Health Technology Assessment Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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FULL TITLE OF THE TRIAL

POSNOC - POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy. A randomised controlled trial of axillary treatment in women with early stage breast cancer who have metastases in one or two sentinel nodes

SHORT TITLE/ACRONYM

POSNOC - A randomised trial of armpit (axilla) treatment for women with early stage breast cancer

Version and Date of Protocol:
Final version 1.0, 21 November 2013

Sponsor:	Derby Hospitals NHS Foundation Trust
Sponsor Protocol Number:	RD-5103-001-13
Chief Investigator:	Amit Goyal
ISRCTN Number:	*Insert when allocated*
Funder:	Health Technology Assessment (HTA), National Institute for Health Research (NIHR)

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UK Breast Intergroup	Association of Breast Surgery (UK)
NCRI Breast Clinical Studies Group	NCRI Radiotherapy Clinical Studies Group
Independent Cancer Patients' Voice	Lymphoedema Support Network

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SUMMARY

POSNOC is a pragmatic, randomised, multicentre, non-inferiority trial.

Aim
For women with early stage breast cancer and one or two sentinel node macrometastases, to assess whether adjuvant therapy alone is no worse than adjuvant therapy plus axillary treatment, in terms of axillary recurrence within 5 years.

Patient Population
Women with unifocal or multifocal invasive breast cancer, largest primary lesion ≤5cm, clinically and ultrasound node negative, who undergo sentinel node biopsy (SNB) and have 1 or 2 sentinel node macrometastases (>2mm), with no extranodal extension.

Stratification
- Institution,
- Age (<50, ≥50),
- Breast-conserving surgery (BCS) or mastectomy,
- Estrogen receptor (ER) status (positive, negative),
- Number of positive nodes (1, 2)

Interventions
The study will compare adjuvant therapy alone with adjuvant therapy plus axillary treatment (axillary node clearance (ANC) or axillary radiotherapy (ART)).

Primary Outcome
Axillary recurrence at 5 years

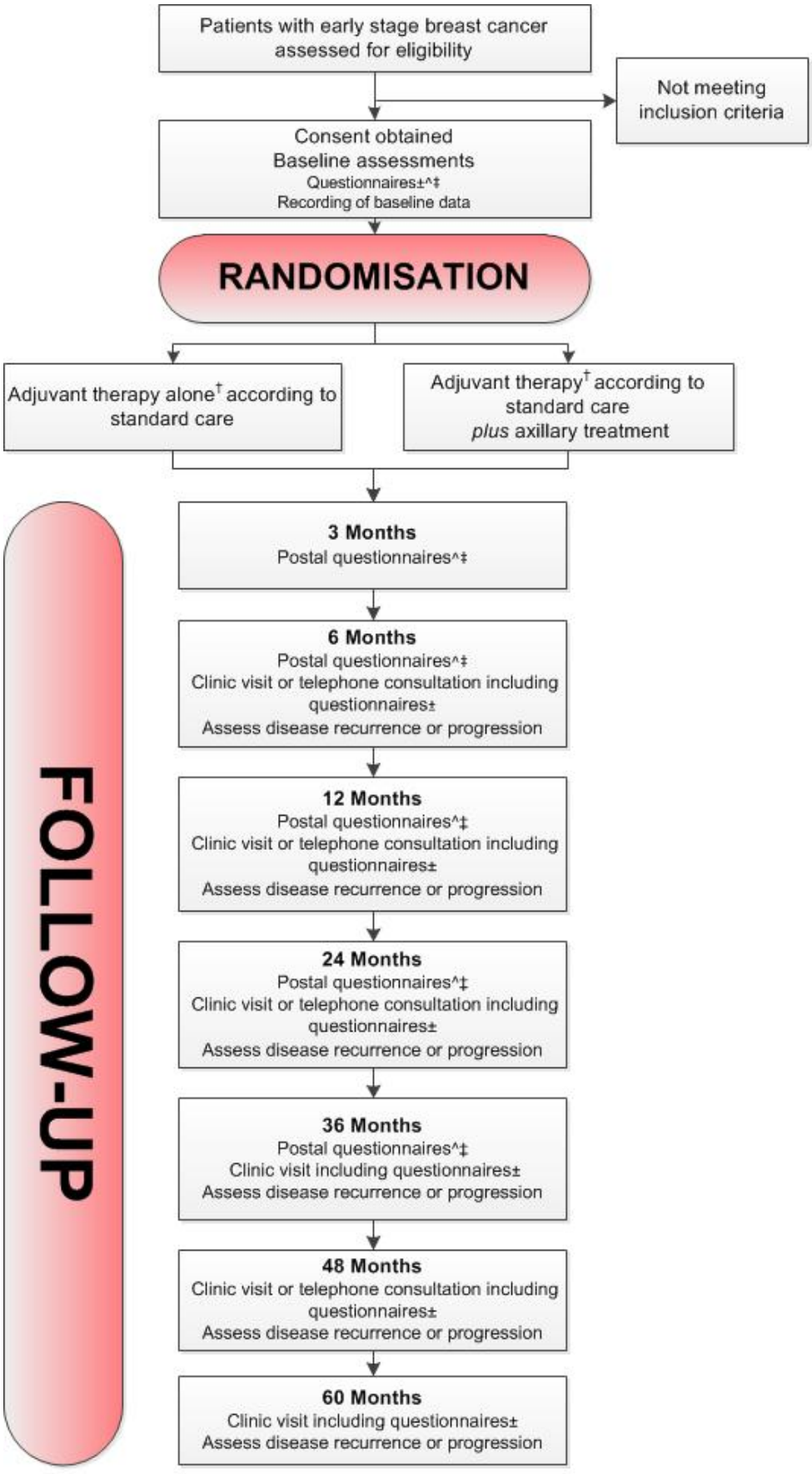
Secondary Outcomes
- Arm morbidity
- Quality of life
- Anxiety
- Local (breast or chest wall) recurrence
- Regional (nodal) recurrence
- Distant metastasis
- Time to axillary recurrence
- Axillary recurrence free survival
- Disease free survival
- Overall survival
- Contralateral breast cancer
- Non-breast malignancy
- Economic evaluation

Sample Size
1900 participants

Duration of Recruitment and Follow-up
Recruitment will be for 45 months. Participants will be followed up for 5 years.

Adjuvant Therapy
All participants will receive adjuvant systemic therapy (chemotherapy and/or endocrine therapy). All participants may receive breast/chest wall radiotherapy. Axillary and supraclavicular fossa radiotherapy is not allowed when randomised to adjuvant therapy alone.

TRIAL FLOW CHART



† Systemic chemotherapy and/or endocrine therapy, with radiotherapy to the breast and chest wall if indicated
± Arm morbidity questionnaires - Lymphoedema and Breast Cancer Questionnaire and QuickDASH
‡ Anxiety questionnaires - Spielberger State/Trait Anxiety Inventory
^ Quality of Life questionnaires - Functional Assessment of Cancer Therapy –Breast +4 and EQ-5D

1 BACKGROUND AND RATIONALE

1.1 Sentinel Node Biopsy

Each year, more than 48,000 women in the UK are diagnosed with breast cancer and the majority (80%) undergo surgical treatment[1]. There is robust evidence that in early breast cancer, sentinel node biopsy (SNB) accurately stages the axilla with low axillary recurrence rates, comparable survival and reduced morbidity when compared with axillary node clearance (ANC)[2-6]. SNB has reduced risk of lymphoedema, shoulder discomfort, sensory deficits, and infections than ANC. Quality of life is superior for patients who undergo SNB[3]. These results have led to widespread adoption of this technique around the world and the Department of Health in the UK supported the NEW START training program which trained UK breast surgeons in this technique[7].

Currently, it is widely accepted that the patient whose sentinel node (SN) is tumour-free does not require further axillary-specific treatment. A quarter of patients (9,600 patients per year) are found to have SN metastases. These patients return for a second operation, ANC or receive axillary radiotherapy (ART).

1.2 Axillary Treatment and Arm Morbidity

The current UK National Institute of Clinical Excellence (NICE) guidelines[8] recommend axillary node clearance or axillary radiotherapy for women with early stage breast cancer and one or two sentinel node metastases. This recommendation is based on the assumption that axillary treatment reduces the risk of axillary recurrence, and might improve survival. Axillary node clearance is usually a second operation, but some hospitals use intra-operative sentinel node assessment and so perform axillary node clearance at the same time as breast conserving surgery or mastectomy.

Axillary treatment damages lymphatic drainage from the arm, and women may subsequently develop lymphoedema. As well as the discomfort of arm swelling this causes restricted shoulder movement, pain, numbness and other sensory problems. For example, following axillary treatment 1 in 5 to 1 in 10 people develop lymphoedema, and between 1 in 5 and 1 in 100 have impairment of shoulder function. Sensory changes and pain may occur in up to 1 in 3 patients[3;9-14]. These adverse effects interfere with daily activities, are distressing, impair quality of life and are costly to the NHS in terms of rehabilitative treatments (such as physiotherapy and lymphoedema clinics), as they are often irreversible and symptom relief is difficult.

1.3 Adjuvant Therapy

All women with 1 or 2 sentinel node metastases will receive systemic therapy (chemotherapy and/or endocrine therapy). Radiotherapy to the breast is required after breast-conserving surgery and may be given after mastectomy. The aim of axillary treatment (ANC or ART) is to reduce the

risk of axillary recurrence. However, systemic adjuvant therapy is now so effective for early breast cancer that axillary treatment may offer no additional protection against axillary recurrence, and so may be overtreatment. This hypothesis is supported by several small studies[15].

In the past, information from axillary clearance with regard to the number of nodes with cancer was used to guide systemic chemotherapy and hormone therapy. However, decisions about these adjuvant therapies are now more commonly based on biological tumour markers and molecular determinants of prognosis and predictors of treatment benefit. Early data from the EORTC AMAROS trial[16] suggests that once patients are found to have cancer spread to lymph glands by SNB; this information is adequate to guide systemic adjuvant therapy, without the need to remove further nodes. In this study chemotherapy was given to 58% (175 of 300) of patients who had axillary node clearance and 61% (162 of 266) who had axillary radiotherapy; and hormone therapy was given to 78% (235 of 300) who had axillary node clearance and 76% (203 of 266) who had axillary radiotherapy. Patients with cancer spread to four or more nodes are candidates for chest wall and supraclavicular fossa radiotherapy[8]. However, the proportion of patients having four or more positive lymph nodes in the AMAROS trial was low (8%)[17]. This figure is estimated to be lower than 5% in the POSNOC trial as ultrasound node negative patients have a lower axillary tumour burden.

1.4 Evidence from Systematic Reviews and Randomised Trials

There is no clear evidence that one form of axillary treatment is better than the other. Axillary radiotherapy has been compared with axillary node clearance in four randomised trials[11;17-19] and several retrospective studies[20;21], with no difference in survival. Regional recurrence with both is low at 1% or 2%; however, both have significant morbidity and are costly to the health services[10;11;13;19-22]. Lymphoedema, sensory changes and pain are more common and more debilitating following axillary node clearance than axillary radiotherapy. Shoulder function impairment is roughly the same after both treatments.

Axillary treatment may now be over treatment for early breast cancer; as diagnosis tends to be earlier so patients present with smaller tumours and a low axillary tumour burden; adjuvant therapy has improved and is better at preventing breast and axillary recurrence[23]; and sentinel node biopsy has already removed the lymph nodes most likely to have metastasis. For example, in one study less than half of patients with sentinel node metastases had metastasis in the remaining nodes at axillary node clearance[7]. Moreover, if adjuvant therapy includes radiotherapy to the breast or chest wall, the lower axilla will be treated inadvertently as it is included in the tangential irradiation field, and some lower level axillary nodes may be removed at mastectomy[24].

There are three randomised trials assessing axillary treatment. The first[18] was a three arm study that recruited 1079 clinically node-negative women. They were randomised to receive either radical mastectomy (mastectomy with axillary node clearance), or total mastectomy with axillary irradiation, or total mastectomy alone without axillary treatment. Women had larger tumours, higher axillary tumour burden compared with today's patients and they did not routinely receive adjuvant systemic therapy. All three arms had similar 25 year overall survival, suggesting that axillary treatment did not improve survival.

The second study[25] randomised 435 clinically node-negative women to breast conservation without axillary treatment or breast conservation plus axillary radiotherapy. Axillary recurrence was low in both groups (no axillary treatment 1.5% vs. 0.5% axillary radiotherapy). Both arms had similar disease free survival.

In the third more recent trial[26] patients with tumours less than 5 cm in size, treated by breast conserving surgery and whole breast radiotherapy, with sentinel node metastases, were randomised to axillary node clearance (n=445) or not (n=446). Axillary recurrence was low, and there were no clear differences between the two groups (axillary clearance 0.5% vs. no axillary clearance 0.9%) at 6.3 years. The trial was terminated before its targeted accrual. There was a potential for bias in this study as the radiation oncologists were aware of the treatment allocation, and it is not reported whether this influenced their decision about how much of the axilla to treat with tangential radiotherapy. Generalisability of the results is limited as some centres recruited fewer than 5 patients, axillary recurrence was not a pre-specified endpoint, mastectomy patients were excluded, and the trial protocol did not mirror NHS practice.

A recent meta-analysis[15] of randomised trials and observational studies which included patients who had sentinel node biopsy concluded that more evidence is needed to guide management of the axilla in patients with early breast cancer and sentinel nodes metastasis.

1.5 Why We Need a Trial Now

Axillary management consensus meeting (Association of Breast Surgery Conference, Bournemouth, 21 May, 2012) vote of 226 UK consultant breast surgeons from 155 hospitals, showed that clinicians are currently at equipoise in terms of effective axillary treatment. Voting results showed that 68.2% would randomise patients in the POSNOC trial, 11.7% were unsure, while 20.1% would not. NICE guidelines stress the need for research to clarify optimum treatment of the axilla in patients with sentinel node metastases[8]. The POSNOC trial will provide evidence relevant to patients and to the NHS. The protocol has been designed to integrate into current NHS practice.

Biological factors may be more important for recurrence than surgical removal or radiation eradication of axillary nodes. If axillary surgery is merely a staging or diagnostic procedure, then adverse effects are likely to be minimal if it is omitted and sentinel node biopsy alone is used to guide subsequent treatment in women with early stage breast cancer who have 1 or 2 sentinel node metastases. Also, axillary treatment (axillary node clearance or axillary radiotherapy) was introduced several decades ago without formal evaluation and is associated with significant short- and long-term morbidity. Since axillary treatment was introduced, chemotherapy and hormone therapy have dramatically improved outcome. Therefore, it is timely to assess whether adjuvant therapy alone is an acceptable alternative to adjuvant therapy plus axillary treatment.

The hypothesis of the POSNOC trial is that low axillary tumour burden patients (clinically and ultrasound negative) with macrometastases in 1 or 2 SNs, receiving systemic therapy, would have non-inferior outcomes whether they are randomised to adjuvant therapy alone or adjuvant therapy plus axillary treatment (ANC or ART).

2 OBJECTIVES

2.1 Primary Objective

For women with early stage breast cancer and one or two sentinel node macrometastases, to assess whether adjuvant therapy alone is no worse than adjuvant therapy plus axillary treatment (i.e. less than 2% absolute risk difference), in terms of axillary recurrence within 5 years.

2.2 Secondary Objectives

(i) To assess lymphoedema and other arm morbidity, quality of life, and anxiety at three years for women in the two allocated groups.

(ii) To assess the following outcomes at five years in the two allocated groups:

- local (breast or chest wall) recurrence,
- regional (nodal) recurrence,
- distant metastasis,
- time to axillary recurrence,
- survival (axillary recurrence free, disease free and overall),
- contralateral breast cancer
- non-breast malignancy

(iii) To determine resource utilization, service implications and cost-effectiveness up to 3 years.

3 TRIAL DESIGN

POSNOC is a pragmatic randomised, multi-centre, non-inferiority trial. Estimated sample size is 1900 participants, with follow up for five years.

3.1 Stratification

- Institution,
- Age (<50, ≥50),
- Breast-conserving surgery (BCS) or mastectomy,
- Estrogen receptor status (ER) (positive, negative),
- Number of positive nodes (1, 2)

3.2 Randomisation

Women will be randomly allocated in a 1:1 ratio to two intervention groups. Sequence generation will be using computer generated random permutated balanced blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure. Participants will be randomised via a study website using a remote, secure internet-based randomisation system developed and maintained by NCTU. The sequence of treatment allocations will be concealed until all interventions have been assigned, recruitment, data collection, and all other trial-related assessments are complete.

It will not be possible to blind clinicians or participants to the treatment allocation. To minimise the potential for bias, we will train and monitor to ensure any breast or chest wall radiotherapy is not influenced by knowledge of whether the woman had axillary treatment, or not. For women randomised intra-operatively we will also monitor to ensure that women allocated no axillary treatment do not have any lymph nodes removed after the sentinel node biopsy. To reduce the potential for participants expectations to influence their responses to the questionnaires, the participant information leaflet and DVD will emphasise that we do not know whether axillary treatment is worthwhile, and that is why we are doing the study.

A procedure for unblinding is not necessary, as the clinicians and participants will know the study allocation.

4 PARTICIPANTS

Women with unifocal or multifocal invasive breast cancer with the largest lesion ≤5cm, who are clinically and ultrasound node negative, have undergone sentinel node biopsy, and have 1 or 2 sentinel node macrometastases (>2mm), with no extranodal extension.

Women will usually be screened for eligibility after their initial breast surgery and sentinel node biopsy. In hospitals where sentinel node histology is checked intra-operatively, allowing axillary treatment if necessary, to be performed at the same time as the breast surgery, women will consent pre-operatively and then randomised intra-operatively if their sentinel nodes are found to be positive.

4.1 Inclusion Criteria

Women will be eligible for inclusion only if **ALL** of the following criteria apply:

- 18 years or older
- Unifocal or multi-focal invasive tumour with lesion ≤5 cm in its largest dimension, measured pathologically or for women who are randomised intra-operatively largest tumour diameter on mammogram or ultrasound
- No axillary nodal metastasis on clinical and ultrasound examination
- At sentinel node biopsy have 1 or 2 sentinel nodes with macrometastases (tumour deposit >2.0mm in largest dimension or defined as macrometastasis on molecular assay)
- Fit for axillary treatment and adjuvant therapy
- Have given written informed consent

4.2 Exclusion Criteria

Women will be excluded if they have:

- bilateral breast cancer
- more than 2 sentinel node macrometastases or extranodal invasion
- neoadjuvant therapy for breast cancer
- previous axillary surgery on the same body side as the scheduled sentinel node biopsy
- not fit or eligible to receive adjuvant systemic therapy
- previous or concomitant malignancy except
    - adequately treated basal or squamous cell carcinoma of the skin or
    - adequately treated *in situ* carcinoma of the cervix or
    - adequately treated *in situ* melanoma
    - contra- or ipsilateral *in situ* breast cancer

4.3 Trial Interventions

All participants will have adjuvant therapy according to local guidelines. Adjuvant therapy will include chemotherapy and/or endocrine therapy for all women, and radiotherapy to breast or chest wall if indicated. Human epidermal growth factor receptor 2 (HER2) targeted treatment may also be administered when indicated.

The trial interventions are either:

(i) Adjuvant therapy alone (intervention)

See above for adjuvant therapy. Axillary and supraclavicular fossa radiotherapy is not allowed when randomised to this group.

(ii) Adjuvant therapy *plus* axillary treatment (Standard Care)

See above for adjuvant therapy. Axillary treatment can be axillary node clearance or axillary radiotherapy as per local guidelines.

5 OUTCOMES

5.1 Primary Outcome

The primary outcome is axillary recurrence at 5 years.

5.2 Secondary Outcomes

Secondary outcomes assessed at 3, 6, 12, 24 and 36 months are:

- Arm morbidity
- Quality of life
- Anxiety
- Economic outcomes

Secondary outcomes assessed at 6, 12, 24, 36, 48 and 60 months are:

- Local (breast or chest wall) recurrence
- Regional (nodal) recurrence
- Distant metastasis
- Time to axillary recurrence
- Axillary recurrence free survival
- Disease free survival
- Overall survival
- Contralateral breast cancer
- Non-breast malignancy

5.3 Criteria for Measurement of Study Endpoints

5.3.1 Description and Definition of Outcomes

- **Axillary recurrence** is defined as cytologically or histologically confirmed recurrence in lymph nodes draining the primary tumour site, i.e. nodes in the ipsilateral axilla, infraclavicular fossa, supraclavicular fossa and interpectoral area.
- **Arm morbidity** will be assessed with questionnaires completed by participants during clinical or telephone follow-up - a) the definition of lymphoedema is 'yes' to the two questions participants will be asked -'heaviness during the past year' and 'swelling now'. These two questions come from the Lymphoedema and Breast Cancer Questionnaire (LBCQ)[27]; b) Shoulder, arm and hand disability is defined as a change from baseline in the QuickDASH[28] score of at least 14 points.

  Quality of life will be assessed with the Functional Assessment of Cancer Therapy-Breast+4 (FACT B+4) questionnaire[29] which asks about physical, social, emotional, functional well-being as well as breast cancer concerns and arm morbidity. Participants indicate, using a five-point scale ranging from 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit), to 4 (very much), to

what degree each item has applied over the past 7 days. The scores of negatively framed statements are reversed for analysis. High FACT scores equate with a good quality of life and lower scores with a poorer one.

The primary Quality of life endpoint is the FACT-B+4 trial outcome index (TOI) score (The TOI score is a sum of the scores of the 28 items included in the physical well-being (7 items), functional well-being (7 items) and breast cancer subscales (14 items) of the FACT-B+4 (range from 0-112)). A change of at least 5 points from baseline in the TOI, is considered to be clinically relevant minimally important difference[30].

The total FACT B+4 score reflects global quality of life and comprises the physical (7 items), functional (7 items), social (7 items) and emotional well-being (6 items) plus the breast cancer concerns and arm morbidity scale (14 items) (total of 41 items; total score ranges from 0-164).

The 5 item arm morbidity subscale score comprises the sum of the scores from items B3, B10, B11, B12, B13 (range 0-20) and will be analysed separately. Analyses will include the proportion of participants in the two allocated treatment groups reporting 'somewhat', 'quite a bit' and 'very much' for each of the 5 items.

- **Anxiety** will be assessed using the Spielberger State/Trait Anxiety Inventory[31]. The STAI consists of 2 questionnaires with 20 items. It assesses anxiety proneness (Trait) and the current state of anxiety or anxiety change (State). Each item is rated on a four point Likert scale. High STAI scores signify greater anxiety. The Trait anxiety is measured only once and the State at each time point.
- **Economic outcomes** will use the EQ-5D utility scores as a measure of health outcome. For more details, see section 13.
- **Local (breast or chest wall) recurrence** is defined as pathologically confirmed recurrence after mastectomy in the skin or soft tissue of the chest wall within the anatomical area bounded by the mid-sternal line, the clavicle, the posterior axillary line and the costal margin or any type of breast carcinoma in the breast after conservation therapy. The date of local recurrence is the date on which the pathology report confirms recurrence.
- **Regional (nodal) recurrence** is defined as recurrent tumour in the lymph nodes in the ipsilateral axilla, infraclavicular, supraclavicular fossa, interpectoral area or ipsilateral internal mammary chain. The date of regional recurrence is the date on which the pathology report confirms recurrence.
- **Distant metastasis** includes all other sites of recurrence and may include those classified as: soft-tissue category, visceral category, central nervous system and skeletal spread. The date of distant metastasis is the date on which radiology or pathology report (whichever comes first) confirms metastasis.
- **Time to axillary recurrence** is the time between the date of randomisation and the date of axillary recurrence, measured in days. The date of axillary recurrence is the date on which pathology report confirms recurrence.

- **Axillary recurrence free survival** is the time between the date of randomisation and date of confirmed axillary recurrence or date of death, whichever comes first, measured in days. Participants who did not experience axillary recurrence and are still alive will be censored at the date of last follow up.
- **Disease free survival** is defined as the time between the date of randomisation and the date of disease progression (i.e. local or regional recurrence or distant metastasis) or death, whichever comes first, measured in days. Participants who do not have progression and are still alive will be censored at the date of last follow up.
- **Overall survival** is the time between the date of randomisation and the date of death from any cause. Participants who are still alive will be censored at the date of last follow up.
- **Contralateral breast cancer** is new primary malignancy in the opposite breast unless obviously contiguous with recurrent chest wall disease or proven on cytology/biopsy to be of metastatic origin.
- **Non-breast cancer** is any new non-breast primary malignancy. except for adequately treated, superficial squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix.

5.3.2 Clinical Care Following Disease Recurrence or Progression

If there is disease recurrence and progression then participants should be treated according to local guidelines.

6 PARTICIPANT IDENTIFICATION

Potential trial participants will be identified at the routine multi-disciplinary meetings. The trial will be introduced and discussed with the patient by the treating clinician during the results clinic appointment (depending on how the patient reacts to the results) followed by a further discussion with the research nurse. Patient information leaflet (PIL) will be given to the patient. Patient information DVD will be used as an adjunct to PIL. The DVD will contain trial explanation together with frequently asked questions relating to randomisation and study visits. If time allows, the DVD will be viewed by the woman in the presence of the research nurse. Women will be encouraged to take the information home and discuss the trial with their family ahead of making an informed decision. Patient will be given sufficient time to consider the information and reach a decision, this may include coming for another clinic visit.

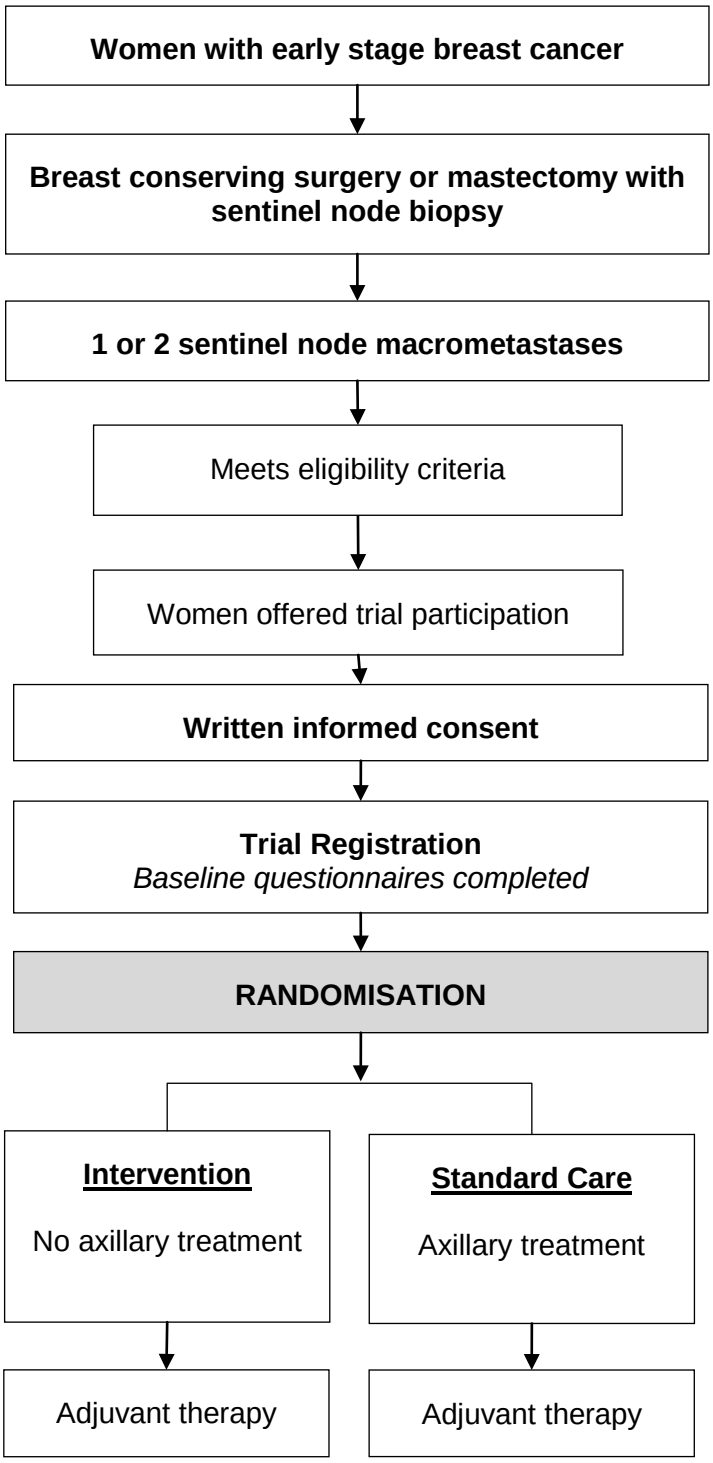
Based on local hospital practices, there are two participant pathways for recruitment:

(i) *After primary breast surgery:* In most hospitals results of the sentinel node biopsy are not available immediately. Women who have a positive sentinel node will be approached with regard to participation in the trial at the first post-operative clinic visit (See section 6.1).

(ii) *Before primary breast surgery:* In a few hospitals (less than 10%) sentinel node assessment is performed in the operating room during primary breast surgery. In these hospitals, women will be approached with regard to the study before surgery. If they are willing to participate consent will be obtained prior to surgery, but they will be randomised intra-operatively only if the sentinel node/s are confirmed as positive (See section 6.2).

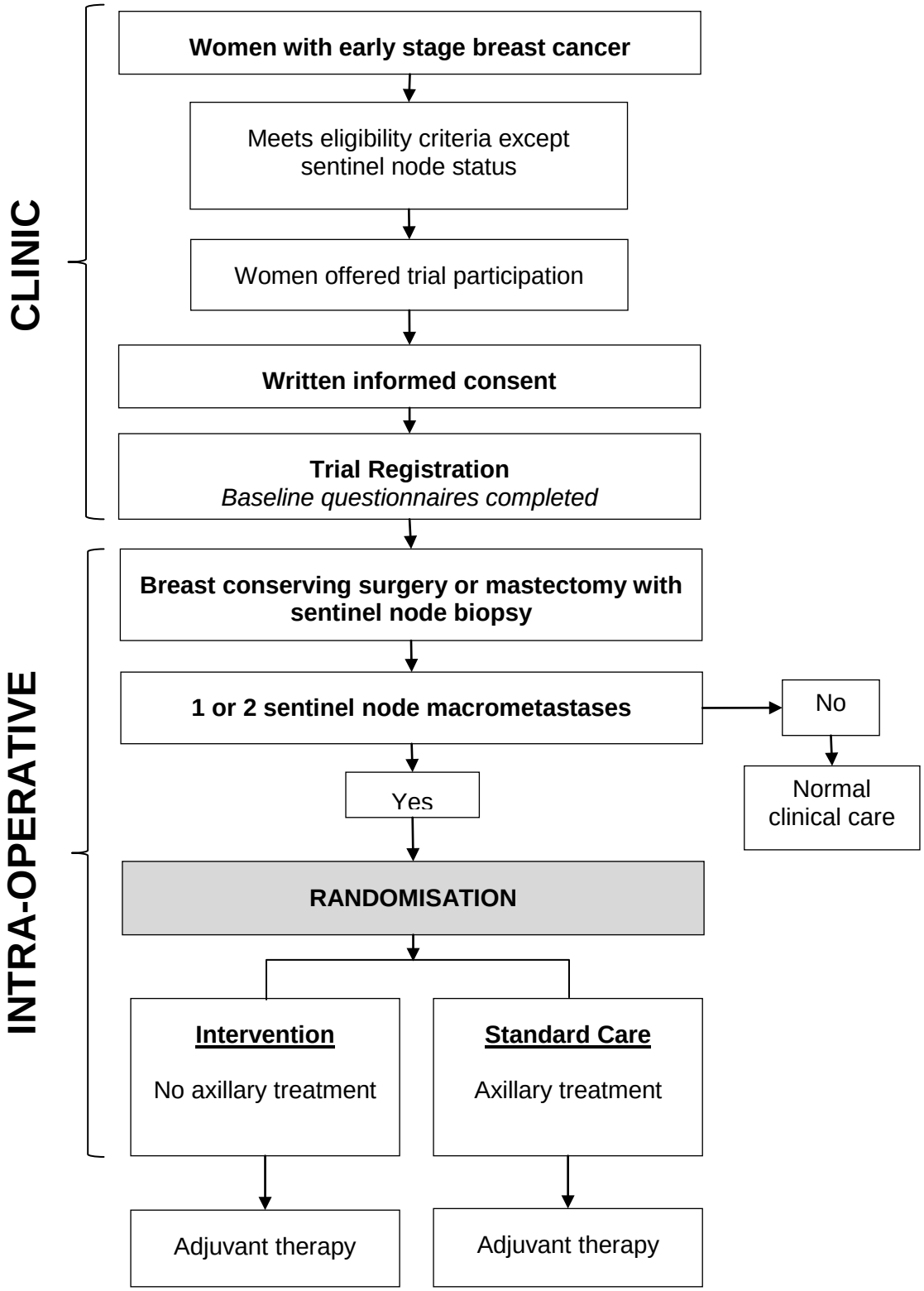
6.1 Pathway 1: After Primary Breast Surgery

After primary breast surgery and sentinel node biopsy, the clinical team will decide whether the participant would be appropriate for axillary treatment. Eligible women will follow the pathway below:



6.2 Pathway 2: Before Primary Breast Surgery

Eligible women will be consented and registered before primary breast surgery. Women will be randomised intra-operatively if macrometastases are found in 1 or 2 sentinel nodes as shown below:



6.3 Registration Procedures

1. Confirm eligibility
2. Obtain written informed consent
3. Trial registration
4. Obtain baseline data for demographics, tumour and nodal characteristics, receptor status, arm morbidity, quality of life and anxiety via questionnaires

6.4 Randomisation

The actual allocation will be disclosed on the computer screen and a confirmation email will follow to the person recruiting the participant.

7 TREATMENT PLAN

7.1 Primary Breast Surgery

Primary breast surgery can consist of either breast conserving surgery or mastectomy.

7.1.1 Breast Conserving Surgery

Participants will undergo resection of the breast tissue, which contains the primary breast tumour with a clear margin of normal tissue around the periphery of the tumour. Circumferential margins must be assessed and deemed tumour free (as per local protocol) by the institutional pathologist. Participants with involved margins should undergo re-excision or mastectomy. This can be performed before or after randomisation.

7.1.2 Mastectomy

Participants may undergo simple, skin sparing or nipple sparing mastectomy with or without immediate breast reconstruction.

7.2 Sentinel Node Biopsy

Sentinel node biopsy should be performed using a combination of blue dye and radioisotope *or* radioisotope alone as per the established institutional protocol. This protocol does not dictate which injection technique or blue dye should be used, but no more than four gross SNs should be removed. At times, the pathologist may identify more lymph nodes than the surgeon and this is acceptable. For hospitals using intra-operative sentinel node assessment, further sampling after randomisation is not allowed. A blue node is defined as any node which is visibly blue or contiguous with a blue lymphatic vessel. A hot node is defined as any node with an isotope count at least 10% of the hottest node *or* a node with counts more than 10 times the background count. Any clinically suspicious nodes should also be removed. All nodes should be labelled and sent to the laboratory separately. Participants with failed localisation are not eligible for the trial.

The number of sentinel nodes removed will be monitored by reviewing the pathology report. Prompt action will be taken if there is any indication that the protocol is not being adhered to. It is expected that in most cases, the trial management group (TMG) will work with the investigator to improve performance. However, the TMG shall suspend site participation, if necessary.

7.3 Pathology

All lymph nodes should be examined according to the predefined local practice: For pathological examination, each sentinel node is processed separately. Immunohistochemical staining may be used selectively to characterize suspicious or micrometastatic disease. The pathology report should mention the results of H&E/IHC staining for each sentinel node and non-sentinel nodes. In case of additional axillary lymphadenectomy the conclusion should consist of the total number of lymph nodes examined and the number with metastases. Whether the lymph node metastasis is considered to be a macrometastasis (> 2 mm) or not, and extranodal invasion should be noted in the pathological report.

Intra-operative molecular analyses can be used to analyse either the whole sentinel node or half of the sentinel node with follow-up histopathology on the remaining half to confirm the results according to local guidelines.

7.4 Axillary Treatment

Participants randomised to standard care will undergo axillary node clearance or axillary radiotherapy as per local guidelines.

7.4.1 Axillary Node Clearance (ANC) for Standard Care

Participants will undergo removal of at least level I and II axillary lymph nodes.

7.4.2 Axillary Radiotherapy (ART) for Standard Care

Participants will undergo axillary irradiation therapy as per local radiotherapy guidelines. Radiotherapy will be monitored as described in the accompanying RT planning and delivery guidelines.

7.5 Adjuvant Therapy

7.5.1 Chemotherapy and Endocrine Therapy

All participants will receive currently accepted adjuvant chemotherapy and HER2 targeted treatment according to pre-defined local guidelines. They may receive currently accepted endocrine therapy in addition to chemotherapy or as a single agent endocrine adjuvant treatment.

7.5.2 Radiotherapy

All participants receiving radiotherapy should be treated according to local guidelines and monitored for compliance according to the POSNOC radiotherapy planning and delivery guidelines (see accompanying radiotherapy manual). Accepted fractionations include 40Gy in 15, 50Gy in 25 or 45Gy in 20 daily fractions. All participants should be CT scanned and 3-D planned in order to optimise target coverage and reduce dose to organs at risk. It is not compulsory to outline any target volumes or organs at risk, however if a centre wishes to do so this is encouraged.

Participants in both groups may receive adjuvant breast or chest wall irradiation therapy as per pre-defined local guidelines. The irradiation therapy for this protocol specifically excludes axillary and supraclavicular fossa irradiation when randomized to adjuvant therapy alone as this would confound the issue being addressed by this study. It is recognised that a variable amount of the axilla may be irradiated unintentionally by standard breast/chest wall tangential fields**.** However, unless definitive RT to the axilla is selected in preference to axillary node clearance surgery, no attempt should be made to irradiate the axilla by adjustment of the superior/posterior tangential field margins.

8 STUDY PARAMETERS

8.1 Study Calendar

Time point	Intervention/Procedure						
	Pathway 1 **After Primary Breast Surgery**				**Pathway 2** **Before Primary Breast Surgery**		
Baseline	• Verify eligibility • Obtain informed consent • Trial Registration				• Verify eligibility except for sentinel node status, this to be obtained during surgery • Obtain informed consent • Trial Registration		
Baseline recordings	Record demographics				Record demographics		
	Record tumour and nodal characteristics Record receptor status						
Baseline questionnaires	1. Lymphoedema and Breast Cancer Questionnaire and QuickDASH 2. Functional Assessment of Cancer Therapy –Breast +4 3. EQ-5D 4. Spielberger State/Trait Anxiety Inventory						
Randomisation	Intervention – adjuvant therapy alone Standard Care – adjuvant therapy plus axillary treatment				Intra-operative randomisation following confirmation of eligibility[¥] Intervention – adjuvant therapy alone Standard Care – adjuvant therapy plus axillary treatment		
Baseline recordings					Record tumour and nodal characteristics Record receptor status		
Systemic therapy	Chemotherapy and/or endocrine therapy						
Radiotherapy	Breast or chest wall radiotherapy, if indicated. *NB: Axillary and Supraclavicular fossa (SCF) radiotherapy is not allowed in the Intervention group.*						
Follow-up (months)	**3***	**6***	**12***	**24***	**36****	**48***	**60****
Lymphoedema and Breast Cancer Questionnaire and QuickDASH (arm morbidity)		X[$$]	X[$$]	X[$$]	X[$$]		
Functional Assessment of Cancer Therapy – Breast +4 and EQ-5D (Quality of life)	X[$]	X[$]	X[$]	X[$]	X[$]		
Spielberger State/Trait Anxiety Inventory (anxiety)	X[$]	X[$]	X[$]	X[$]	X[$]		
Assessment of disease recurrence or progression		X	X	X	X	X	X

[¥] For ineligible participants, no further data will be collected
* Follow up will be clinic visits or telephone consultation (doctor or nurse led)
** Follow up will be clinic visits (doctor or nurse led).
[$] Questionnaires are posted by SHORE-C with up to two reminders (by post or telephone).
[$$] Questionnaires are completed in clinic or over telephone by site staff.
Shaded areas indicate that those recordings are not performed at that time points in that particular pathway

NB: the date of the follow-up appointments are calculated from the date of randomisation.

8.2 Study Assessments

8.2.1 Baseline

Baseline data will be collected from the participant's medical notes and questionnaires.

8.2.2 Follow-up Assessments

Follow-up will be at 6, 12, 24, 36, 48 and 60 months post randomisation. The 36 and 60 months follow-up will be a clinic visit (doctor or nurse led), however follow-up at other time points may be conducted by a research nurse over the telephone, according to local practice.

Assessments:

1. Follow-up eCRFs will be completed in the clinic or over the telephone to record information on primary and secondary outcomes at 6, 12, 24, 36, 48 and 60 months,
2. Lymphoedema and Breast Cancer Questionnaire (two questions) and QuickDASH questionnaire will be completed in the clinic or over the telephone at 6, 12, 24 and 36 months,
3. Postal questionnaires with up to two reminders, FACT B+4, Spielberger State/Trait Anxiety Inventory and EQ-5D at 3, 6, 12, 24 and 36 months.

9 Participant Ceasing Participation

Women are free to stop study participation at any time without giving a reason. Participants may stop taking part in the Quality of Life study but may continue with the treatment follow-up phase. Stopping participation in the Quality of Life (QoL) study will be recorded in the QoL specific database.

Ceasing participation in trial follow-up will be recorded in the eCRF. Data already collected will be included in the analysis, unless participants specifically request for their data not to be used.

Women who consent to take part but cease participation prior to randomisation will receive routine NHS care. Further research data will not be collected for these women and any data already collected will be securely kept at site until the end of the study and then destroyed in a confidential manner.

Participants who withdraw will not be replaced.

9.1 Trial Discontinuation

The sponsor and Funder reserve the right to discontinue this study at any time for failure to meet expected recruitment goals, for safety or any other administrative reason. The Sponsor and Funder shall take advice from the Trial Steering Committee as appropriate in making this decision.

All participation may be stopped if the study sponsor or REC terminate the study prior to the planned end date.

9.2 Participant Retention

Once a woman has been randomised, the study site will make every reasonable effort to follow the participant for the entire study duration. We anticipate a maximum of 5% loss to follow up over 5 years.
All reasonable attempts will be made to contact any participant lost to follow-up during the course of the study in order to complete assessments.

9.3 Definition of End of Study

The end of the study is defined as the “last data collection for the last participant”.

10 Adverse Events

In this study the participants are women with early stage breast cancer, who are at risk of adverse outcome due to their condition. The study is comparing two different policies for treatment of early stage breast cancer, to assess whether their effects are comparable. Adverse events (AE) that could be influenced by the trial interventions are therefore outcomes for the study. Data on these events will be recorded on the case report forms.

10.1 Serious Adverse Events

For POSNOC any unexpected and serious adverse event, considered to be potentially related to the trial, will be reported as an SAE. All SAEs will be followed until resolution or the event is considered stable.

Although death is one of the outcomes for this study, death before completion of the five-year follow-up will be considered as a serious adverse event (SAE).

10.2 Safety Reporting

Whilst it is not anticipated there will be any serious adverse events directly related to the study, it is important that this protocol includes a process for dealing with any unexpected serious adverse events in the unlikely event they occur.

All unexpected Serious Adverse Events (SAEs) that occur in participants recruited to the POSNOC trial should be reported via the trial SAE form and submitted to Nottingham CTU on fax number 0115 7484091.

PI's have the responsibility of safety reporting for the participants recruited to POSNOC at their sites. It is the responsibility of the CI to review any SAEs submitted by investigator sites.

All unexpected SAEs will be reported to the NCTU within one working day. The Chief Investigator will submit, regularly for the duration of recruitment to the trial or upon request, a safety report to the Data Monitoring Committee which will include all reported unexpected SAEs. The Data Monitoring Committee will have immediate oversight of all unexpected SAEs.

10.3 Annual Progress Reports

The CI will send the annual progress report to the main REC (the anniversary date is the date of the REC 'favourable opinion' letter) and to the sponsor.

11 DATA COLLECTION

The trial data will be collected via the study electronic case report form (eCRF), worksheets and questionnaires. The agreed data collection time points are specified in the Study Calendar in section 8.1.

11.1 Data Forms and Data Entry

Trial data will be recorded prior to discharge from hospital and at each follow up visit. The data will be entered at site into electronic case report forms (eCRF) directly or onto worksheets. The worksheet data must be transferred into the eCRF within 5 days of data collection. Participants will be identified only by their unique study number.

The trial database will be developed and maintained by the trial coordinating centre at the Nottingham Clinical Trials Unit (NCTU). Access to the database will be restricted and secure. Data quality and compliance with the protocol will be assessed throughout the trial by central statistical monitoring and site visits.

Processing of trial data and monitoring for consistency, validity and quality will be undertaken by NCTU according to their agreed monitoring plan. Data checks will include out-of-range data, cross-checks for conflicting data, missing data and data queries.

The completed Quality of Life (QoL) questionnaires (FACT B+4, and Spielberger State/Trait Anxiety Inventory) and the EQ-5D will be sent to SHORE-C (Sussex University) for entry into their trial specific questionnaire database. SHORE-C will process and monitor follow-up questionnaire data as the questionnaires are received. The SHORE-C database will be transferred to the NCTU for reconciliation with the NCTU trial database for the purpose of statistical analysis. Participants who do not return their questionnaires will be telephoned after two weeks by SHORE-C researchers. Missing data and data queries will be addressed by SHORE-C directly to the participant by sending a data query by post or telephone.

11.2 Flagging with the Health and Social Care Information Centre (HSCIC)

All women recruited to the study will be ‘flagged’ after discharge through the Data Linkage and Extract Service at the Health and Social Care Information Centre (HSCIC). Information from the Health and Social Care Information Centre may be used to help contact participants, check their health status. This will avoid causing unnecessary distress to the family, as it will avert inappropriate contact if the woman has died following discharge from hospital. It will also reduce losses to follow up.

11.3 Source Data

Source documents shall be filed at the local site and may include but are not limited to consent forms, current medical records, worksheets and participant questionnaires. QoL and EQ-5D questionnaires will be held at SHORE-C. The predefined data in the eCRF's may also be source data.

12 STATISTICS

The trial statisticians will draft the Statistical Analysis Plan (SAP), which will be reviewed by the Trial Management Group (TMG), the Trial Steering Committee (TSC), and the Data Monitoring Committee (DMC). The finalised SAP will be approved and signed by the CI, trial statistician and chair of the TSC.

12.1 Sample Size

For women who have adjuvant therapy plus axillary treatment, 2% have axillary recurrence at 5 years[32]. With an absolute non-inferiority margin of 2%, to show that the axillary recurrence rate in the adjuvant therapy alone group at 5 years is not more than 4%, with a one-tailed test for non-inferiority, 1800 women need to be randomised (with 80% power).

12.1.1 Drop-out Rate

Within the NHS, failure to attend for breast cancer follow up clinic visits is unusual. For this study, we anticipate a maximum of 5% loss to follow up over 5 years. This is realistic, for example in one recent UK breast cancer trial of local treatment[33] losses to follow up were 1.6% at 5 years. Allowing for 5% lost to follow up over the 5 years, gives a sample size of 1900 women. We estimate that to recruit 1900 women we would require 50 sites and 45 months recruitment.

12.1.2 Non-inferiority Margin

Following consultation with relevant breast cancer consumer groups, lay people, and with breast surgeons and oncologists we have opted for a 2% non-inferiority margin. The consensus across all these groups was that a 2% margin for axillary recurrence is an acceptable trade-off for the increase in arm morbidity associated with axillary treatment.

Axillary recurrence following axillary treatment is estimated to be 2% at 5 years. Therefore, a 2% non-inferiority margin means accepting that 4% of women who have adjuvant therapy alone will have axillary recurrence at 5 years. This is lower than the level recommended by the Association of Breast Surgery, whose guidelines state that axillary recurrence at 5 years should be less than 5%[34]. This margin appears to be acceptable to women with early breast cancer, as demonstrated in a trial of alternative treatments[17] that used a 2% non-inferiority margin based on axillary recurrence and successfully recruited 4806 participants.

12.2 Statistical Methods

Trial Feasibility Phase

The trial has an internal feasibility phase where an assessment will be made after 12 months recruitment as to whether to continue with the study. This assessment will be made by the independent Trial Steering Committee (TSC), in consultation with the Data Monitoring Committee.

The assessment will be against criteria for recruitment, compliance with the intervention, and retention agreed a priori with these committees.The TSC will then recommend to the funder and the sponsor whether the trial should continue.

Recruitment to the trial will continue whilst the feasibility assessment is being conducted.

12.3 Statistical Analysis

Analysis will be at the end of the five years follow up of the last recruited participant. The detailed Statistical Analysis Plan will be developed by the Trial Statisticians in consultation with the Trial Management Group, and agreed with the TSC before database lock and unblinding of the data.

Recruitment at each site will be summarised, along with the main reasons why eligible women were not recruited. For women recruited to the trial, baseline characteristics in the two allocated groups will be described, and compliance with the allocated intervention documented.
The primary analysis will be per protocol for the primary and secondary endpoints. Intention to treat (ITT) analysis will not be performed as the primary analysis because if there are individuals who default from the allocated intervention, the observed difference between the two groups may be reduced. Therefore, an ITT analysis may wrongly declare non-inferiority and is not appropriate for this study.

The primary objective is to assess whether adjuvant therapy alone is non-inferior to adjuvant therapy plus axillary treatment based on the primary endpoint of axillary recurrence at 5 years. The non-inferiority margin has been set at 2% based on consultation with clinicians and women who have had breast cancer. Non-inferiority of adjuvant therapy alone over adjuvant therapy plus axillary treatment will be accepted if the upper boundary of a standard two-sided 95% confidence interval around the estimated difference in axillary recurrence rate lies below 2%.

Secondary intention to treat and CACE (Complier Average Causal Effect) analyses will be performed for the primary and secondary endpoints. All outcome measures will be compared between the two groups by standard methods, including summary statistics and confidence intervals for measures of effect size. Proportional hazards regression analysis will be performed for time-to-event outcomes such as time to axillary recurrence, axillary recurrence free, disease free and overall survival up to 5 years. Appropriate adjustments will be conducted in case of violations of assumptions of proportionality of hazards and time independence. Other secondary binary outcomes will be compared between the two groups by estimating the differences and ratios of proportions including the Miettinen-Nurminen confidence intervals[35].

Competing risk methodology will be applied for estimating the disease free survival and the axillary recurrence free survival where death is a competing event.

Subgroup analyses

The following pre-specified subgroup analyses based on criteria at trial entry shall be performed:

1. Number of sentinel node macrometastases: 1, 2
2. Age : <50 years, ≥50 years
3. Breast surgery: mastectomy, breast conserving surgery
4. Estrogen receptor (ER) status: positive, negative
5. Tumour grade: grades 1 or 2, grade 3

A two-way subgroup analysis will be performed for the outcomes: axillary recurrence and arm morbidity (measured by LBCQ (2 questions), QuickDash and FACT B+4 arm morbidity subscale). First an interaction term of "treatment group by factor" will be used in a factorial model. If the interaction term reaches significance level of 0.1, the primary endpoint will also be compared between the treatment groups for each subgroup separately. The effect sizes and confidence intervals will be reported.

For adjuvant therapy plus axillary treatment arm, axillary recurrence and arm morbidity (measured by LBCQ (2 questions), QuickDash and FACT B+4 arm morbidity subscale) will be described for participants undergoing axillary radiotherapy and axillary node clearance.

Quality of Life

Quality of life outcomes will be analysed according to per protocol analysis. Any missing data and / or imputation will follow standardised rules as defined by the relevant manual for the relevant questionnaires. Any changes in state anxiety over time will be examined using analysis of covariance (ANCOVA) with trait anxiety and baseline state as covariates. Mean change scores for FACT B+4, TOI and subscales will be compared between groups using unpaired t tests at each time point and using ANCOVA over time adjusting for the baseline dependant variable.

12.4 Analysis Population

Participants who receive their allocated treatment will be included in the primary per protocol analysis. Secondary analysis will be intention to treat and CACE including all participants randomised to each treatment group regardless of their received intervention.

12.5 Missing Data

Every effort will be made to minimise the occurrence of missing data. All missing data items will be tabulated by treatment arm and reasons given where possible. We will examine the plausibility that primary outcome data are missing at random (MAR) and multiple imputation techniques will be used to handle missing values as appropriate. Sensitivity analyses will be considered for testing

the robustness of the MAR assumption. A complete case analysis will be performed for secondary outcomes with less than 1% missing data, otherwise techniques similar to primary outcome will be applied.

13 HEALTH ECONOMIC ANALYSIS

The objective of the economic evaluation in this trial is to determine the average costs per participant for the test and control regimens, in relation to the outcomes achieved. As both participant survival and health-related quality of life (HRQL) will be measured, it will be possible to carry out a cost-utility analysis, relating differences in costs to differences in quality adjusted life-years (QALYs).

For each participant, all clinical events (i) relevant to management and consequences following the initial sentinel node biopsy (adjuvant therapy alone or adjuvant therapy plus axillary treatment) (ii) up to the end of follow-up (iii) which occur in the hospital setting, will be recorded. These include primary treatments, re-admissions for complications or recurrences and associated adverse events. Events deemed unrelated to the consequences of the sentinel node biopsy or axillary treatment will not be included. At 6 months follow-up, participants will be asked to recall the extent to which they accessed primary care or other non-hospital services. The trial is being evaluated from the NHS perspective and all clinical events will be costed at current tariffs (reference costs), irrespective of the particular hospital sites of treatment. On the basis of each participant's record and the tariffs, a total hospital cost for each participant for the duration of follow-up will be calculated. Unit costs of non-hospital events generated by participants (if any) will be obtained from recognised authorities, e.g. the Personal Social Services Research Unit.

For the economic evaluation, HRQL will be evaluated using the EQ-5D-5L (EuroQoL) instrument in a longitudinal design for all participants entered in the study. Nominally, the instrument will be completed at baseline and, thereafter at 3, 6, 12, 24 and 36 months post randomisation. Mean change scores for EQ-5D-5L Index and EQ-5D-5L VAS will be compared between groups using unpaired t tests and over time using ANCOVA adjusting for the baseline variability of the dependent variable included in the model. Plotting scores over 36 months for each participant permits the calculation of the "area under the curve", i.e. the number of quality-adjusted life years (QALYs) accruing post-intervention, up to a theoretical maximum of three. The sums of QALYs for participants accruing in test and control groups will be analysed for significant differences, following allowances for mortality (if occurring). It is anticipated, at 3 years following the initial biopsy, any HRQL differences between test and control participants which might have been present earlier will have disappeared.

The incremental cost effectiveness ratio (ICER) will be calculated as the ratio of the differences in mean costs per participant and the differences in QALYs gained, between intervention and standard care groups. The participant-specific data will provide confidence intervals for costs and outcomes. Those for the ICER will be estimated by Monte Carlo simulation based on the intervals for costs and outcomes.

The breast and sentinel node biopsy procedure, systemic treatment, radiotherapy to breast or chest wall will not be included in the determination of costs, because all participants will undergo this.

14 REGULATORY AND PARTICIPANT INFORMED CONSENT

14.1 Research Ethics Approval

The Chief Investigator (CI), or their delegate, will obtain approval from the Research Ethics Committee (REC), which will be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Principal Investigator (PI) will require a R&D trust approval letter before approaching potential participants for the study.

All subsequent amendments to the protocol and associated documents will be submitted for approval prior to their implementation. The CI will provide reports to REC at the intervals stipulated in the REC guidelines.

14.1.1 Ethical Considerations

The ethical issue is that women randomised to adjuvant therapy alone will not undergo axillary node clearance or axillary radiotherapy and this may be unsettling. Women may be worried that they will potentially have inferior outcomes in terms of cancer recurrence and longevity.

This will be addressed by advising women clearly that we do not know which one is better and both treatments are acceptable. Communication training sessions will be held at participating sites and a participant information DVD will be used to complement the participant information leaflet. The information including randomisation and clinical equipoise will be given in a balanced way. Patient groups such as Independent Cancer Patients' Voice (ICPV) will explore the interpretation of study information.

14.2 Consent

Potential participants are women whose sentinel node is positive. Based on local hospital practices, there are two pathways for recruitment into the trial. In most hospitals, the results of the biopsy are not available until after the sentinel node biopsy surgery but in a few hospitals (less than 10%), the sentinel node assessment is done whilst the woman remains anaesthetised in the operating room. Women who come back to the clinic to discuss their surgery results will be consented post breast surgery (Pathway 1). At hospitals where sentinel node analysis is performed during the surgery, women will be approached and consented for the trial prior to their breast surgery (Pathway 2). Participant in pathway 2 will be made aware that they will be randomised only if the sentinel node is positive.
Consent will be taken by appropriately trained healthcare professionals in the research team.

If the woman does not wish to participate, she will not be required to give a reason. Clinical care will not be influenced by whether or not she agrees to participate. A local site screening log will be

maintained recording all potentially eligible women not approached to give consent, women who decline participation, and reasons for non-participation (if available).

The original consent form (CF) will be kept in the Site Study File and a copy will be given to the participant and a copy will be held in the participant's medical notes.

14.3 Confidentiality

Information about participants will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Caldicott Guardian, Research Governance Framework for Health and Social Care, conditions of REC approval and NHS information governance policy.

A unique identification number will be automatically attributed to each participant randomised in the study.

Participants' addresses and telephone numbers will be captured in a separate secure database and will be used by researchers at NCTU and SHORE-C (Sussex University). SHORE-C will be posting questionnaires to the participants' homes and may contact them by telephone in case of queries. Participant contact details will be confidentially destroyed after the last questionnaire has been received and the queries have been resolved.

14.4 Access to Data

Data collection forms will be treated as confidential documents, and held securely. The PI at each site will make a separate confidential record of the participant to permit identification of all participants enrolled in the study. This information will be stored securely and separately to the anonymised study data.

Access to all data at site will be restricted to personnel approved by the local Principal Investigator, and recorded on a delegation log. Access will also be given to the sponsor, REC and NCTU representatives.

15 QUALITY ASSURANCE

This trial will be conducted in accordance with the current approved protocol, ICH GCP, Research Governance Framework for Health and Social Care, principles of the Declaration of Helsinki, all applicable Standard Operating Procedures (SOPs) and all local Trust policies that impact on the conduct of research and any subsequent amendments.

15.1 Site Start-up and Training

Before trial recruitment begins, a meeting with the Principal Investigators and the local research team will be organised to discuss protocol issues, trial interventions and related clinical issues, data collection issues, and trial procedures.

Each hospital will have a trial Site Initiation Visit (SIV), combining training in the trial procedures from NCTU and QoL metrics by SHORE-C, before their first participant is recruited. SIVs will be coordinated with SHORE-C and NCTU attending the meeting.

15.2 Monitoring

Trial monitoring will be by central monitoring combined with site visits. Central monitoring will be used to monitor patterns of recruitment at sites, reasons for non-recruitment of potentially eligible participants, characteristics of participants recruited, time of recruitment, etc. It will also be used to assess compliance with the protocol, which may include checking compliance with the trial interventions.

Based on assessment of data processing and central monitoring, the TMG will decide if any further action needs to be taken.

When site visits are performed, a random sample of participants will have their data monitored at source (Source Document Verification). Any major discrepancies or concerns at a site visit will trigger a more extensive audit of trial data at that site.

The investigator at a site will permit direct access to source data and study related documentation for study-related monitoring, audits and inspections by the REC, the sponsor and the Nottingham Clinical Trials Unit (NCTU). This study will be monitored by the NCTU according to a monitoring plan, agreed with the sponsor, and the NCTU procedures for monitoring. In line with the responsibilities set out in the Research Governance Framework, the investigator will ensure that the trial manager, sponsor and/or REC representatives are given access to all trial-related documents, including participant medical notes to enable source data verification and trial related facilities.

15.3 Radiotherapy Quality Assurance

There is worldwide evidence to justify the inclusion of radiotherapy quality assurance (RTQA) programmes as an integral part of clinical trial protocols[36-39]. They serve to improve protocol compliance and, in a multi-centre setting, minimise variations ensuring clinical trial outcomes reflect differences in randomisation schedules rather than departures from study protocol.

The NCRI Radiotherapy Trials QA (RTTQA) group will be responsible for implementing and coordinating the Radiotherapy Quality Assurance programme. The QA programme is outlined below:

Pre-trial QA - Prior to site activation, the following must be completed:

- Facility questionnaire – Details of treatment technique, immobilisation, verification and dosimetry will be recorded.
- Control case - All centres must submit a test participant case to the RTTQA group, for review, demonstrating planned radiotherapy treatment to the breast/chest wall, axilla and supraclavicular fossa. The outlining, planning and treatment of this participant case should reflect how the centre intends to plan and treat all participants recruited to POSNOC.

On-trial QA – Ongoing QA requirements

- Retrospective individual case reviews – All centres must export data of their first ten radiotherapy plans to the RTTQA group. Data will include participant history, CT data, structure set, plan and dose files. The retrospective review process should include at least three plans with radiotherapy to the nodal region.
- Ongoing data collection - All radiotherapy plans will be exported to the RTTQA group, regardless of which study allocation. A random sample of plans will be reviewed from each site during trial recruitment.

The sites will be required to adhere to the specific radiotherapy planning and delivery guidelines when treating participants in the study. For data anonymisation and export please see section ‘Data Collection’.

The NCRI Radiotherapy Trials QA (RTTQA) group will promote POSNOC radiotherapy planning and delivery guidelines compliance for the duration of trial recruitment by systematically reviewing a sample of radiotherapy plans submitted by centres.

RTTQA will monitor compliance to the RT planning and delivering guidelines. Any RT guidelines deviations, non-compliance or areas of concern will be recorded and if required, discussed with the TMG and individual centres. The RTTQA has the responsibility for collection and storage of

radiotherapy data related to the RT QA programme. There will be a named RT QA contact for the POSNOC trial.

16 TRIAL MANAGEMENT

16.1 Trial Management Group

Day-to-day management of the study will be the responsibility of the Trial Management Group (TMG), which will meet every one to two months during the recruitment phase and every six months thereafter.

The TMG will review recruitment, retention, compliance and data quality to ensure efficient study conduct according to the research timeline. They will report to the independent Trial Steering Committee (TSC) .

16.2 Trial Steering Committee

The Trial Steering Committee (TSC) will provide independent oversight of the study. They will meet (in person or by telephone conference) prior to commencement of the study, and then at regular intervals until completion (at least annually). Specific tasks of the TSC are:

- to approve the trial protocol
- to approve necessary changes to the protocol based on considerations of feasibility and practicability
- agree trial stopping rules for the feasibility and the main trial
- to receive reports from the Data Monitoring Committee
- to resolve problems brought to it by the co-ordinating centre and TMG
- to ensure publication of the trial results

16.3 Data Monitoring Committee

A separate and independent Data Monitoring Committee (DMC) will be convened. It is anticipated that the members will meet once to agree terms of reference and on at least three further occasions to monitor accumulating data and oversee safety issues. This Committee will be independent of the study organisers and the TSC. During the period of recruitment to the study, data reports will be supplied, in strict confidence to the DMC, together with any other reports that the committee may request. This may include reports of data from other comparable trials. In the light of these data reports, the DMC will advise the Steering Committee if, in its view, there are any ethical or safety issues that may necessitate modification to the protocol or closure of the trial.
The TSC, TMG, clinical collaborators and Coordinating Centre staff (except those who supply the confidential analyses) will remain ignorant of the data reports.

The frequency of interim reports will depend on the judgement of the Chairman and other independent DMC members. We anticipate that there might be two interim reports and one final report.

16.4 Indemnity

NHS indemnity scheme will apply in the event of a claim by, or on behalf of, participants for negligent harm. There will be no special arrangements for non-negligent harm but the normal NHS complaints mechanism will be available to all participants.

16.5 Public and Patient Involvement

As part of the development of the project and protocol, women from the Derby Breast Cancer Support Group, Bosom Buddies (Guildford Breast Cancer Support Group) and Independent Cancer Patients' Voice (ICPV) have commented at all stages on the design and acceptability of the study. The Breast Cancer Care and Lymphoedema Support Network have had the opportunity to contribute to this protocol.

Independent Cancer Patients' Voice is an independent patient advocate group (http://independentcancerpatientsvoice.org.uk/). Two members of ICPV will provide a patient perspective throughout the duration of the study.

16.6 Security and Back-up of Data

Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).Electronic data will be backed up every 24 hours.

16.7 Archiving

The CI is the "Custodian" of the data. Data and all appropriate study documentation will be archived for 5 years after the end of the study, including the final report and publication in peer reviewed journal. The trial master file and study documents held by the CI and NCTU on behalf of the sponsor will be archived in secure archive facilities by Derby Hospitals NHS Foundation Trust. This archive will include all study databases and associated meta-data encryption codes.

Quality of life questionnaires and the accompanying database will be securely archived by SHORE-C.

Exported radiotherapy data will be securely archived by the RTTQA group.

16.8 Dissemination policy

16.8.1 Dissemination plan

The dissemination of the study results will be via a study report and research papers for publication in peer reviewed journals, and presentation at relevant conferences. Reporting will be in compliance with CONSORT recommendations. Publication of the results will be based on outcomes at 5 years following the last recruited patient. No interim publication of results is planned, any unscheduled interim publication would require approval of the TSC.

A summary of the results will be made available to participants through a newsletter (unless they state they do not wish to receive this), and will also be publicised through Independent Cancer Patients' Voice, Cancer Research UK, Breast Cancer Care, Breakthrough Breast Cancer and Lymphoedema Support Network.

16.8.2 Policy for Publication and Authorship

The publication and authorship policy shall be agreed with the collaborators. The first author will be the CI of the study. Authorship will be named authors on behalf of a collaborative group, the named authorship is for those who have made a significant contribution. Additional authors will be those who have contributed to the overall success of the study.

Outcomes by treatment group will not be available for publication before the first results paper has been published.

17 REFERENCE LIST

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Appendices

1. Glossary of abbreviations / acronyms

AE	Adverse Event
ANC	Axillary Node Clearance
ART	Axillary Radiotherapy
BCS	Breast-conserving surgery
CACE	Complier Average Causal Effect
CF	Consent Form
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Record Form
DMC	Data Monitoring Committee
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen receptor
FACT B+4	Functional Assessment of Cancer Therapy-Breast+4
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
HRQL	Health-Related Quality of Life
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention To Treat
ICPV	Independent Cancer Patients' Voice
LBCQ	Lymphoedema and Breast Cancer Questionnaire
MAR	Missing At Random
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
QoL	Quality of Life
QALYs	Quality Adjusted Life-Years
RCT	Randomised Control Trial
REC	Research Ethics Committee
RTTQA	NCRI Radiotherapy Trials QA
R&D	Research and Development department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCF	supra clavicular fossa
SHORE-C	Sussex Health Outcomes Research & Education in Cancer
SIV	Site Initiation Visit
SN	Sentinel Node
SNB	Sentinel Node Biopsy
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TOI	Trial Outcome Index
TSC	Trial Steering Committee

2. Protocol authorisation

Chief Investigator Agreement

The clinical study as detailed within this research protocol (Final version 1.0, 21/112013**)** or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health and Social Care (2005), the World medical association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name:

Signature and Date:

Sponsor Agreement

The clinical study as detailed within this research protocol (Final version 1.0, 21/11/2013) or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health and Social Care (2005), the World medical association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Sponsor Representative Name:

Signature and Date:

Principal Investigator Declaration

I confirm I have read and understood this protocol (Final version 1.0, 21/11/2013) and agree to conduct the study in accordance with the protocol.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date: