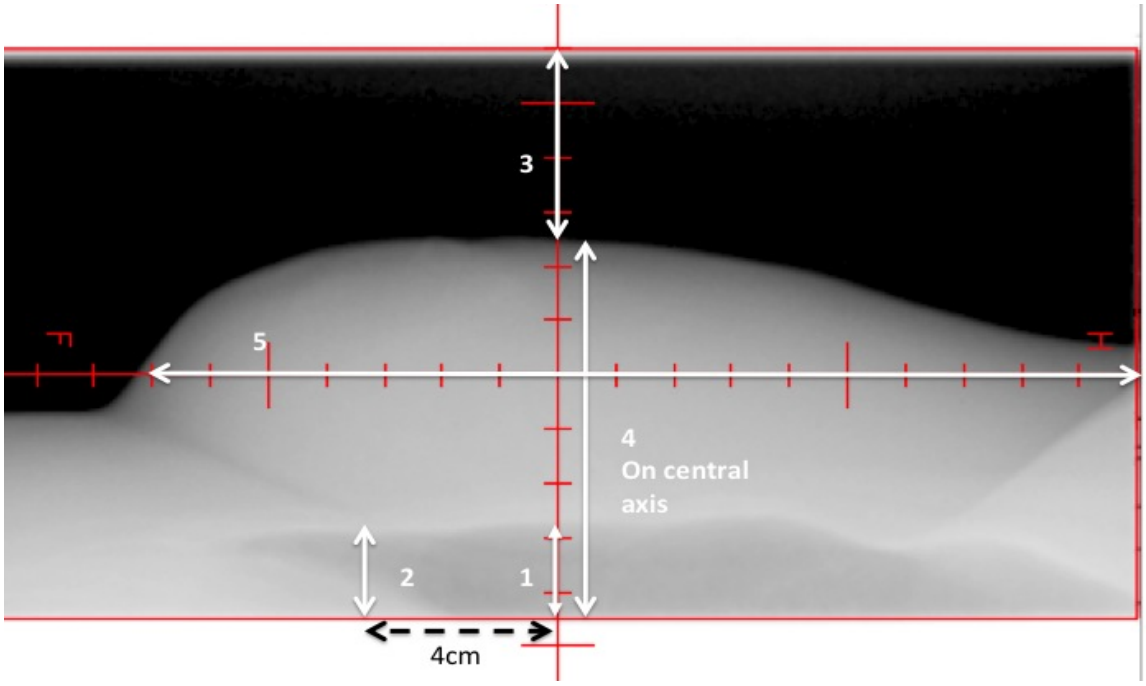
- Five portal images received by patienrs not in the study will result in approximately 3mSv, fifteen portal images received by study patients will result in approximately 9mSv.

- The reported doses are for the particular patient model used in the reference quoted above, for the size of patient in the S4A study, there may be differences from the values quoted above.

All images are taken and assessed prior to treatment and a cine type time lapse image is taken on fraction 2 to provide additional information with regard to breathing motion. For purposes of assessing random and systematic error images from day 1 to 3 and then a weekly image will be used for both control and S4A intervention arms. The systematic error is calculated using the dataset from the first three images and adjustments made on fraction 4. On the first fraction the set-up is verified by the team of treating radiographers but also utilising the additional skills of the advanced practitioner in breast radiotherapy. Thereafter, images are reviewed online by the senior radiographer and further verified offline by a radiographer trained in portal image assessment. Tolerances used are 0.5cm on the central lung depth.

Measurements as determined by the OnTarget documentation will be recorded and assessed using the verification images as shown in Figure 1 below.

Figure 1 Measurement Parameters taken from on-treatment imaging.



1 CLD- Central Lung Distance

2 CrLD- Cranial Lung Distance

3 CBESD Central Beam Edge Skin Distance

4 CIW Central Irradiated Width

5 CCD Cranio-Caudal Distance

13.0 Radiotherapy Quality Assurance

Planning technicians will contour the heart and lungs as per existing protocol, with these checked by the prescribing Clinician. For quality assurance a second check of contouring by a second Clinician will be undertaken on the first five patients of each trial arm (ten patients in total). A second physics check of the treatment plan on these first ten cases will also be undertaken to enhance study QA.

13.1 Support Bra Use- Fidelity Checks

As the main focus of this study is the introduction of a support bra it is vital that the support bra is fitted and used in the manner that it is intended. Staff at the Host Institution will be trained in fitting and use of the Support 4 All bra. However, it is also important that during the conduct of the trial bra fidelity (ie how accurately the bra is fitted and how faithfully the therapy radiographers, dosimetrists/physicists and patients stick to the guidelines on its use) is assessed and there is not drift over time in how accurately staff implement the bra intervention. Fidelity assessment will be undertaken at random time points during the period of the trial, at times unknown to the treatment staff (but negotiated in advance with the department management team) to ensure accurate assessment of fidelity. We will aim to independently assess the fidelity of at least 12 cases (approximately 25% of the trial sample). An example fidelity checklist can be found in Appendix 4. In addition, the fidelity checking sessions will provide the observers with the opportunity to observe and discuss any challenges the radiographers experience while using the bra across a range of different patient sizes.

14.0 Staff Training

In order to ensure appropriate and safe use of the Support 4 All bra HP and KR will undertake formal training with the radiography staff at the Host Institution on how to fit, and adjust the bra as well as use of the accessory equipment (inflation methods) and the purpose and use of the patient self reporting booklets. A full-day programme will be delivered (and repeated as necessary) covering the following topics:

- Background to the SuPPORT 4 All study.
- Results of the experimental data to date.
- The Support 4 All bra, step-by-step guide to the design and all the components.
- Measuring a patient for the correct sized Support 4 All bra.
- How the bra fits into the radiotherapy planning and treatment process.
- The supplementary patient self-reporting booklets- purpose and how to complete and use them.
- Clinical Feasibility study data collection tools and process.
- Practical session fitting and adjusting the Support 4 All Bra.

15.0 Serious Adverse Event Reporting

15.1 Definitions

Adverse Event: any untoward medical occurrence in a patient or clinical trial subject administered a research procedure. Events may not necessarily have a causal relationship with the procedure.
Related Adverse Event: an adverse event assessed by the Principal Investigator or Chief Investigator as reasonably likely to be related to the administration of the research

Serious Adverse Event: any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. The following summaries will be presented: the number and percentages of patients reported as having Serious Adverse Events (SAE) in each treatment arm; as well its associated 95% confidence interval for the estimate (Altman et al 2000); the number and percentages recorded as having all forms of Adverse Events (AE) in each arm; this will be presented as overall and stratified by AE classification .As well as the difference in adverse event rates between each treatment arm and its associated 95% confidence interval for the difference(35).

15.2 Reporting Serious Adverse Events

These will be reported on S4A serious adverse events (SAE) case report form.

All SAEs should be reported within 24 hours of the investigator becoming aware of the event, by completing the S4A SAE form. The SAE form must be completed, signed and dated by the Principal Investigator or nominated person identified on the delegation log.

The lead Clinicians (Dr Caroline Lee or Dr Omar Din) will review all SAEs to assess relatedness and expectedness. Any relevant follow up information, including any resolution of the event, should be completed on the original S4A SAE form and reported in line with Sheffield Teaching Hospitals standard reporting procedure.

The SAE log should be completed and the SAE form filed in the Site File.

15.3 Reporting Related and Unexpected Serious Adverse events

If a SAE is defined as related and unexpected by the lead Clinicians (Dr Caroline Lee or Dr Omar Din), the CI (Heidi Probst) will report the SAE to the main REC within 15 days from the date the event was first reported.

16.0 Health Economics Assessment

This is a feasibility study; therefore economic evaluation will be exploratory in nature. We will employ a cost-effectiveness analysis (CEA) approach to make an assessment of economic impact of using the prototype bra. The main economic endpoints to be measured across both intervention and control cohorts will be:

1) Measure of time savings (or time increases) of NHS staff associated with using the bra
- Time taken for the CT radiotherapy planning session.
- Time taken for the radiotherapy dosimetry planning.
- Time taken for each treatment session.
- The number of extra or repeated on treatment imaging exposures.
- Additional time required to re-plan any cases.

2) Measure of patient outcomes
- Calculated dose to organs at risk (including mean heart dose for patients treated for a left breast cancer, and mean ipsilateral lung dose).
- Treatment accuracy (random and systematic errors).

The two groups (standard no immobilization versus bra for immobilization) will be compared to estimate the incremental cost-effectiveness ratio. The relevant costs of services and cost savings (potential benefits) to the NHS will be derived from the reference costs provided by the Department of Health and Personal Social Service Research Unit (PSSRU). All costing will be expressed in British pound sterling and no discounting will be used as the study is conducted for a short period.

The data collected will be used to calculate the benefits achievable from the support bra balanced against the potential cost to the NHS for the purchase and use of the product in normal practice.

17.0 Statistics

As the trial is a pragmatic parallel group RCT data will be reported and presented according to the CONSORT 2010 statement (Schultz et al 2010). As a pilot/feasibility study the main analysis will be mainly descriptive and focus on confidence interval estimation and not formal hypothesis testing. We will report rates of consent, recruitment and follow-up by randomized group. Outcome measures will be summarised overall and by randomized group, to inform sample size estimation for the main trial.

17.1 Set up error

The set up error is defined as the deviation between the actual and expected position, calculated as a shift in the isocentric position when an image is compared against its corresponding reference.

The reference image is taken from the planning CT scan. Following this scan a digitally reconstructed radiograph will be produced of the reference treatment angles and these are then used as the standard reference images.

Each patient will have on-treatment imaging on days 1-3, day 9 and day 12.

For each patient and image fraction we will estimate the individual set up errors for the following parameters:

1 CLD- Central Lung Distance

2 CrLD- Cranial Lung Distance

3 CBESD Central Beam Edge Skin Distance

4 CIW Central Irradiated Width

5 CCD Cranio-Caudal Distance

For each individual patient (patient *i*) will estimate the individual mean set-up error, m_i and random set-up error $\square_i$, set up errors for each of the parameters listed above.

For all patients in the support bra group we will calculate the overall population mean set-up error M_{pop} and the population systematic set-up error and the population random set-up error for each of the five parameters. We will also calculate 95% confidence intervals for the overall population mean set-up error M_{pop} and the population random set-up error. This will be repeated for patients in the control group.

We will then compare the study estimates of the population mean set-up error M_{pop} and the population random set-up parameters between the Support bra and control groups with a two independent samples *t* test. We will estimate a 95% confidence interval for the difference between the Support bra and control groups in these parameters for the five parameters from the two independent samples *t* test(36).

We will use this data from this pilot/feasibility study to inform the sample size calculation for the definitive RCT.

This information along with the acceptability of the study design and protocol to patients; patient recruitment and attrition/retention rates will enable us to determine whether or not the definitive RCT is feasible.

17.2 Skin Toxicity

Skin toxicity will be measured using the Radiation Therapy Oncology Group (RTOG) toxicity scoring scale for acute skin reactions.

The following summaries will be presented: the number and percentages of patients reported as having an RTOG grade 1, 2 or 3 in each treatment arm as well as its associated 95% confidence interval; as well as the difference in skin reactions between each treatment arm and its associated 95% confidence interval for the difference(35). The incidence of dry or moist desquamation in the inframammary fold will also be recorded and compared between control and intervention arms.

18.0 Research Governance

The study will be registered with the local R&D department and Sheffield Hallam University will act as the sponsor for the Trial. Three committees will be established to govern the conduct of this study: the Trial Steering Committee (TSC), an independent Data Monitoring and Ethics Committee (DMEC) and a Trial Management Group (TMG). The TSC will consist of a neutral chair with clinical and research expertise in radiotherapy, an independent radiographer and two patient representatives. The Committee will meet at 6 months from the start of the trial. The DMEC will consist of a statistician and 2 independent research radiographers with clinical trial expertise. Trial monitoring procedures and site monitoring will be undertaken at a level appropriate to a risk assessment performed by the sponsor or their delegate.

19.0 Trial Management

19.1 Trial Management Group (TMG)

A TMG will be set up and will include:

- The chief investigator –Professor Heidi Probst
- Trial statistician Professor Stephen Walters
- A research radiographer from the Host Institution- Sarah Hieschler.
- The Principal Investigator- Gillian Brown
- A member of the project design team- Heath Reed
- The lead for regulatory requirements for the project- Dr Joe Langley
- Lay representation- Dr Helen Crank
- Lead for PPI- Professor Karen Collins.

The TMG role and responsibilities will be defined in a set of operating procedures.

19.2 Trial Steering Committee (TSC)

The TSC will be made up of an independent chair, two patient representatives from our patient and public involvement group and an independent radiographer. The purpose of the TSC is to monitor progress of the trial and to ensure adherence to the protocol and the principles of Good Clinical Practice.

19.3 Independent Data Monitoring and Ethics Committee (DMEC)

Members of the TMG will propose the DMEC membership and these will be subject to approval by the TSC. The purpose of this group is to monitor progress of the trial and they will be expected to meet at least once (in confidence) during the data collection phase of the trial to review outcomes, reporting these to the TSC where it is deemed appropriate to do so before the end of the trial period.

20.0 Trial Administration and Logistics

20.1. Protocol Compliance

This clinical feasibility study will be conducted in accordance with Good Clinical Practice guidelines and the standards required by the Health and Social Care governance framework for England

21.0 Patient Protection and Ethical Considerations

Risks

The main risk with using a support bra is the potential to increase the surface (skin) dose that the patient receives compared to the skin dose they would experience if the bra were not used. To minimise this risk the bra has been designed using low attenuation materials and we have undertaken a series of experimental tests to assess the likely increase in surface dose. A graph showing the surface dose for no bra, the SuPPORT 4 All bra and thermoplastic material is presented in Appendix 2. Some centres currently use thermoplastic material to immobilise breast tissue. It is estimated using a single point dose measurement test that the SuPPORT 4 All bra increases the surface dose by approximately 6% compared with approximately 11% increase in surface dose when thermo-plastic material is used. An increase of 6% in surface dose is considered within a clinically acceptable spectrum and below that likely to be experienced for those women receiving radiotherapy to the breast at radiotherapy centres where thermoplastic immobilisation methods are employed.

For women in the intervention arm we propose to undertake two CT planning scans:

1. One scan with the S4A bra.
2. One scan without any immobilisation.

This extra CT scan will mean those women in the intervention arm will have an additional radiation exposure. The details of the additional radiation dose is defined below:

CT Planning control group (normal procedure of one CT scan for planning)

Calculated dose per procedure (ie one from control arm) is 7.2 mSv (Local DLP = 258 mGy.cm) (ImPACT CT Patient Dosimetry Calculator Version 1.0.4 27/05/2011 & confirmed by 'Doses to Critical Organs following Radiotherapy and concomitant imaging of Larynx and Breast', Harrison et al, BJR 80 (2007), 989-995).

CT Planning Intervention Group

Calculated dose per procedure (two procedures for the intervention arm) is 7.2 mSv (Local DLP = 258 mGy.cm) (ImPACT CT Patient Dosimetry Calculator Version 1.0.4 27/05/2011 & confirmed by 'Doses to Critical Organs following Radiotherapy and concomitant imaging of Larynx and

Breast', Harrison et al, BJR 80 (2007), 989-995). **Those in the intervention arm require two planning CT scans**.

Pre-Treatment Mega-voltage image- one procedure required for both control and intervention arm: 4 Monitor Unit / image (Local Exposure) 0.6 mSv/MU (Doses to Critical Organs following Radiotherapy and concomitant imaging of Larynx and Breast, Harrison et al, BJR 80 (2007), 989-995).

On-treatment mega-voltage images delivered as part of the radiotherapy fraction no additional dose.

This study will recruit patients who will be receiving standard whole breast radiotherapy. Both arms of the study receive the same radiotherapy treatment. Therefore there is no additional risk arising from this element of standard of care treatment. Patients in the intervention arm (Arm B) receive 1 additional CT planning scan. This study requires exposures to ionising radiation which are detailed in sections 8-12 above. A small fraction of the total radiation dose required by the study is additional to routine clinical care, for Arm B only. The radiation dose for Arm A is identical to that for routine clinical care. Because the patients suitable for the study are generally larger, the breast dose for MV Verification is assumed to be higher as a consequence. For the purposes of ethical assessment this is estimated to be 4MU for the pre-treat MV image.

The total protocol dose for Arm A is 9.6 mSv and for Arm B is 16.8 mSv. This is equivalent to 4.2 and 7.3 years of average natural background radiation in the UK respectively.

Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study is estimated as 0.07 % for Arm A and 0.1% for Arm B. The additional risk to participants in Arm B is 0.04%. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

Burdens

The main burden for participants of this study is the completion of a package of questionnaires aimed at identifying the impact of the support bra on:

- Body image
- Empowerment
- Patient comfort
- Patient modesty
- Skin reactions and
- Acceptability of the bra.

The patients will not be required to attend any further appointments other than those required as standard for radiation therapy. Follow up questionnaires will be sent to participants to complete and return (with stamped addressed envelopes). We have a user representative group (n=11) that have helped refine the bra design and given input to the design of some of the questionnaire tools.

We also have a user representative on our project team who has been involved in the decisions about which outcome tools to use and when they should be given to patients in order to balance burden with developing understanding of the usefulness for the support bra.

Potential Benefits

For those in both the control arm and the intervention arm of the study a benefit is the use of the patient self-reporting tools for skin reactions and for reporting changes in the breast. These self-reporting tools may enable the patient to take an active role in their own care, reporting skin reactions and changes within the breast, potentially increasing the opportunity for greater patient empowerment or facilitating the opportunity for communication between patient and healthcare professional.

For those in the intervention arm there are potential benefits to participation in this feasibility trial as follows:

1. Using the support bra may enable the treatment to be given with the use of only one permanent tattoo thus improving the overall cosmetic outcome of treatment. Results from the BRITER study showed that those women that received ultra violet (non-visible) tattoos reported better body image scores post treatment compared with those women that received traditional black tattoos(37).

2. Using the support bra will improve modesty during treatment enabling the patient to remain covered for the duration of the planning scan and each radiotherapy treatment.

3. For women with larger breasts the support bra may enhance the ability to achieve a homogenous dose distribution at lower beam energies (i.e 6MV rather than 8MV), and potentially may reduce the dose received by organs at risk such as the lung and heart on the affected side. Our phantom and experimental tests to date would indicate this as a potential possibility as a result of the bra design lifting the breast away from the chest wall.

Appendix 1

Assessment Matrix

References

1. Group RTO. Acute Radiation Morbidity Scoring Criteria 2014 [Available from: http://www.rtog.org/ResearchAssociates/AdverseEventReporting/AcuteRadiationMorbidityScoringCriteria.aspx.
2. Andrews CS. Developing a Measure of Cultural-, Maturity-, or Esteem-Driven Modesty Among Jewish Women. Research and theory for nursing practice. 2014;28(1):9-37.
3. Bulsara C, Styles I, Ward AM, Bulsara M. The psychometrics of developing the patient empowerment scale. Journal of psychosocial oncology. 2006;24(2):1-16.
4. Holden RJ, Karsh B-T. The Technology Acceptance Model: Its past and its future in health care. Journal of Biomedical Informatics. 2010;43(1):159-72.
5. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Mühlbacher A, Regier DA, et al. Constructing Experimental Designs for Discrete-Choice Experiments: Report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value in Health. 2013;16(1):3-13.
6. Statistics. OfN. Breast Cancer: Incdence, Mortality and Survival. 2012.
7. Organisation WH. GLOBOCAN data 2008 [Available from: http://www.who.int/research/en/.
8. Hector C WS, Evans PM. . A simulation of the effects of set-up error and changes in breast volume on conventional and intensity-modulated treatments in breast radiotherapy. Phys Med Biol. 2001;46(5):1451-71.
9. Chen SA SD, Mister D, Liu T, Godette K, Torres MA. . Radiation field design and patterns of locoregional recurrence following definitive radiotherapy for breast cancer. Int J Radiat Oncol Biol Phys. 2013;85(2):309-14.
10. Munshi A KS, Bhutani R, Jalali R, Budrukkar A, Dinshaw KA. Factors Influencing Cosmetic Outcome in Breast Conservation. Clinical oncology. 2009;21(4):285-93.
11. Gierga DP TJ, Sharp GC, Jiang SB, Doppke KP, Katz AB, et al. . Target Registration Error with Three-Dimensional Surface Imaging in Setup of Image-Guided Partial Breast Irradiation. . International Journal of Radiation Oncology*Biology*Physics 2005;63(supplement 1):S536-S7.
12. Probst H, Dodwell, D, Gray, J.C, Holmes, M. An evaluation of the accuracy of semi-permanent skin marks for breast cancer irradiation. Radiography. 2006;12(3):186-8.
13. Probst HB, Christopher; Dodwell, David; Green, David; Hart, John. A systematic review of methods to immobilise breast tissue during adjuvant breast irradiation. Radiography. 2014;20(1):70-81.
14. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;312(11):665-73.
15. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. Seminars in surgical oncology. 1992;8(3):161-6.
16. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 1995;333(22):1456-61.
17. Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med. 1993;328(22):1587-91.
18. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 2000;355(9217):1757-70.
19. Bartlett FR, Yarnold JR, Kirby AM. Breast radiotherapy and heart disease - where are we now? Clinical oncology. 2013;25(12):687-9.
20. Group EBCTC. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomised trials. . The New England Journal of Medicine 1995;33:1444-55.

21. McGale PD, Sarah C; Hall, Per; Adolfsson, Jan; Bengtsson, Nils-Olof; Bennet, Anna M.; Fornander, Tommy; Gigante, Bruna; Jensen, Maj-Britt; Peto, Richard; Rahimi, Kazem; Taylor, Carolyn W; Ewertz, Marianne. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiotherapy and Oncology. 2011;100(2):167-75.
22. Taylor CWB, Dorthe; Darby, Sarah C; Gagliardi, Giovanna; Hall, Per; Jensen, Maj-Britt; McGale, Paul; Nisbet, Andrew; Ewertz, Marianne. Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977–2001. Radiotherapy and Oncology. 2011;100(2):176-83.
23. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98.
24. Hayden A RM, Tiver K. Deep inspiration breath hold technique reduces heart dose from radiotherapy for left sided breast cancer. Journal of Medical Imaging Radiation Oncology. 2012;56(4):464-72.
25. Betgen A AT, Sonke JJ, van Vliet-Vroegindeweij C, Bartelink H. Assessment of set-up variability during deep inspiration breath hold radiotherapy for breast cancer patients by 3D-surface imaging. Radiotherapy and Oncology. 2013;106:225-30.
26. Offersen BVO, Marie; Kroman, Niels; Overgaard, Jens. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: A systematic review. Radiotherapy and Oncology. 2009;90(1):1-13.
27. Jagsi R, Ben-David MA, Moran JM, Marsh RB, Griffith KA, Hayman JA, et al. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys. 2010;76(1):71-8.
28. Bentzen SM, Yarnold JR. Reports of unexpected late side effects of accelerated partial breast irradiation--radiobiological considerations. Int J Radiat Oncol Biol Phys. 2010;77(4):969-73.
29. Donovan EM, James H, Bonora M, Yarnold JR, Evans PM. Second cancer incidence risk estimates using BEIR VII models for standard and complex external beam radiotherapy for early breast cancer. Medical Physics. 2012;39(10):5814-24.
30. Bentel GC ML, Whiddon CS, Prosnitz LR. . Acute and late morbidity of using a breast positioning ring in women with large/pendulous breasts. . Radiotherapy and Oncology. 1999;50:277-81.
31. . !!! INVALID CITATION !!! (27, 28).
32. Bulsara CE, Styles I. Development of a Cancer Related Patient Empowerment Scale Using the Polytomous Rasch Measurement Model. 2013. 2013;2(1).
33. Royal College of Radiologists IoPaEiM, Society and College of Radiographers, . On Target: Ensuring Geometric Accuracy in Radiotherapy. London: 2008 November 2008. Report No.
34. Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. International journal of radiation oncology, biology, physics. 2011;79(1):10-8.
35. Altman D.G. MD, Bryant T.N., Gardner M.J. . Confidence intervals and statistical guidelines. Statistics with Confidence. London: British Medical Journal; 2000.
36. Schulz KF AD, Moher D, for the CONSORT Group. . CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. . British Medical Journal. 2010;340(c332).
37. Kirby AM. Survivorship issues following breast radiotherapy [PDF]. 2015 [Available from: http://www.londoncanceralliance.nhs.uk/media/98584/dr-anna-kirby-survivorship-issues-following-breast-radiotherapy.pdf.

Appendix Assessment Matrix

	Prior to randomisation	Post randomisation	RT CT planning Session	Treatment			Post Treatment		
				Week 1	Week 2	Week 3	Week 7	3 months	1 year
Eligibility Checklist	☐								
Informed consent	☐								
Patient measured	☐		☐						
Randomisation Checklist	☐								
Radiotherapy planning		☐ those in the intervention arm will undergo 2 scans 1 with the S4A bra 1 without.							
Radiotherapy Treatment				☐	☐	☐			
Radiotherapy verification				☐ (days 1-3)	☐	☐			

Body Image questionnaire			□			□	□	□	
Technology Acceptance			□						
RTOG HCP			□	□	□	□			
RTOG patient self reporting tool			□	□	□	□	□		
Presence of dry/moist desquamationinfra-mammary fold			□	□	□	□	□		
Breast Oedema patient self reporting tool			□	□	□	□	□		
RT Patient comfort questionnaire			□	□	□	□			
RT modesty and experience questionnaire				□		□			
Patient empowerment questionnaire			□	□	□	□	□		