University Hospitals of Derby and Burton NHS Foundation Trust

BREAST CANCER TRIALS AUSTRALIA & NEW ZEALAND

NOTTINGHAM CLINICAL TRIALS UNIT POSNOC

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 6.0, 26 Mar 2020

Sponsor: University Hospitals of Derby and Burton NHS Foundation Trust
Sponsor Protocol Number: RD-5103-001-13

ISRCTN Number: ISRCTN54765244
ClinicalTrials.gov: NCT02401685

Funder	
UK	Health Technology Assessment (HTA), National Institute for Health Research (NIHR)
Australia & New Zealand (ANZ)	National Health and Medical Research Council (NHMRC)

Trial Website: www.posnoc.co.uk

Protocol authorised by:		
Name & Role	Date	Signature
Associate Professor Amit Goyal Chief Investigator	31/7/2020	
Dr Teresa Grieve Sponsors Representative		

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Dr Teresa Grieve Sponsors Representative	31st August 2020	Dr Teresa M. Grieve Digitally signed by Dr Teresa M. Grieve Date: 2020.07.31 15:29:53 +01'00'

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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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Protocol Amendments
The following amendments and/or administrative changes have been made to the protocol since the previous version 5.0

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
MA19	26 Mar 2020	6.0	Minor amendment	• As a result of COVID-19 we are implementing remote consent. • Clinic questionnaires may be sent to patients by post to complete where the research team have been unable to complete with the patient over the telephone

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SUMMARY

POSNOC is a pragmatic, randomised, multicentre, non-inferiority, international (UK, Australia & New Zealand) trial.

Aim
For women with early stage breast cancer and one or two nodes with 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, who undergo sentinel node biopsy (SNB) and have 1 or 2 nodes with macrometastases (>2mm or defined as macrometastasis on molecular assay).

Stratification
- Institution,
- Age (<50, ≥50)
- Breast-conserving surgery (BCS) or mastectomy
- Estrogen receptor (ER) status (positive, negative)
- Number of positive nodes (1, 2)
- Intra-operative sentinel assessment using OSNA (yes, no)

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 within 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
- Cost to the National Health Service (NHS) over 3 and 5 years
- Quality-adjusted life years (QALYs) based on responses to the EQ-5D-5L
- Incremental cost per reduction in axillary recurrence at 5 years
- Incremental cost per QALY gained at 3 years

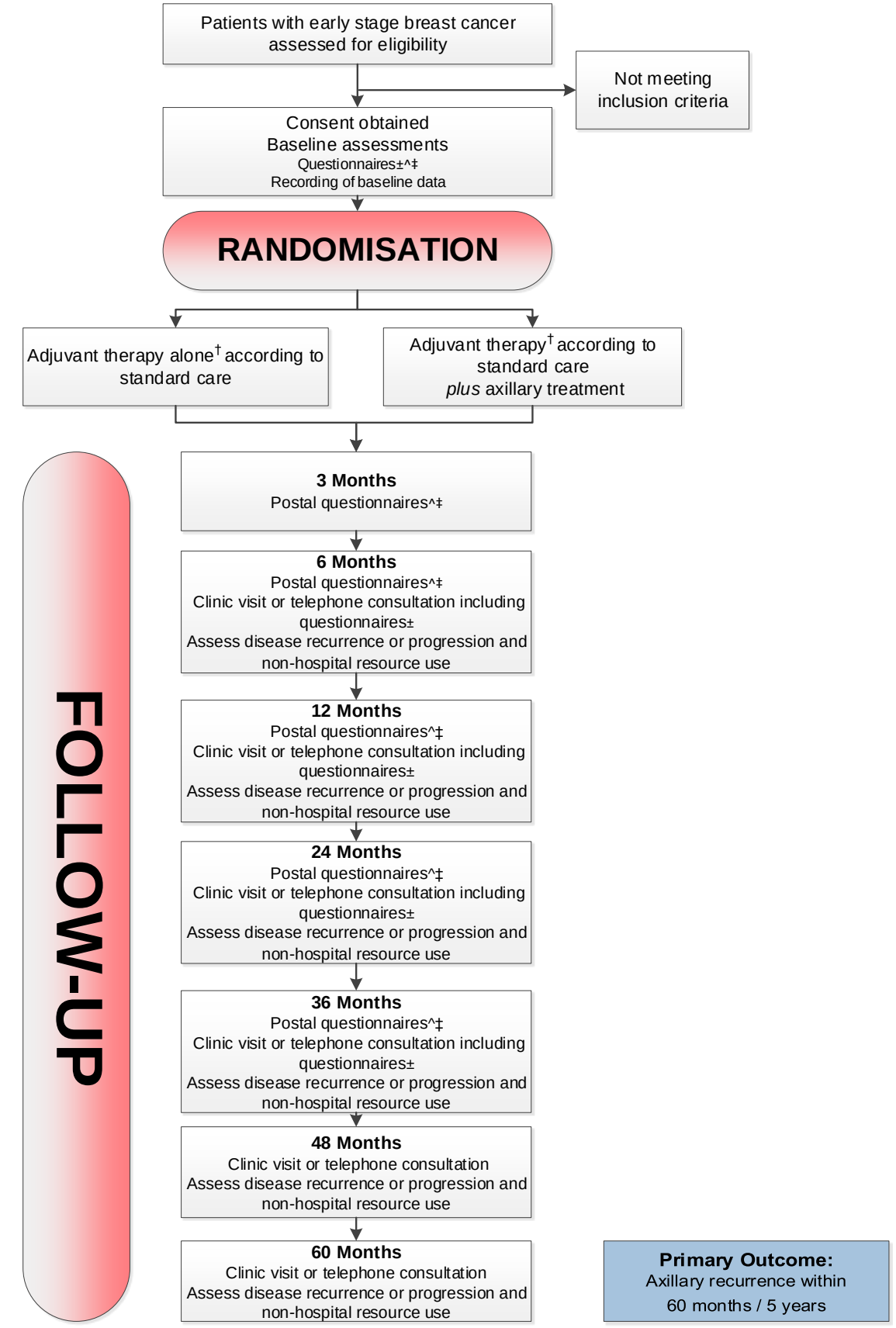
Sample Size
1900 participants

Duration of Recruitment and Follow-up
Recruitment is planned to last for 84 months. Participants will be followed up for 5 years from date of the randomisation.

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

Most 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 European Organisation for Research and Treatment of Cancer (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]. The proportion of patients having four or more additional positive lymph nodes (besides sentinel node) in the AMAROS trial was low (8%)[17]. This figure is estimated to be lower than 5% in the POSNOC trial as pre-operative axillary ultrasound is routinely performed in current practice before sentinel node biopsy and patients with FNA or biopsy proven high volume disease on imaging undergo ANC rather than SNB[18].

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;20] and several retrospective studies[21;22], 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;20-23]. 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[24]; 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 may be treated inadvertently as it may be included in the tangential irradiation field, and some lower level axillary nodes may be removed at mastectomy[25].

There are three randomised trials assessing axillary treatment. The first[19] 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[26] 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[27] 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. This study has been criticised for not meeting its recruitment goal, approximately 40% of patients had micrometastases, too many patients were lost to follow-up (19.4%), and there was a lack of radiation therapy quality assurance. Missing radiotherapy data for more than two-thirds of all randomised patients, significant number of radiotherapy protocol deviations (18.9% of patients received regional nodal RT using ≥3 fields) and the use of high tangent fields[28] in half of the patients seriously confound the interpretation of this trial. A recent post Z11 survey shows that most US radiation oncologists treat the undissected axilla in women with micro or macro metastases with axillary radiotherapy[29]. Therefore, it appears that clinicians in the US are interpreting Z11 in line with AMAROS study that showed that axillary radiotherapy is a less morbid alterative to axillary lymph node dissection (ALND) in women with low volume nodal disease[30]. This is not surprising given that Z11 lacked radiotherapy quality assurance. Furthermore, the generalisability of the results is limited mastectomy patients were excluded and pre-operative axillary ultrasound was not performed in contrast to standard 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 nodes with 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 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).

1.6 Axillary ultrasound (AUS) detected nodal disease

AUS has been embedded into routine breast practice in the UK. The sensitivity of axillary ultrasonography (AUS) has increased in recent years, enabling detection of even low-volume axillary nodal metastases. Women with ultrasound-detected disease undergo ANC, as they are believed to have a higher axillary tumour burden. Studies show that overall, patients with AUS-positive disease have a larger number of involved nodes and are more likely to have tumours with extracapsular invasion at ANC[31-35]. Proceeding to ANC in patients with axillary metastasis detected by AUS therefore appears to be the logical step in management. However, ANC cannot be expected to benefit around 40 percent of patients in the AUS-positive group with only one or two nodes with macrometastases at ANC[33-35]. Our data shows that tumour size and number of abnormal nodes seen on ultrasound scan could potentially be used to select patients who could proceed to SNB instead of ANC. As an example, a woman with tumour size of 20 mm or less and one abnormal node on ultrasound scan would have a 78 per cent chance of having two or fewer metastases at ANC[36] . Therefore, women with ultrasound detected disease who proceed to sentinel node biopsy and are found to have 1 or 2 nodes with macrometastases, will be eligible for POSNOC.

1.7 Extracapsular invasion

Most of the published literature relating to extracapsular invasion (ECI) in nodes removed during sentinel node biopsy is from pre-axillary ultrasound era. AUS is able to detect most women with macroscopic ECI and these women undergo ANC rather than SNB. Women found to have ECI during SNB are more likely to have microscopic disease and role of ANC in these women is unclear. Some centres in the UK use intraoperative molecular tests (e.g. OSNA) to analyse the SN. During this test, the whole lymph node is mashed by the technician and therefore the presence or absence of ECI is not known. To ensure consistency between OSNA and non-OSNA centres, and to clarify the role of axillary treatment in women with microscopic ECI, these women will be eligible for POSNOC.

2 OBJECTIVES

2.1 Primary Objective

For women with early stage breast cancer and one or two nodes with 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) Economic Evaluation

a. To compare quality-adjusted life years (QALYs) using the area under the curve method based upon responses to the EQ-5D-5L measured at baseline, 3, 6, 12, 24, and 36 months post randomisation
b. To compare costs to the NHS 6, 12, 24, 36, 48 and 60 months follow-up
c. To estimate cost-effectiveness measured in terms of the incremental cost per reduction in axillary recurrence from the perspective of the NHS over 60 months
d. To estimate cost-utility based on incremental cost per QALY gained from the perspective of the NHS over 36 months

3 TRIAL DESIGN

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

3.1 Randomisation

Participants will be allocated to one of the two intervention groups, via a remote, secure internet-based randomisation system developed and maintained by the Nottingham Clinical Trials Unit (NCTU).

An authorised member of the site research team will login using their unique username and a password. Once logged in they will enter required participant details and the system will allocate the participant to a treatment arm (in real-time).

Allocations will be assigned using the Simon and Pocock minimisation method (weighted toward minimising the imbalance in trial arms with probability 0.8), in order achieve a 1:1 ratio. The minimisation will be stratified by the recruitment site and minimised across the following variables:

- Age (<50, ≥50)
- Breast-conserving surgery (BCS) or mastectomy
- Estrogen receptor status (ER) (positive, negative)
- Number of positive nodes (1, 2)
- Intra-operative sentinel assessment using OSNA (yes, no)

The sequence of treatment allocations will be kept concealed until all interventions have been assigned, recruitment, data collection, and all other trial-related assessments are complete.

Due to the nature of the intervention it will not be possible to blind clinicians or participants to the treatment allocation. To minimise the potential for bias, sites will be instructed to follow trial specific radiotherapy planning and delivery guidance. This will ensure any breast or chest wall radiotherapy is not influenced by knowledge of whether the woman had axillary treatment, or not. Women randomised intra-operatively will also be monitored 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 participant's expectations to influence their responses to the questionnaires, the participant information leaflet and DVD will emphasise that it is not known whether axillary treatment is worthwhile, and that is why the study is being conducted.

4 PARTICIPANTS

Women with unifocal or multifocal invasive breast cancer with the largest lesion ≤5cm, who have undergone sentinel node biopsy, and have 1 or 2 nodes with macrometastases (>2mm). The criteria and procedure for sampling lymph nodes showing abnormal morphology on ultrasound should be agreed locally. Women will be enrolled from academic and non-academic hospitals with an established and functional Breast MDT (multidisciplinary team). At the time of the current protocol update, 98 sites were participating in the trial.

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 be asked to give their consent pre-operatively and then be randomised intra-operatively if their sentinel nodes are found to be positive. Alternatively these hospitals may follow the non-intraoperative pathway, however women need to be consented at the appropriate time points.

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 largest invasive tumour diameter on radiology should be used for women who are randomised intra-operatively or undergo sentinel node biopsy before neoadjuvant therapy (tumour size should be based only on the single largest tumour; do not add the sizes together from the multiple foci)
- At sentinel node biopsy have 1 or 2 nodes with macrometastases (tumour deposit >2.0mm in largest dimension or defined as macrometastases on molecular assay)
- Fit for axillary treatment and adjuvant therapy
- Have given informed consent

4.2 Exclusion Criteria

Women will be excluded if they have:

- Bilateral invasive breast cancer
- more than 2 nodes with macrometastases
- neoadjuvant therapy for breast cancer except
    - if sentinel node biopsy performed prior to neoadjuvant therapy in women with early breast cancer
    - short duration of neoadjuvant endocrine therapy is acceptable (up to 3 months)
- previous axillary surgery on the same body side as the scheduled sentinel node biopsy
- not receiving adjuvant systemic therapy
- previous cancer less than 5 years previously or concomitant malignancy except
    - basal or squamous cell carcinoma of the skin
    - *in situ* carcinoma of the cervix
    - *in situ* melanoma
    - contra- or ipsilateral *in situ* breast cancer

4.3 Trial Interventions

All participants will receive 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 within 5 years.

5.2 Secondary Outcomes

Secondary outcomes will be assessed at the following time points:

Secondary Outcome	Assessment time point (months)						
	3	6	12	24	36	48	60
Arm morbidity	X	X	X	X	X		
Quality of life	X	X	X	X	X		
Anxiety	X	X	X	X	X		
Costs to the NHS	X	X	X	X	X	X	X
Quality-adjusted life years (QALYs)	X	X	X	X	X		
Incremental cost per QALY gained					X		
Incremental cost per reduction in axillary recurrence							X
Local (breast or chest wall) recurrence		X	X	X	X	X	X
Regional (nodal) recurrence		X	X	X	X	X	X
Distant metastasis		X	X	X	X	X	X
Time to axillary recurrence		X	X	X	X	X	X
Axillary recurrence free survival		X	X	X	X	X	X
Disease free survival		X	X	X	X	X	X
Overall survival		X	X	X	X	X	X
Contralateral breast cancer		X	X	X	X	X	X
Non-breast malignancy		X	X	X	X	X	X

5.3 Criteria for Measurement of Study Endpoints

5.3.1 Description and Definition of Outcomes

- **Axillary recurrence** is defined as pathologically (cytology or biopsy) and/or radiologically confirmed recurrence in lymph nodes draining the primary tumour site, i.e. nodes in the ipsilateral axilla, infraclavicular fossa, supraclavicular fossa and interpectoral area. The date of axillary recurrence is the date on which imaging or pathology report (whichever comes first) confirms recurrence.

- **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)[37]; b) Shoulder, arm and hand disability is defined as a change from baseline in the QuickDASH[38] 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[39] 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[40].

  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[41]. 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 include costs to the NHS, QALYs based on responses to the EQ-5D-5L, and the primary outcome, auxiliary recurrence. For more details, see section 13.
- **Local (breast or chest wall) recurrence** is defined as pathologically (cytology or biopsy) and/or radiologically 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 imaging or pathology report (whichever comes first) confirms recurrence.

- **Regional (nodal) recurrence** is defined as pathologically (cytology or biopsy) and/or radiologically confirmed 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 imaging or pathology report (whichever comes first) confirms recurrence.
- **Distant metastasis** is defined as confirmed metastasis (positive pathology and/or definitive evidence on imaging) in 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 imaging 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 at the next suitable clinic appointment and will be followed by a further discussion with the research nurse. A Patient information leaflet (PIL) will be given to the patient and a Patient information DVD will be used as an adjunct to the PIL. The DVD will contain a 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. Patients will be given at least one day to consider the information and reach a decision, this may include coming for another clinic visit.

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

(i) *After primary breast surgery (See section 7.1):* In most hospitals, the 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 (Pathway 1 - See section 6.1).

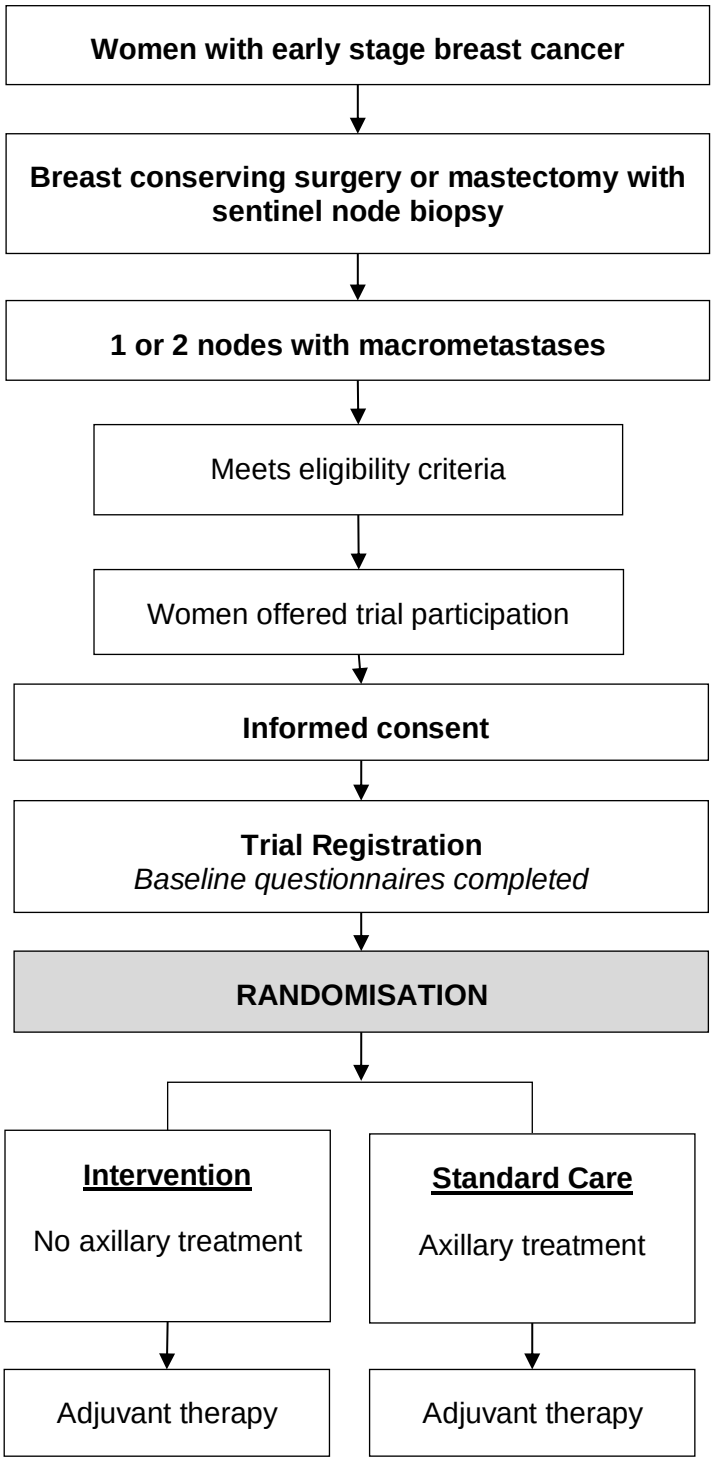
(ii) *Before primary breast surgery:* In a few hospitals (less than 10%) sentinel node assessment is performed in the operating room during primary breast surgery. In these hospitals, women will be approached with regard to the study before surgery. If they are willing to participate consent will be obtained prior to surgery, but they will be randomised intra-operatively only if the sentinel node/s are confirmed as positive (Pathway 2 -See section 6.2).

(iii) *Post chemotherapy*: Some patients may be psychologically overwhelmed by their post-surgery results and therefore timing to discuss the study needs to be tailored to a patient's condition. Women may be approached to discuss the trial during and after chemotherapy but before starting axillary treatment (ANC or ART) (Pathway 3 - See section 6.3).

(iv) *Sentinel node biopsy prior to neoadjuvant therapy:* In hospitals where the sentinel node biopsy is performed prior to neoadjuvant therapy patients can be approached during or after their neoadjuvant therapy but before starting axillary treatment (ANC or ART) (Pathway 4 - See section 6.4).

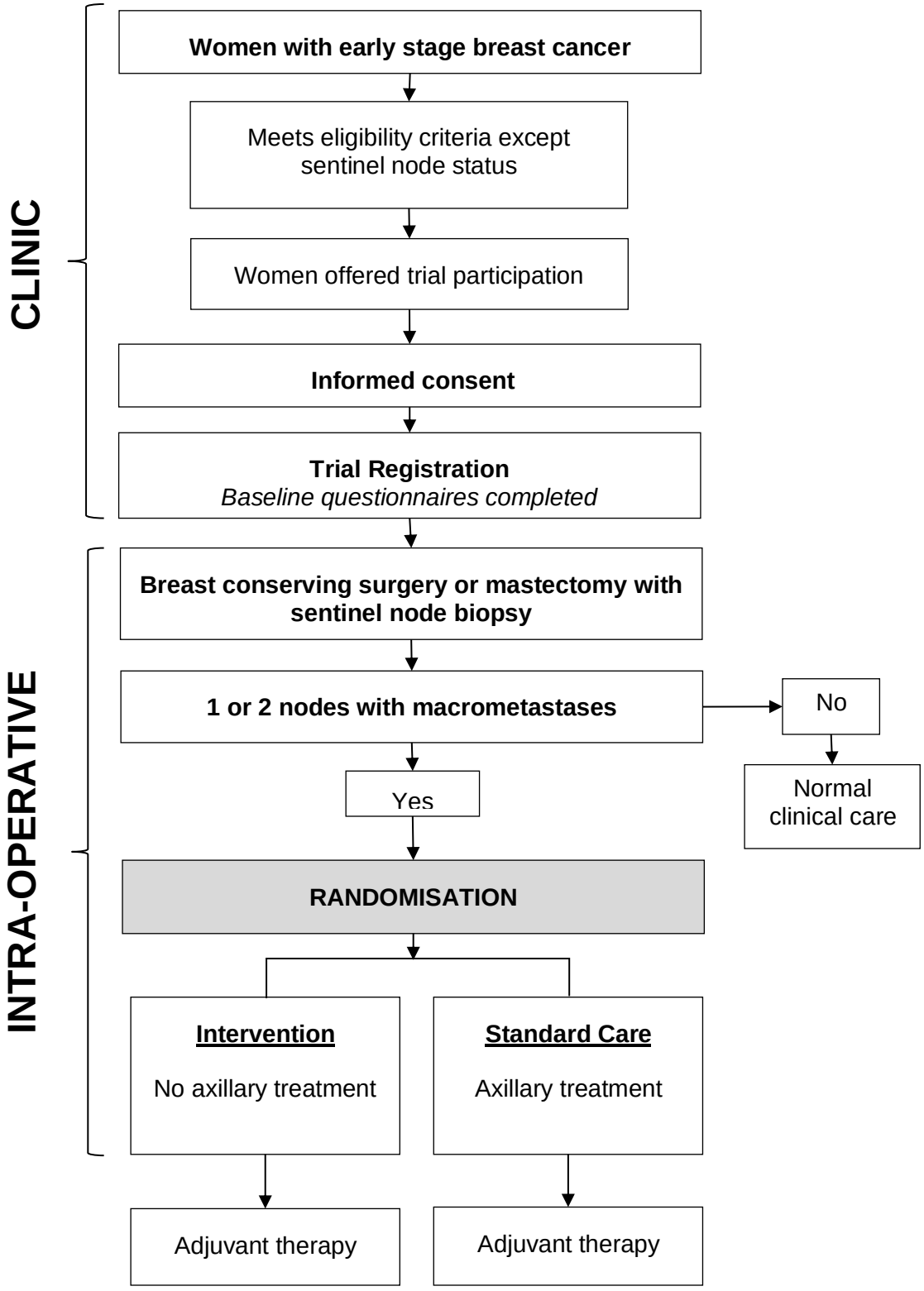
6.1 Pathway 1: After Primary Breast Surgery

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



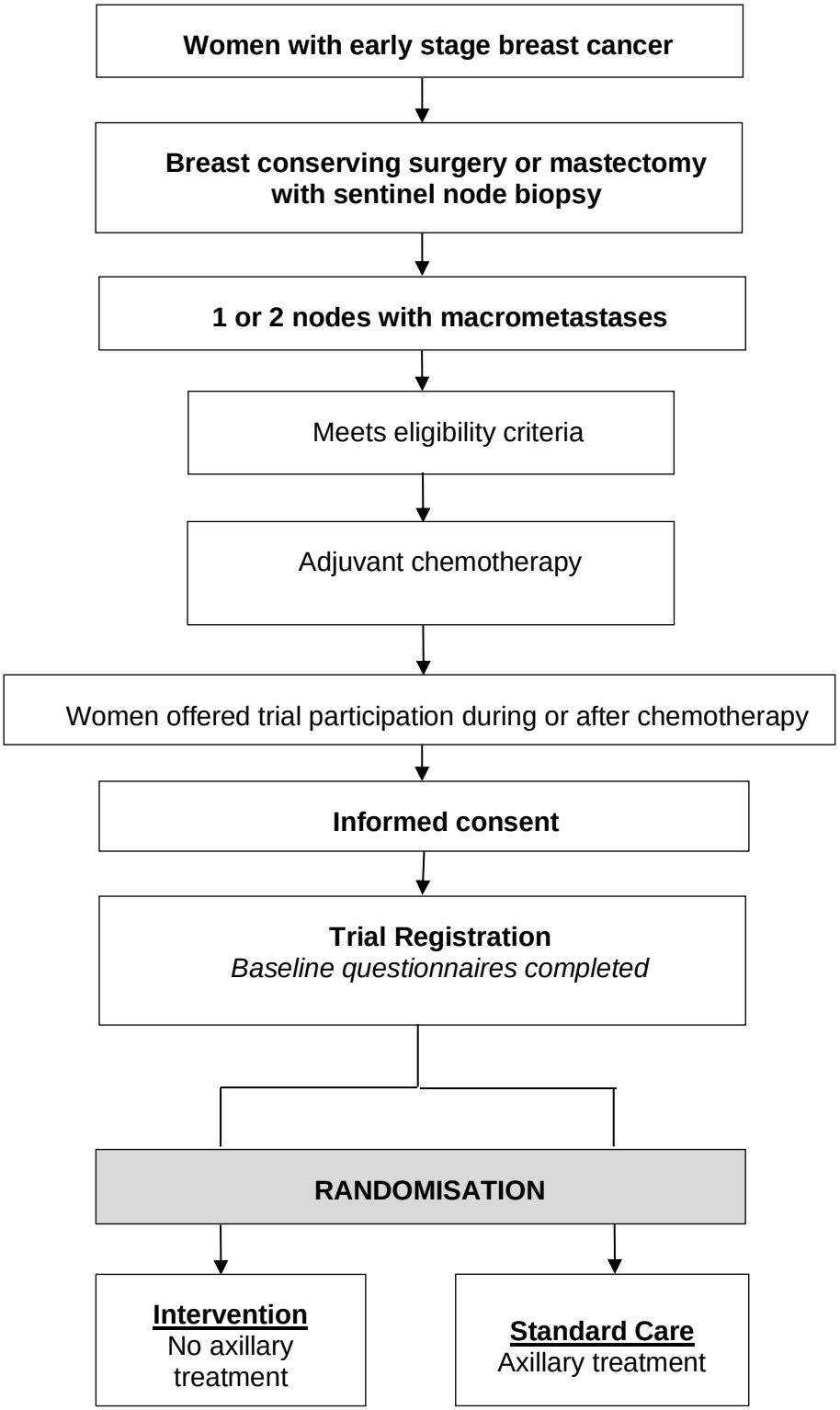
6.2 Pathway 2: Before Primary Breast Surgery

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:



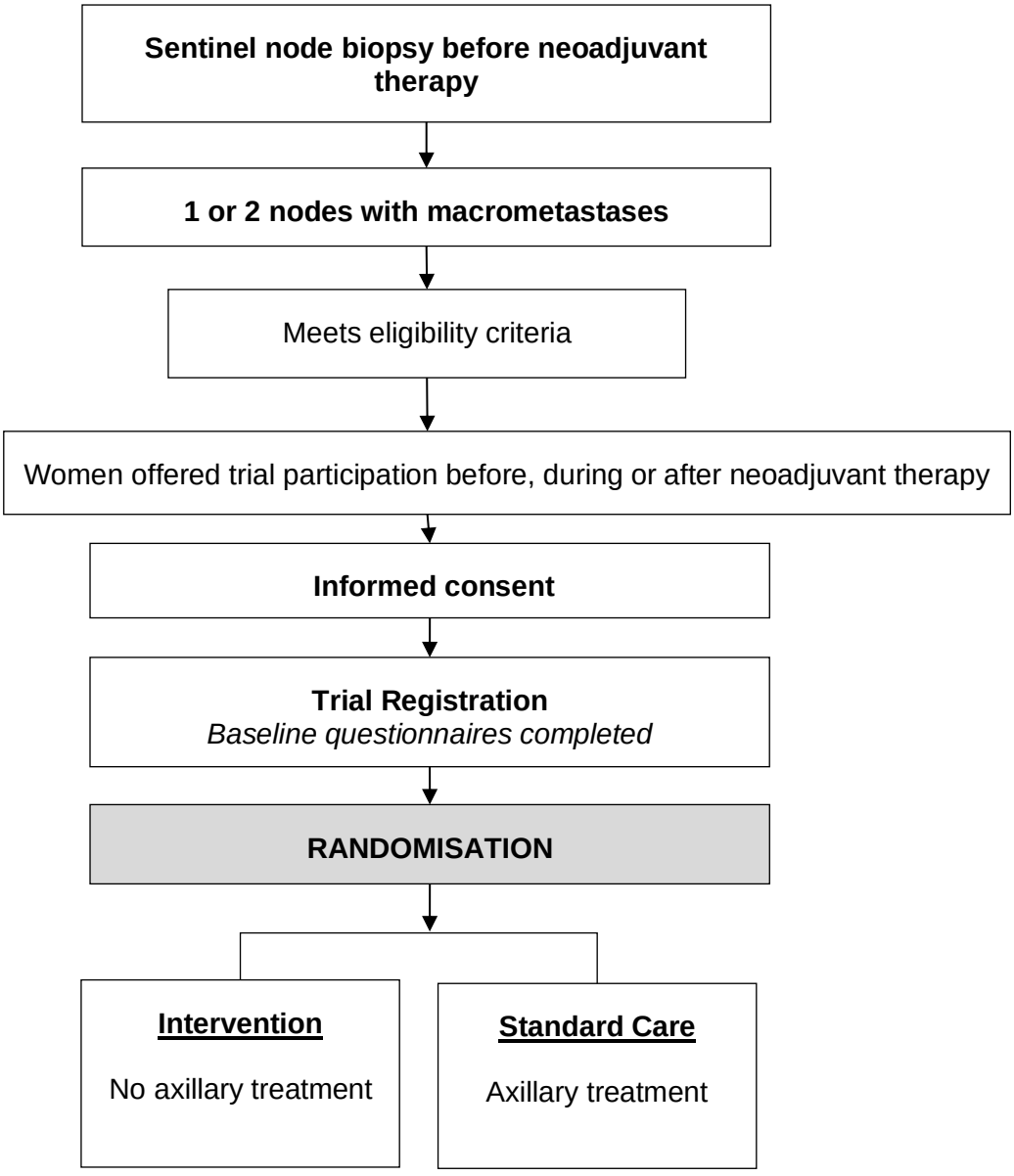
6.3 Pathway 3: Post Chemotherapy

Eligible women will be consented and registered during or after adjuvant chemotherapy but before starting axillary treatment (ANC or ART). Eligible women will follow the pathway below:



6.4 Pathway 4: Sentinel node biopsy prior to neoadjuvant therapy

Eligible women will be consented and registered before, during or after neoadjuvant therapy but before starting axillary treatment (ANC or ART). Eligible women will follow the pathway below:



6.5 Registration Procedures

1. Confirm eligibility
2. Obtain informed consent
3. Obtain baseline data for demographics, tumour and nodal characteristics (depending on pathway), receptor status, arm morbidity, quality of life and anxiety via questionnaires
4. Complete participant details on randomisation system (NB. This must not be done prior to obtaining consent)

6.6 Randomisation

Once a patient has been registered on the database, the patient will be randomised. The actual allocation will be disclosed on the computer screen and a confirmation email will follow to the person recruiting the participant. For more details, see section 3.1.

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 as per local protocol. 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 as per local protocol. This protocol does not dictate the injection technique or tracer/s to be used, but it is recommended that no more than four gross nodes should be removed. This is not an exclusion criteria. 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, undergoing axillary node sampling are eligible for the trial.

The number of nodes removed at sentinel node biopsy 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 haematoxylin and eosin (H&E)/ immunohistochemistry (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 macrometastasas (> 2 mm) or not, and extranodal invasion should be noted in the pathological report. The extent of extranodal invasion (radial extension) should be noted (≤2 mm, >2mm).

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 PROCEDURES

8.1 Study Calendar

Time point	Intervention/Procedure						
	<u>Pathway 1</u> After Primary Breast Surgery	**<u>Pathway 2</u> Before Primary Breast Surgery**	**<u>Pathway 3</u> Post Chemotherapy**	**<u>Pathway 4</u> Post Neoadjuvant therapy**			
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	• Verify eligibility • Obtain informed consent • Trial Registration	• Verify eligibility • Obtain informed consent • Trial Registration			
Baseline recordings	Record demographics						
	Record tumour and nodal characteristics Record receptor status		Record tumour and nodal characteristics Record receptor status	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-5L Spielberger State/Trait Anxiety Inventory						
Randomisation	Intervention – adjuvant therapy alone or Standard Care – adjuvant therapy plus axillary treatment	Intra-operative randomisation following confirmation of eligibility¥ Intervention – adjuvant therapy alone or Standard Care – adjuvant therapy plus axillary treatment	Intervention – adjuvant therapy alone or Standard Care – adjuvant therapy plus axillary treatment	Intervention – adjuvant therapy alone or Standard Care – adjuvant therapy plus axillary treatment			
Baseline recordings		Record tumour and nodal characteristics Record receptor status					
Systemic therapy	Chemotherapy and/or endocrine therapy		Endocrine therapy				
Radiotherapy	Breast or chest wall radiotherapy, if indicated. *<u>NB: Axillary and Supraclavicular fossa (SCF) radiotherapy is not allowed in the Intervention group.</u>*						
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	X[$]	X[$]	X[$]	X[$]	X[$]		

–Breast +4 and EQ-5D-5L (Quality of life)							
Spielberger State/Trait Anxiety Inventory (anxiety)	X[$]	X[$]	X[$]	X[$]	X[$]		
Assessment of disease recurrence or progression and non-hospital resource use		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)
$ 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 with an additional postal questionnaire assessment at 3 months.

The 6, 12, 24, 36, 48 and 60 month follow-up will be a clinic visit (doctor or nurse led) or may be conducted by a research nurse over the telephone, according to local practice. If contact cannot be made with the participant then medical notes can be used.

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. Questionnaires may be sent to patients by post to complete where the research team have been unable to complete with the patient over the telephone.
3. The number of breast cancer related GP visits, physiotherapy visits, lymphoedema visits, pain team visits and hospital admissions will be collected in the clinic or over the telephone at 6,12, 24, 36 and 60 months,
4. Postal questionnaires with up to two reminders, FACT B+4, Spielberger State/Trait Anxiety Inventory and EQ-5D-5L at 3, 6, 12, 24 and 36 months. Questionnaires may be completed in clinic by patients who have not provided a postal address or who require assistance.

8.2.3 SWAT

A Study Within a Trial (SWAT) will be incorporated into the POSNOC study. The aim is to determine whether the addition of a pictorial aid to the patient information leaflet (PIL) will improve recruitment in the POSNOC trial. Recruitment is one of the most important challenges for multi-centre trials. Various techniques have been developed and tested over the years and new methodologies are continuing to be developed. An enhanced PIL may help with patients understanding of the trial and therefore boost recruitment.

The SWAT design is as follows:

Population: All UK sites involved in the POSNOC trial

Intervention:	Enhanced PIL: A clearly illustrated pictorial aid at the end of the current approved PIL to depict the randomisation process and crucial information about the two treatments being tested
Control:	The current approved POSNOC PIL without the pictorial aid
Outcomes:	Proportion of women randomised to the POSNOC trial

The SWAT will use a cluster randomised design, and the unit of allocation will be UK sites that are participating in POSNOC. All women at a site who are identified as potentially eligible and are approached about the POSNOC trial will be provided with either the standard PIL or an enhanced PIL with the pictorial aid, dependent upon the random allocation of the site. Allocation of sites will be stratified by recruitment to POSNOC in the last 12 months.

9 End of Participation and Trial

9.1 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. A maximum of 5% loss to follow up is expected over 5 years.

If contact cannot be made and the participant has not withdrawn their consent to participation in the trial, outcome data will be obtained from hospital records and/or NHS digital where possible. If it is not possible to obtain the primary outcome the participant will be designated as lost to follow-up.

9.2 Participant Withdrawal

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 the 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.

9.3 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. An independent Data Monitoring Committee shall monitor accumulating data and oversee safety issues. The DMC will advise the TSC if, in its view, there are any ethical or safety issues that may necessitate closure of the trial. For more details about the role of DMC, see section 16.3.

All participation may be stopped if the study sponsor or Research Ethics Committee (REC) terminate the study prior to the planned end date.

9.4 Definition of End of Study

The end of the study is defined as database lock.

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 (CRFs).

10.1 Serious Adverse Events

In accordance with the ICH GCP (R2) guideline, a serious adverse event or reaction is any untoward medical occurrence that:

- results in death,
- is life-threatening (i.e. the patient was at risk of death at the time of the event/reaction),
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is a medically important event or reaction (i.e. important medical event/reaction that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

For the POSNOC trial, study treatment consists of standard adjuvant therapy with or without standard axillary treatment. This protocol does not contain investigational agent(s).

The following events do not need to be specifically reported as SAEs as they are outcomes for the trial and are therefore captured within the CRF:

- Local (breast or chest wall) recurrence
- Regional (nodal) recurrence
- Distant metastasis
- Death
- Axillary recurrence
- Contralateral breast cancer
- Non-breast malignancy
- Surgical complications (in patients undergoing ANC)
- Arm morbidity

In addition, side effects of chemotherapy and/or radiotherapy are not required to be reported as SAEs.

Any SAE not listed above as being exempt from SAE reporting will be considered unexpected. All unexpected SAEs must be reported on an SAE form within one working day of becoming aware of the event (see section 10.2). The local site Principal Investigator (PI) shall assess expectedness, seriousness and causality. All SAEs will be followed up until the event is considered resolved, or resolved with sequelae.

The assessment of causality will be made by the PI using the following definitions:

- *Related*: The adverse event is clearly related to the investigational agent/procedure - i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- *Not Related:* The adverse event is clearly not related to the investigational agent/procedure- i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

10.2 Safety Reporting

All unexpected Serious Adverse Events (SAEs) as defined above 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 or nctu-sae@nottingham.ac.uk. Unexpected SAEs will be reported from when a participant is randomised until completion of their 60 month follow up visit or the time at which the participant is no longer part of the POSNOC trial.

PI's have the responsibility of safety reporting for the participants recruited to POSNOC at their sites. On behalf of the Sponsor, the CI will review any SAEs submitted by investigator sites and provide their medical assessment of the SAE.

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 report to the Data Monitoring Committee which will include all reported unexpected SAEs.

10.3 Annual Progress Reports

An annual progress report will be submitted 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) 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 time point. The data will be entered at site into electronic case report forms (eCRF) directly or onto worksheets by study personnel. The worksheets are used to aid data collection and are not source data. If used data must be transferred into the eCRF within 5 days of data collection. Participants will be identified only by their unique participant ID number.

The trial database will be developed and maintained by the trial coordinating centre at the 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 monitoring and site visits where required.

Processing of trial data and monitoring for consistency, validity and quality will be undertaken by NCTU according to the trial monitoring plan, data validation document and data management 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-5L 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 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 NHS Digital

All women recruited to the study (in the UK) will be ‘flagged’ after discharge through the Data Linkage and Extract Service at NHS Digital. Information from NHS Digital 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 reduce losses to follow up and will also enable longer term follow up data (greater than 5 years) to be reported.

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 and participant questionnaires. QoL and EQ-5D-5L questionnaires will be held at SHORE-C. Where there is no other record of the data the eCRF's may be the primary source document data.

11.4 Data Access

Access to the trial datasets will be limited to the central co-ordinating site (NCTU) and to the trial statisticians. The datasets will be provided to the sponsor at the end of the trial for archiving purposes.

11.5 Data Sharing Statement

Requests for data collected for POSNOC from parties outside the TMG will be considered by the TMG and NCTU Data Sharing review panel. For approved requests the dataset will be prepared by the NCTU and will be provided as a summary.

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[42]. With an assumed axillary recurrence rate in the adjuvant therapy alone group also of 2%, absolute non-inferiority margin of 2%, 80% power and 2.5% one-sided alpha, a total of 1700 women are required for analysis in order to show that the axillary recurrence rate in the adjuvant therapy alone group at 5 years is not more than 4% using the Miettinen-Nurminen score interval[43]. Allowing for up to 10% non-compliance with treatment allocation and non-collection of primary outcome data, the target sample size to be randomised is 1900.

12.1.1 Loss to follow up

Within the NHS, failure to attend for breast cancer follow up clinic visits is unusual. For this study, a maximum of 5% loss to follow up over 5 years is anticipated. This is realistic, for example in one recent UK breast cancer trial of local treatment[44] losses to follow up were 1.6% at 5 years. For any participants that cannot be contacted, primary outcome status should be available from medical notes or from NHS Digital. If it is not possible to obtain the primary outcome the participant will be designated as lost to follow-up.

12.1.2 Non-inferiority Margin

Following consultation with relevant breast cancer consumer groups, lay people, and with breast surgeons and oncologists a 2% non-inferiority margin was selected. 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%[43]. 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.

Stopping guidelines shall be defined in consultation with the DMC.

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. The Trial Statistician will be blinded throughout the trial until the data is unblinded.

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 endpoint is whether axillary recurrence has occurred by 5 years or not. A binary endpoint of this form is judged to be of greatest relevance, in this trial.

The primary analysis will assess whether adjuvant therapy alone is non-inferior to adjuvant therapy plus axillary treatment based on the primary endpoint of axillary recurrence within 5 years. Non-inferiority of adjuvant therapy alone over adjuvant therapy plus axillary treatment will be accepted if the upper boundary of the Miettinen-Nurminen two-sided 95% confidence interval around the estimated difference in axillary recurrence rate lies is no greater than 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 and 95% confidence intervals. 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
6. Sentinel node assessment technique: OSNA, non-OSNA
7. Extranodal invasion: present, absent

Subgroup analyses for the outcomes will be performed: axillary recurrence and arm morbidity (measured by LBCQ (2 questions), QuickDash and FACT B+4 arm morbidity subscale). The outcomes for each treatment will be described by factor subgroup, and will present between-group effects and 95% confidence intervals for each factor level. Interaction terms in the appropriate regression models will be included, and estimated interaction effects and 95% confidence intervals presented for all subgroup analyses conducted. Due to the limited power available to detect all except large interactions, these subgroup analyses will be regarded as exploratory.

Analyses for surgical complications following treatment of ANC will be of a descriptive nature.

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. The plausibility that primary outcome data are missing at random (MAR) will be examined 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 economic evaluation will be carried out from the perspective of the NHS over a three year and five year time horizon. A three year time horizon was adopted for the cost-utility analysis as it was anticipated, at three years following the initial biopsy, any health-related quality of life (HRQoL) differences between the intervention and standard care participants which might have been present earlier will have disappeared. Costs will be based upon the costs of the randomised interventions received and on the use of subsequent care and services.

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, 12, 24, 36, 48 and 60 months follow-up, participants will be asked to recall the extent to which they accessed primary care (e.g. GP) or other non-hospital services (e.g. physio visits) for their breast cancer. Information relating to healthcare resource use will be collected via the eCRF. Costs will be estimated using routine sources (e.g. NHS reference costs, PSSRU). On the basis of each participant's record and the costs collected from routine sources, a total hospital cost and a total non-hospital cost will be derived for each participant for the duration of follow-up. These total costs will be combined to estimate the total cost per participant from which the total average cost per randomised group will be calculated. 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.

1) **Cost-effectiveness analysis** based on the incremental cost per reduction in axillary recurrence. Mean costs for each randomised arm will be calculated as will mean axillary recurrence. In the cost-effectiveness analysis these will then be presented as point estimates of mean incremental costs and effects (reduced axillary recurrences) and the incremental cost per reduction in axillary recurrence at five years post-randomisation.
2) **Cost-utility analysis** based on the incremental cost per QALY gained. QALYs will be based on the area under the curve approach[45] using responses to the EQ-5D-5L completed at scheduled time points; baseline, 3, 6, 12, 24, and 36 months post randomisation. The total average QALYs accruing in the intervention and standard care groups will be analysed for significant differences, following allowances for mortality (if occurring). Both mean cost and QALYs will be presented for each randomised group and incremental mean costs and QALY calculated along with the incremental cost per QALY gained.

For both the cost-effectiveness and cost-utility analyses the results will be presented as point estimates of mean incremental costs and effects as well as in stochastic analyses plots of cost and

effects and cost-effectiveness acceptability curves. Both deterministic and stochastic sensitivity analyses will be adopted to address any uncertainty in our estimation of costs, effects and cost-effectiveness. Costs and effects will be discounted at UK recommended rates[46] as they are being estimated beyond a one year time horizon.

14 REGULATORY AND PARTICIPANT INFORMED CONSENT

14.1 Regulatory approvals

The trial will not be initiated before all the relevant regulatory approvals have been obtained.

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 it is not known 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

Consent will be taken by appropriately trained healthcare professionals in the research team. As a result of COVID-19 we have implemented remote consent over the telephone at both registration and randomisation provided there are two delegated individuals on the line to verify the consent at site, and the whole process is documented in writing in the source notes.

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 informed consent form (ICF) 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 (if medical notes are electronic then if possible a copy will be uploaded to the system). A copy of the consent form will be sent to the NCTU for central monitoring purposes, patients provide their consent to this on the ICF.

14.3 Confidentiality

Information about participants will be kept confidential and managed according to the requirements of the Data Protection Act (2018), NHS Caldicott Guardian, UK Policy Framework for Health and Social Care Research (2017), 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.

14.4 Access to Data

Data collection forms will be treated as confidential documents, and held securely. 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, regulatory authorities 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 usually 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 both attending the meeting where possible.

15.2 Monitoring

Trial monitoring will be in accordance with the monitoring plan and will be a combination of central monitoring and “triggered” site visits when required. 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.

If site visits are performed, a random sample of participants may have their data monitored at source (Source Data 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 regulatory authorities, the sponsor and the NCTU. In line with the responsibilities set out in the UK Policy Framework for Health and Social Care Research (2017), the investigator will ensure that the trial manager, sponsor and/or regulatory authorities 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[47-50]. 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 National 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 National 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 approx. every one to two months during the recruitment phase and approx. 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. 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 not receive copies of these data reports.

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

16.4 Indemnity

The 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 University Hospitals of Derby and Burton NHS Foundation Trust. This archive will include all study databases and associated 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 participant. 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.

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Appendices

1. Glossary of abbreviations / acronyms

AE	Adverse Event
ALND	Axillary Lymph Node Dissection
ANC	Axillary Node Clearance
ANCOVA	Analysis of Covariance
ANZ	Australia and New Zealand
ART	Axillary Radiotherapy
AUS	Axillary Ultrasonography
BCS	Breast-conserving surgery
CACE	Complier Average Causal Effect
CF	Consent Form
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computerised Tomography
DASH	Disabilities of the Arm, Shoulder and Hand
DMC	Data Monitoring Committee
ECI	Extracapsular invasion
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
H&E	Haematoxylin and Eosin
HRQL	Health-Related Quality of Life
HTA	Health Technology Assessment
IHC	Immunohistochemistry
ITT	Intention To Treat
ICPV	Independent Cancer Patients' Voice
LBCQ	Lymphoedema and Breast Cancer Questionnaire
MAR	Missing At Random
NCTU	Nottingham Clinical Trials Unit
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
MDT	Multidisciplinary team
OSNA	One-Step Nucleic acid Amplification
PI	Principal Investigator at a local centre
PIL	Patient Information Leaflet
PSSRU	Personal Social Services Research Unit
QoL	Quality of Life
QALYs	Quality Adjusted Life-Years
REC	Research Ethics Committee
RT	Radiotherapy
RTTQA	NCRI Radiotherapy Trials Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCF	Supraclavicular 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
SWAT	Study Within A Trial
TMG	Trial Management Group
TOI	Trial Outcome Index
TSC	Trial Steering Committee
UKANZ	United Kingdom, Australia and New Zealand