FULL TITLE OF THE STUDY ATNEC - Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy	
SHORT TITLE/ ACRONYM ATNEC: A randomised trial investigating the requirement for axillary treatment, after chemotherapy, for patients with early stage breast cancer.	
Version and Date of Protocol:	V1.0 09/Jul/2020
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust
Chief Investigator:	Amit Goyal
Sponsor Reference:	DHRD/2017/130
IRAS Number:	280105
ISRCTN number: **ClinicalTrials.gov:**	ISRCTN *(pending application)* ClinicalTrials.gov: NCT04109079
Funder(s):	Health Technology Assessment (HTA), National Institute for Health Research (NIHR)
Trial website	https://sites.google.com/nihr.ac.uk/atnec

NHS University Hospitals of Derby and Burton NHS Foundation Trust
WARWICK CLINICAL TRIALS UNIT
RTTQA Radiotherapy Trials Quality Assurance
FUNDED BY NIHR | National Institute for Health Research

TABLE OF AMENDMENTS:

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

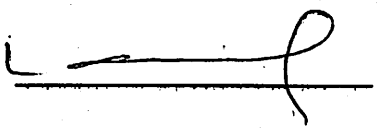
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the collaborators' SOPs, and other regulatory requirements.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

ATNEC Trial Protocol version 1.0 09-Jul-2020

This protocol has been approved by:

Name: Associate Professor Amit Goyal Trial Role: Chief Investigator

Signature: 

Date: 1 9 July 2020 DD / MON / YYYY

KEY STUDY CONTACTS

Chief Investigator:	Amit Goyal Consultant Oncoplastic Breast Surgeon & Associate Professor Royal Derby Hospital, Derby, DE22 3NE Tel: 01332785538 Email: amit.goyal@nhs.net	
Sponsor's representative:	Teresa Grieve Assistant Director of Research and Development University Hospitals of Derby & Burton NHS Foundation Trust Royal Derby Hospital Derby, DE22 3NE Tel: 01332 724639 Email: dhft.sponsor@nhs.net	
WCTU Lead & Senior Trial Statistician:	Janet Dunn Professor of Clinical Trials & Warwick Clinical Trials Unit Lead Warwick Clinical Trials Unit, University of Warwick Coventry CV4 7AL Tel: 024 7657 5847 Email: j.a.dunn@warwick.ac.uk	
Trial Statistician	Andrea Marshall Associate Professor of Statistics Warwick Clinical Trials Unit, University of Warwick Coventry CV4 7AL Tel: 024 7615 0176 Email: Andrea.marshall@warwick.ac.uk	
Trial Manager:	Sophie Cramp Warwick Clinical Trials Unit, University of Warwick Coventry, CV4 7AL Tel: 02476524438 Email: atnec@warwick.ac.uk	
Senior Project Manager	Helen Higgins Warwick Clinical Trials Unit, University of Warwick Coventry CV4 7AL Tel: 024 76151178 Email: h.higgins@warwick.ac.uk	
Radiotherapy Quality Assurance	Zohal Nabi & Romaana Mir National Radiotherapy Trials QA (RTTQA) Group Mount Vernon Cancer Centre, Northwood, Middlesex, HA6 2RN Tel: 020 3826 2322 Email: ATNECqa.enh-tr@nhs.net	
Trial Health Economist	Tara Homer Senior Research Associate, Health Economics Group, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, NE2 4AX Tel: 0191 208 8457 Email: tara.homer@ncl.ac.uk	
Co-Investigators:		
	Duncan Wheatley Consultant Clinical Oncologist Royal Cornwall Hospitals NHS Trust Email: duncanwheatley@nhs.net	Luke Vale Professor of Health Economics, Health Economics Group, Population Health Sciences Institute, Newcastle University

		Newcastle upon Tyne, NE2 4AA Email: luke.vale@newcastle.ac.uk
	Shama Puri Consultant Radiologist Royal Derby Hospital, Derby, DE22 3NE Email: shama.puri@nhs.net	Beatrix Elsberger Consultant Breast Surgeon Email: b.elsberger@nhs.net
	Samreen Ahmed Consultant Medical Oncologist University Hospitals of Leicester NHS Trust Email: samreen.ahmed@uhl-tr.nhs.uk	Abeer Shaaban Consultant Pathologist University Hospitals Birmingham NHS Foundation Trust Email: abeer.shaaban@uhb.nhs.net
	Julie Bruce Professor of Clinical Trials Warwick Clinical Trials Unit, University of Warwick Coventry CV4 7AL Email: Julie.Bruce@warwick.ac.uk	Valerie Speirs Chair in Molecular Oncology Institute of Medical Sciences University of Aberdeen Email: Valerie.speirs@abdn.ac.uk
	Jacqui Shaw Professor of Translational Cancer Genetics University of Leicester Email: Js39@le.ac.uk	Sophie Gasson PPI Engagement Research Fellow Warwick Clinical Trials Unit, University of Warwick Coventry CV4 7AL Email: S.Gasson@warwick.ac.uk
	Janice Rose Patient advocate NCRI Breast CSG Email: jan.rose3012@outlook.com	Helen Teresa Edwards Patient advocate Independent Cancer Patients' Voice (ICPV) Email:edwardsdevine@hotmail.com
Funder:	Health Technology Assessment (HTA), National Institute for Health Research (NIHR) (HTA NIHR128311)	
Clinical Trials Unit:	Warwick Clinical Trials Unit University of Warwick Coventry, CV4 7AL Tel: 02476524438 Email: atnec@warwick.ac.uk	

STUDY SUMMARY

Study Title:	ATNEC - Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy.
Sponsor Study Reference:	DHRD/2017/130
Study Design:	A multi-centre phase III randomised controlled trial with embedded economic evaluation in which participants will be randomised in a 1:1 ratio.
Study Participants:	T1-3N1M0 breast cancer patients aged 18 years or older, with needle biopsy proven nodal metastases, who after neoadjuvant chemotherapy (NACT) have no residual cancer in the lymph nodes on dual tracer sentinel node biopsy and removal of at least 3 lymph nodes (sentinel nodes and marked involved node).
Planner Number of Sites:	~100
Planned Sample Size:	1900 (950 per arm)
Stratification	- Institution - Type of breast surgery (breast conserving surgery (BCS) vs mastectomy) - Receptor status (triple negative vs HER2 positive vs ER status positive and/or PR status positive and HER2 negative)
Intervention:	Participants in the experimental arm will not receive further axillary treatment (axillary lymph node dissection [ALND] or axillary radiotherapy [ART]), after NACT and surgery.
Comparison/Control:	Participants in the control group will receive further axillary treatment (ALND or ART) after NACT and surgery, as per local guidelines.
Follow Up Duration:	At least 5 years
Planned Recruitment Start Date:	01 March 2021
Planned Recruitment End Date:	01 March 2026
Planned Study End Date:	28 February 2030
Research Question/ Aims:	To assess whether, omitting further axillary treatment (ALND and ART) for patients with early stage breast cancer and axillary nodal metastases on needle biopsy, who after NACT have no residual cancer in the lymph nodes on sentinel node biopsy, is non-inferior to axillary treatment in terms of disease free survival (DFS), and reduces the risk of lymphoedema at 5 years.

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
Health Technology Assessment (HTA), National Institute for Health Research (NIHR) (HTA NIHR128311)	Financial

ROLES & RESPONSIBILITIES

Sponsor
The Sponsor, University Hospitals of Derby & Burton NHS Foundation Trust, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The sponsor is not providing funds for this study but has taken on responsibility for ensuring finances are in place to support the research.

Funder
This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (Reference - HTA NIHR128311). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Study Management Committees

Trial Management Group (TMG)
The TMG will meet regularly to oversee the day-to-day management of the trial, including all aspects of the conduct of the trial. Any problems with study conduct and participating centres will be raised and addressed during TMG meetings.

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

Trial Steering Committee (TSC)
The TSC will oversee and supervise the progress of the trial and ensure that it is being conducted according to the protocol and the applicable regulations. The TSC is an independent body that includes a majority of members who are not involved with the running of the trial. They will meet prior to commencement of the study, and then at regular intervals until completion (at least annually).

The TSC will take responsibility throughout the trial for:

- Proposals for substantial protocol amendments and provision of advice to the funder regarding approvals of such amendments
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the Independent Data Monitoring and Ethics Committee
- Informing and advising on all aspects of the trial

Data Monitoring and Ethics Committee (DMEC)
A separate and independent DMEC will be convened. It is anticipated that the members will meet once prior to commencement of the study to agree terms of reference and on at least three further occasions to monitor accumulating data and oversee safety issues.
The DMEC will review the accruing study data and will assess whether there are any safety issues that should be brought to the participant's attention or any reasons to terminate the study. They will also review the scientific validity and the conduct of the study.

Protocol Contributors
A number of protocol contributors have been involved in the development of this protocol, these include; Chief Investigator, Co-Investigators (including patient and public representatives) and the Trial Management team. Protocol contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

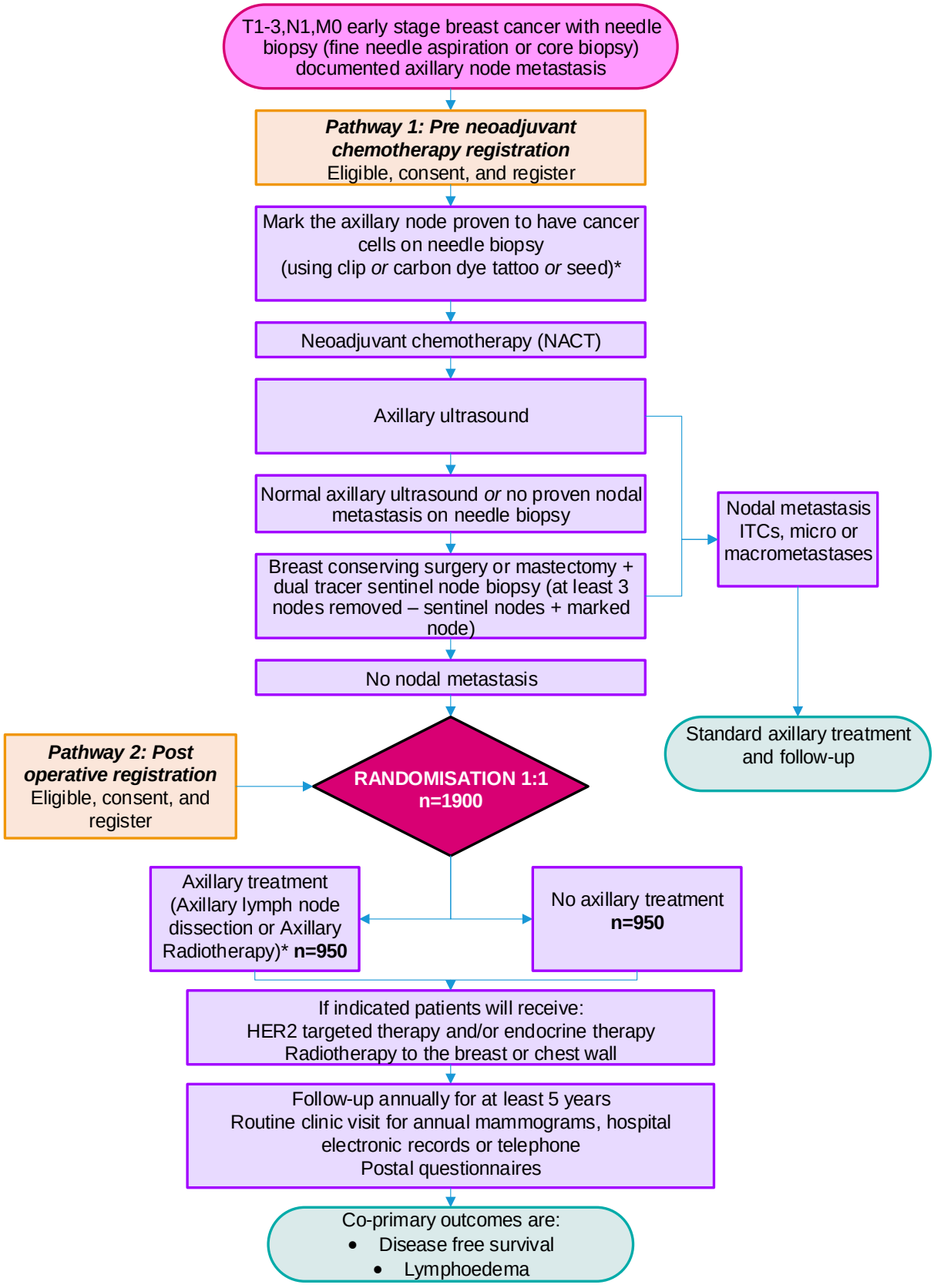
CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALND	Axillary Lymph Node Dissection
ANS	Axillary Node Sampling
ART	Axillary Radiotherapy
AUS	Axillary Ultrasonography
BCS	Breast-conserving surgery
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COSD	Cancer Outcomes and Services Dataset
CRF	Case Report Form
CT	Computerised Tomography
CTRad	Clinical and Translational Radiotherapy Research Working Group
CTU	Clinical Trials Unit
DASH	Disabilities of the Arm, Shoulder and Hand
DMEC	Data Monitoring and Ethics Committee
DN4	Doleur Neuropathique
EDC	Electronic Data Capture
ER	Estrogen receptor
FNA	Fine Needle Aspiration
FNR	False Negative Rate
GCP	Good Clinical Practice
HEAP	Health Economic Analysis Plan
HER2	Human epidermal growth factor receptor 2
H&E	Haematoxylin and Eosin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICPV	Independent Cancer Patient's Voice
ICJME	International Committee of Medical Journal Editors
IRAS	Integrated Research Application System
ISF	Investigator Site File
ITC	Isolated Tumour Cells
ISRCTN	International Standard Randomised Controlled Trials
LBCQ	Lymphoedema and Breast Cancer Questionnaire
NACT	Neoadjuvant Chemotherapy
NCRI	National Cancer Research Institute
NICE	National Institute for Health Care Excellence
NHS R&D	National Health Service Research & Development
pCR	Pathological Complete Response
PI	Principal Investigator
PIC	Participant Identification Centre
PIL	Patient Information Leaflet
PIS	Participant Information Sheet
PPI	Patient Public Involvement
PSA	Probabilistic Sensitivity Analysis
QA	Quality Assurance
QALY	Quality-adjusted Life Year
QC	Quality Control
QoL	Quality of Life
RCT	Randomised Control Trial

REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedure
SN	Sentinel Node
SNB	Sentinel Lymph Node Biopsy
SSDL	Site Signature and Delegation Log
TMG	Trial Management Group
TMF	Trial Master File
TNO	Trial Number
TSC	Trial Steering Committee
UHDB	University Hospitals of Derby and Burton NHS Foundation Trust
WCTU	Warwick Clinical Trials Unit

STUDY FLOW CHART



*as per local standard of care; ITCs, isolated tumour cells

1. BACKGROUND

There are around 55,000 new cases of breast cancer diagnosed each year. Axillary ultrasound, with needle biopsy of suspicious lymph nodes, is used in the initial diagnostic work-up of breast cancer patients. Patients with needle biopsy proven positive nodes are increasingly referred for neoadjuvant chemotherapy (NACT) to shrink the cancer before surgery. Currently after chemotherapy, all patients then undergo breast surgery (lumpectomy to remove the cancerous lump or mastectomy to remove the breast) and treatment to their axilla, either removal of all lymph nodes in the axilla (axillary lymph node dissection (ALND)) or radiotherapy to axilla (ART). National Institute for Health and Care Excellence (NICE) recommends ALND to patients who have a preoperative ultrasound-guided needle biopsy with pathologically proven lymph node metastases [1].

After ALND a drain is left in the wound to drain excess fluid or blood for a few days afterwards. The operation lasts one to two hours and may require an overnight stay in the hospital. This procedure delays the return to usual activities and paid work [2].

Axillary radiotherapy (ART) is radiation targeted at the axilla and is used instead of ALND in some hospitals based on local guidelines. The radiation is given five days a week for three to five weeks. Axillary radiotherapy is offered only in some specialist centres, and so patients may need to travel a considerable distance for treatment.

ALND or ART damages lymphatic drainage from the arm and both are associated with increased risk of lymphoedema, restricted shoulder movement or shoulder discomfort, pain, sensory changes and numbness[2]. These adverse effects interfere with daily activities, impair health-related quality of life (QoL) and are costly to the NHS in terms of rehabilitative treatments as they can be chronic and often irreversible with limited symptom relief.

The findings of a systematic review suggest that more than one in five women who survive breast cancer will develop arm lymphoedema [3]. Lymphoedema has a negative psychosocial impact on affected individuals resulting in negative self-identity, emotional disturbance, psychological distress, marginalization, perceived diminished sexuality and social isolation [4].

The cost of axillary treatment in the UK NHS is around £2600 per patient (National HRG tariff). Additional costs come from demand on the lymphoedema clinics, physiotherapy, follow-up clinics and pressures on primary care (e.g. district nurses for drain removal after ALND). These are estimated to be around £500 per patient and a simple cost analysis suggests an average overall cost saving of £3100 per patient from having no further axillary treatment.

The improvement in the life expectancy of patients with breast cancer raises important questions about how to improve the QoL for those sustaining complications of breast cancer treatment. The risks and benefits of axillary treatment should be carefully considered by clinicians and patients.

NACT results in eradication of cancer in the axillary lymph nodes in 40% to 70% of patients [5, 6]. This has raised questions about the benefit of further axillary treatment in these patients with no evidence of residual disease in the lymph nodes. A meta-analysis[7] and two prospective multicentre studies (Z1071 and SENTINA) [8, 9] showed that the presence or absence of residual disease in the lymph nodes after chemotherapy can be accurately and reliably determined by dual tracer sentinel lymph node biopsy (SNB) and by removing at least three axillary lymph nodes. All patients in the two studies underwent ALND following SNB. The Z1071 trial [8] showed that the sentinel node was successfully identified and removed in 92.5% patients and the false-negative rate (FNR) was 12.6%. The SENTINA trial [9] reported 80% success rate of SNB and 14% FNR. The FNR decreased when dual mapping agents were used and was less than 10% when ≥3 nodes were removed. Additionally, marking the abnormal

axillary lymph nodes at the time of needle biopsy with either a clip or by tattooing to allow for localisation and removal of the known metastatic node following NACT further reduces the FNR [10, 11]. In around 80% of cases, the marked node is the sentinel node when at least three nodes are removed [12]. A meta-analysis showed that the combination of SNB with removal of the marked node reduces the FNR to less than 5% [13].

SNB is minimally invasive and associated with lower risk of arm morbidity and improved patient QoL outcomes compared with ALND or ART [2]. However, we need to ensure that de-escalation of axillary treatment to limit treatment-related morbidity does not compromise the risk of cancer recurrence and survival. This study will determine whether, omitting further axillary treatment (ALND and ART) for patients with early stage breast cancer and axillary nodal metastases on needle biopsy, who after NACT have no residual cancer in the lymph nodes on SNB, is non-inferior to axillary treatment on outcomes of cancer recurrence, lowers the risk of arm lymphoedema at five years, and whether it represents a worthwhile use of NHS resources.

2. RATIONALE

We undertook a survey to identify current clinical practice amongst breast cancer centres in the UK. Of the 70 responding hospitals, 79% performed ALND, 9% undertook ART and 12% SNB or axillary node sampling (ANS) [unpublished data]. The survey showed that clinicians are at equipoise and 99% of the respondents expressed willingness to randomise patients in the ATNEC trial.

This research question has been identified as a priority by patients at many different cancer support groups and events, including the Macmillan patient focus group, Independent Cancer Patients' Voice, Dragon's Den at the National Cancer Research Institute's (NCRI) consumer forum, NCRI Breast CSG, UK Breast Intergroup and NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad). The NCRI Living with and Beyond Cancer Initiative highlights that it is important to cancer patients to live better with and beyond cancer. The number one priority concerns looking at the long-term side effects of cancer treatment, confirming the importance of this study to patients [14].

The ATNEC research question has also been identified as a key research gap by Association of Breast Surgery [15]. The UK multidisciplinary guidance published in 2019 advises that patients with no residual disease in the sentinel nodes after NACT should receive ART and recommends that clinicians should participate in the ATNEC study to answer this important research question [16]. Thus we anticipate that the study results will lead to updated NICE and specialty guidelines and will change clinical practice in the future.

3. AIMS, OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

3.1. Objectives

The *primary objectives* are to assess whether, omitting further axillary treatment (either ALND or ART) for patients with early stage breast cancer and axillary nodal metastases on needle biopsy, who after NACT have no evidence of residual cancer in the lymph nodes on SNB, is non-inferior to axillary treatment in terms of disease free survival (DFS), and reduces the risk of lymphoedema at five years.

Secondary objectives are:

I. To compare arm morbidity and quality of life between and within the two allocated groups over five years.
II. To compare axillary recurrence free interval, breast or chest wall recurrence, regional (nodal) recurrence, distant metastasis, and overall survival, contralateral breast cancer, non-breast malignancy between the two allocated groups over five years.
III. Economic evaluation

a. To compare costs to the NHS and to participants over five years
b. To compare quality-adjusted life years (QALYs) over five years.
c. To estimate cost-effectiveness measured in terms of incremental cost per disease free interval from the perspective of the NHS and patients over five years
d. To estimate cost-effectiveness measured in terms of incremental cost per lymphoedema event avoided from the perspective of the NHS and patients over five years
e. To estimate cost-effectiveness measured in terms of incremental cost per QALY gained from the perspective of the NHS and patients over five years
f. To extrapolate costs and outcomes over the lifetime of patients with early stage breast cancer and estimate the cost-effectiveness measured in terms of incremental cost per QALY gained from the perspective of the NHS and patients

IV. Qualitative Evaluation
a. To identify and investigate recruitment issues and develop effective and realistic strategies to ensure overall success of the trial

3.2. Outcome

3.2.1. Co-primary outcomes:

- Disease-Free Survival (DFS); defined and calculated as the time from randomisation until the date of first event of either a loco-regional invasive breast cancer relapse, distant relapse, ipsilateral or contralateral new invasive primary breast cancer or death by any cause or the censor date.

- Lymphoedema is self-reported based on two items from the validated Lymphoedema and Breast Cancer Questionnaire (LBCQ) (arm “swelling now” and arm “heaviness in the past year”). These items have been shown to be predictive of arm swelling of a 2 cm or more change in arm circumference, but provide a simpler patient-friendly measure which has been used in other studies [17-19]. Lymphoedema will be defined as ‘yes’ to both questions at five years.

3.2.2. Secondary outcomes:

- Arm function will be assessed using the shortened version of the Disability of the Arm, Shoulder and Hand (DASH), the 11-item QuickDASH questionnaire [20].

- Pain intensity and characteristics will be measured using questions from the Douleur Neuropathique (DN4) and Pain Numeric Rating Scale (NRS) and will relate to the areas affected by surgery and cancer treatment.

- Axillary recurrence free interval, calculated from the date of randomisation to the date of axillary recurrence or the censor date. 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 axillary recurrence.

- Overall survival; calculated as the time from randomisation until the date of death by any cause or the censor date.

- 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 local 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 local 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 the imaging or pathology report (whichever comes first) confirms metastasis.

- Contralateral breast cancer is defined as a 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 defined as any new non-breast primary malignancy, except for basal or squamous cell cancer of the skin, in situ carcinoma of the cervix, or in situ or stage 1 melanoma.

- Economic evaluation
    - Costs to the NHS and patients for each randomised group
    - QALYs based on responses to the EQ-5D-5L administered at baseline, 12, 24, 36, 48, and 60 months post-randomisation
    - Incremental cost per disease free interval over five years
    - Incremental cost per lymphoedema avoided over five years
    - Incremental cost per QALY gained over five years
    - Incremental cost per QALY over the estimated lifetime of a participant with early stage breast cancer

4. STUDY DESIGN

A phase III randomised, multicentre, trial of standard axillary treatment (either ALND or ART) compared with no further axillary treatment after NACT and surgery for early stage breast cancer.

An integrated feasibility study, with embedded qualitative research, will assess the willingness of clinicians and patients to participate in the ATNEC trial.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

Eligible participants will be/should have:

- Age ≥ 18
- Male or female
- T1-3N1M0 breast cancer at diagnosis (prior to NACT)
- FNA or core biopsy confirmed axillary nodal metastases at presentation
- Oestrogen receptor and HER2 status evaluated on primary tumour
- Received standard NACT as per local guidelines (Patients undergoing neoadjuvant endocrine therapy as part of another clinical trial are eligible)

- Ultrasound of the axilla at completion of NACT
- Undergo dual tracer sentinel node biopsy after NACT and at least 3 nodes removed (sentinel nodes and marked node). If axillary node sampling is performed following failed localisation of sentinel nodes, patient will be eligible if at least 3 nodes removed (including the marked node).
- No evidence of nodal metastases post NACT (isolated tumour cells, micro or macro metastasis)

5.2. Exclusion Criteria

Participants will be excluded if they have any one of the following:

- Bilateral invasive breast cancer
- Sentinel node biopsy prior to NACT
- Marked node not removed *except* where at least one node removed shows
    - evidence of down-staging with complete pathological response e.g. fibrosis or scarring and at least 3 nodes removed
- Previous axillary surgery on the same body side as the scheduled targeted sampling
- Any previous cancer within last 5 years or concomitant malignancy *except*
    - basal or squamous cell carcinoma of the skin
    - in situ carcinoma of the cervix
    - in situ or stage 1 melanoma
    - contra- or ipsilateral in situ breast cancer

6. STUDY PROCEDURES

6.1. Screening and Consent

6.1.1. Participant Identification

The target population are patients with operable, early stage breast cancer with confirmed axillary nodal metastases on initial needle biopsy who receive NACT.

Potential trial participants will be identified at the routine multi-disciplinary meetings, where patients' eligibility will be assessed. 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.

6.1.2. Patient Information Leaflet (PIL)

The aim of the PIL is to provide information about the research study to potential ATNEC participants and to prepare the patient for the possibility of being invited to take part in a research study at an early stage in the patient pathway. This is a short leaflet to introduce the study.

6.1.3. Patient Information Sheet (PIS)

A more detailed PIS will be given to those patients deemed eligible for the trial. The trial will use two PIS; one for participants entering the trial pre-operatively (Recruitment Pathway 1 – see Section 6.2.1.1) and one for participants who are deemed eligible following BCS or mastectomy (Recruitment Pathway 2 – see Section 6.2.1.2).

Patients will be encouraged to take the information sheet home and discuss the trial with their family ahead of making an informed decision. Patients will be given sufficient time to consider the information and reach a decision, this may include coming back to the centre for another clinic visit.

6.1.4. Informed Consent

If a patient has read the PIS, and is happy to participate in the trial, they will be consented and registered into the study. The patient must be given the opportunity to ask questions and to be satisfied with the responses, prior to written consent being given.

6.1.4.1 Responsibilities

It is the responsibility of the Principal Investigator (PI) at each site, or trained delegate, to obtain informed consent for each participant, prior to performing any trial related procedure. The PI may delegate responsibility for obtaining informed consent to other appropriate members of the site research team, for example Consultant Radiologists, Radiographers, Clinical Nurse Specialists and Research Nurses, who must be appropriately trained in obtaining informed consent and in Good Clinical Practice (GCP). Delegation of responsibility for obtaining informed consent must be indicated appropriately on the Site Signature and Delegation Log (SSDL). Participant eligibility should be confirmed by the PI or Investigator(s) who are delegated this task on the SSDL. Other members of the Research Team (e.g. Research Nurse) may assist with this process but responsibility remains with the PI.

6.1.4.2 Process for obtaining informed consent

Full consent must be in writing. This may be obtained in-person, during a scheduled clinic consultation, or remotely, through the patient completing the informed consent form (ICF) at home. When completed remotely, the patient should return all sections of the signed form to a named individual at the recruiting site; this can be done using any of the following methods:

- by post
- electronically (e.g. patient sends a scan or photograph of the completed consent form to an approved NHS email address)
- in person (at patient's next clinic visit)

The local PI, or designee receiving consent, must countersign the consent form. There is no requirement that the counter signature date matches the date of the participant signature where this has been completed remotely, but the counter signatory must be satisfied that the consent is genuine. Where the participant has returned an image of the signed form, this should be printed. If the printed image is unsuitable for countersignature, the investigator should sign a blank consent form and attach the printed image.

A patient cannot be randomised to the trial until evidence of written informed consent has been received by the recruiting site.

Verbal consent

For participants entering the study via recruitment pathway 1 (see section 6.2.1), initial consent for registration may be given verbally during a remote telephone or video consultation. As with written consent, verbal consent can only be obtained by the PI or qualified delegate who is listed on the SSDL. The patient must be provided with the PIS and afforded the same opportunity to consider the study, and to ask questions, as they would have when attending a consultation in person. A documentation of remote verbal consent form must be completed by the site, to evidence that verbal consent has been given. Once verbal consent is given, a patient can be registered to the study, but randomisation cannot take place until full written consent has been received.

A copy of the fully signed consent form, and where applicable the documentation of remote verbal consent form, must be given to the patient. The site must ensure that the patient's participation in the trial is recorded in the patient notes and is communicated to the patient's GP.

The PIS, ICF and documentation of remote verbal consent form are available in electronic format to facilitate printing onto local headed paper. Original ICFs must be retained on site (the original should

be retained in the trial site file, with a copy filed in the relevant participant's hospital notes and a copy given to the participant). A copy should not be sent to the ATNEC Trial Office.

If the PIS and/or ICF are modified during the course of the trial, sites will be notified of the procedure to follow for participants already consented and for prospective participants.

6.1.5. Screening/Enrolment Log

Participating sites will be expected to maintain a screening log of all potential study candidates. This log will include limited information about the potential candidate (e.g. date of birth and gender), the date and outcome of the screening process (e.g. enrolled into study, reason why not approached for consent, reason why candidate declined to participate).

6.2. Trial Entry

6.2.1. Pathways for Trial Entry

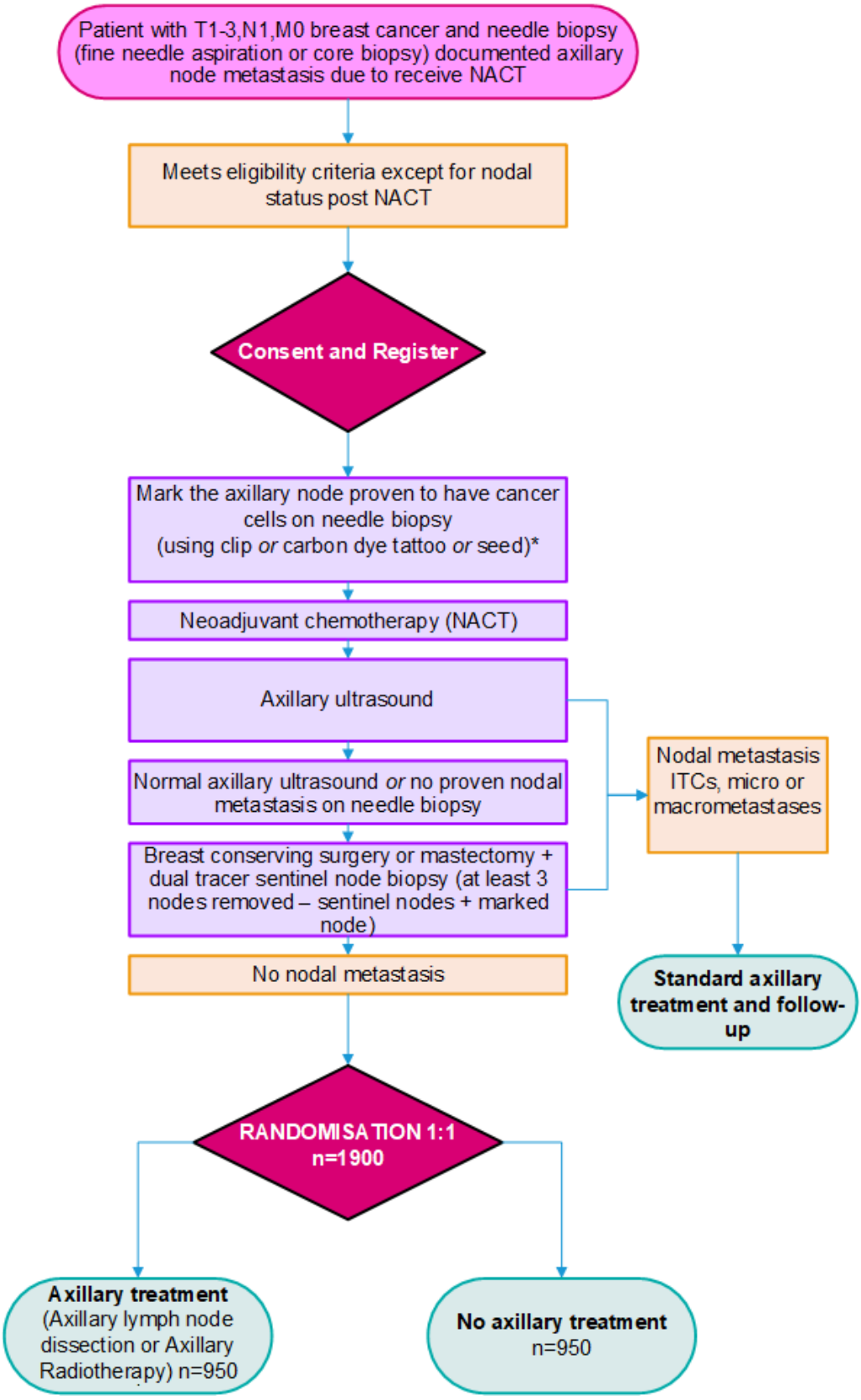
Based on local hospital practices, there are two patient pathways for recruitment into ATNEC:

(i) **Pre-neoadjuvant chemotherapy registration:** The majority of participants will be approached before neoadjuvant chemotherapy. Trial entry via this pathway will be a two-step process. If patients are deemed eligible, and give their informed consent to participate, they will be registered on to the study. Participants will only be randomised to the main study after surgery, when there is evidence of no residual disease in the sentinel nodes (Pathway 1 – see section 6.2.1.1).

(ii) **Post-operative registration:** Patients may be approached after breast surgery (BCS, with or without oncoplastic techniques, or mastectomy, with or without immediate reconstruction), if they fulfil the eligibility criteria. Patients with no residual disease in the sentinel nodes will be consented and randomised (Pathway 2 – see section 6.2.1.2).

6.2.1.1 Recruitment Pathway 1: Pre neoadjuvant chemotherapy

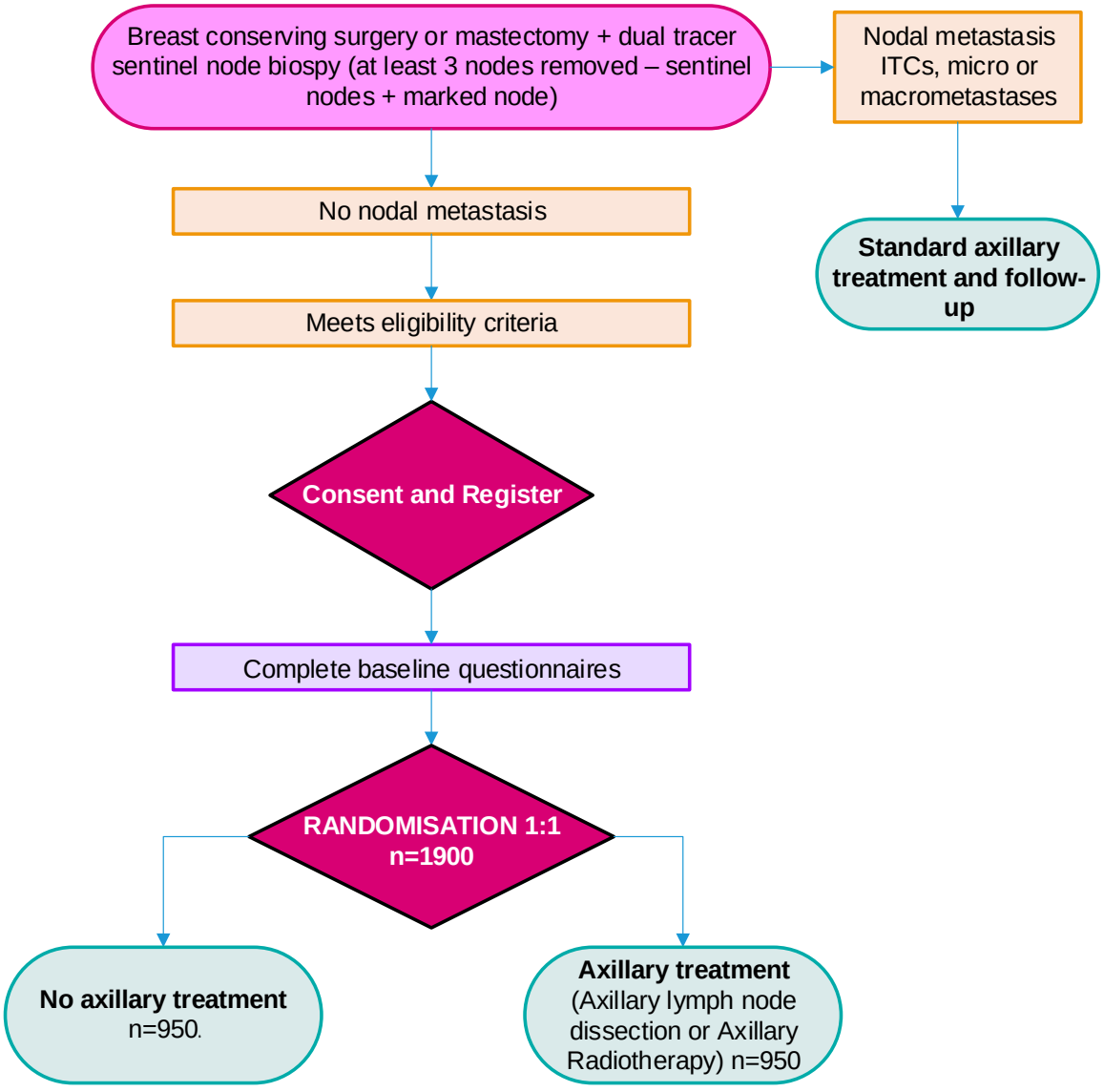
Eligible patients will be consented and registered before NACT. Patients will be randomised after sentinel node biopsy post-NACT if no cancer spread is found in the nodes as shown below:



*as per local standard of care

6.2.1.2 Recruitment Pathway 2: Post neoadjuvant chemotherapy

Post NACT, patients will undergo breast surgery (BCS, with or without oncoplastic techniques, or mastectomy, with or without reconstruction) and sentinel node biopsy. Eligible patients will follow the pathway below:



6.3. Registration and Randomisation Procedure

6.3.1. Registration

Written informed consent must be obtained prior to registration and must be recorded on the appropriate ICF. Prior to participant registration, research staff at site should have completed an Eligibility Checklist and Registration Form. The participant can be registered by logging on to the ATNEC registration/randomisation portal (link below).

Patients can be registered via the ATNEC database:

https://ctu.warwick.ac.uk/ATNEC

Site staff authorised to register and randomise participants to the ATNEC trial will be provided with a username and password to access the registration and randomisation system as part of the site set up process.

In the unlikely event the registration/randomisation portal is not available please contact the dedicated WCTU registration/randomisation line on 02476150402 (Mon-Fri 9am-5pm) excluding bank holidays & Christmas closure.

As part of the registration process, the participant will be assigned a unique trial number (TNO) that will be used to identify the participant and should be recorded on the CRF and on any further correspondence with the ATNEC Trial Office.

At the end of the registration process, the site research team will:

- Ensure that the participant's TNO is added to the ICF before taking 2 photocopies (original to be kept in the ISF, 1 copy in hospital notes, 1 copy to the participant)
- Add the participant's details to the Participant Screening/Enrolment Log

The ATNEC Trial Office will email confirmation of trial registration to the PI and main contact for the site research team.

6.3.2. Randomisation

Recruitment Pathway 1:

For those that are enrolled via Recruitment Pathway 1, the registration/randomisation procedure will commence following confirmation that there is no residual disease in the sentinel nodes, post-NACT and surgery. For participants who are not eligible for randomisation, treatment outcome and follow-up data will be collected as described in Section 6.5.1.

Before randomising a patient, ensure that eligibility has been confirmed and that a Randomisation Form has been completed.

The TNO allocated during registration will be used as part of the randomisation process. Sites should log on to the ATNEC registration/randomisation portal to randomise the participant. Sites should access the portal via the link below:

Patients can be randomised via the ATNEC database:

https://ctu.warwick.ac.uk/ATNEC

In the unlikely event the registration/randomisation portal is not available please contact the dedicated WCTU registration/randomisation line on 02476150402 (Mon-Fri 9am-5pm) excluding bank holidays & Christmas closure.

Participants will be randomised to: Axillary treatment or No Axillary treatment. Once a participant has been randomised, an email will be sent to the PI and lead contact at site confirming the participant's randomisation details and trial treatment arm allocation. Following randomisation, the site research team should ensure that the participant's details are updated onto the local site's participant screening/enrolment log.

Recruitment Pathway 2:

For those entering via recruitment pathway 2, the registration/randomisation procedure will be simultaneous and will commence following confirmation that there is no residual disease in the sentinel nodes, post-NACT and surgery. Before randomising a participant, written informed consent must have been obtained, pre-registration and pre-randomisation eligibility confirmed, and a Randomisation Form completed.

Sites should log on to the ATNEC registration/randomisation portal to randomise the participant. Sites should access the portal via the link below:

Patients can be randomised via the ATNEC database:

https://ctu.warwick.ac.uk/ATNEC

In the unlikely event the registration/randomisation portal is not available please contact the dedicated WCTU registration/randomisation line on 02476150402 (Mon-Fri 9am-5pm) excluding bank holidays & Christmas closure.

As part of the randomisation process, the participant will be assigned a unique trial number (TNO) that should be used to identify the participant and be recorded on all CRFs and on any correspondence with the ATNEC Trial Office.

At the end of the registration/randomisation process, the site research team will:

- Ensure that the participant's TNO is added to the ICF before taking 2 photocopies (original to be kept in the ISF, 1 copy in hospital notes, 1 copy to the participant)
- Add the participant's details to the Participant Screening/Enrolment Log

The ATNEC Trial Office will email confirmation of the participant's randomisation details, TNO and trial treatment arm allocation to the PI and main contact for the site research team.

6.3.3. Method of Implementing the Treatment Arm Allocation

Randomisation will be performed by computer using a minimisation algorithm, stratified by the following variables:

- institution
- type of breast surgery (BCS or mastectomy)
- receptor status (triple negative, HER2+, ER/PR+ and HER2-)

The randomisation system will ensure that there is no bias between the two trial groups. Participants will be randomised strictly sequentially, and allocation between trial arms will be in a 1:1 ratio. The computer minimisation programme will be developed and held centrally at the WCTU.

6.4. Interventions

6.4.1. Primary Breast Surgery

Primary breast surgery can consist of either BCS (with or without oncoplastic techniques) or mastectomy (with or without reconstruction).

6.4.2. Breast Conserving Surgery (BCS)

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 will undergo re-excision or mastectomy as per local protocol. This can be performed before or after randomisation.

6.4.3. Mastectomy

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

6.4.4. Marking the lymph node

The involved node can be marked using a clip, black carbon dye, or seed (iodine, radiofrequency, magnetic or other subject to CE marking) as per local practice (see Appendix 1). Sites can adapt the pathways as per local preference and change pathways during the duration of the study. The node may be marked at the time of needle biopsy or at a separate visit.

Training shall be provided to sites that are naive to marking and removal of marked nodes during SNB. Training will comprise – a) theory training at site initiation using PowerPoint presentation and procedure videos, b) if needed - mentored first case of marking the node by radiologist/radiographer, and SNB (with removal of the marked node) by the surgeon. Node marking training will be documented on the ‘Node Marking Training Log’, which will be stored in the Investigator Site File at site. A copy of the log will be sent to WCTU for oversight purposes.

6.4.5. Sentinel Node Biopsy

SNB should be performed using the dual tracer technique as per local protocol and at least three nodes should be removed (including the marked node). 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 criterion. At times, the pathologist may identify more lymph nodes than the surgeon and this is acceptable.

In around 80% of cases, the marked node is the sentinel node when at least three nodes are removed. For sites using a clip to mark the node, an x-ray of the specimen should be performed at SNB to ensure that the clipped node is removed. Pathology reports will be reviewed to ensure compliance i.e. at least three nodes removed during SNB. If, at the time of surgery there is no mapping of blue dye or radioactive

colloid apparent, then axillary node sampling or ALND will be performed as per the local guidelines. Participants with failed localisation, undergoing ANS are eligible for the trial.

If marked node is not retrieved, the participant is eligible if at least three nodes removed, and histology report shows evidence of down-staging with complete pathological response in a node/s e.g. fibrosis or scarring.

6.4.6. Pathology

The breast specimen and all axillary lymph nodes should be examined and reported according to predefined local practice that meets the guidelines published by the Royal College of Pathologists. The Residual Cancer Burden (RCB) is recommended as the gold standard for neoadjuvant chemotherapy assessment of breast and nodal response in clinical trials [21].

6.4.7. Axillary Treatment

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

6.4.7.1 Axillary Lymph Node Dissection (ALND) for Standard Care

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

6.4.7.2 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 radiotherapy quality assurance (RT QA) planning and delivery guidelines (see Section 9 for further details).

6.4.8. Neoadjuvant and Adjuvant Therapy

6.4.8.1 Chemotherapy and Endocrine Therapy

All participants will receive currently accepted chemotherapy, HER2 targeted treatment and endocrine therapy according to pre-defined local guidelines.

The type and number of cycles of chemotherapy given, is at the discretion of the multi-disciplinary team (MDT), following standard protocols. Although it is usually recommended that patients receive a minimum of 4 cycles of NACT, this is not always possible due to factors such as toxicity or the patient declining further chemotherapy. Data suggests that patients who achieve a pathological complete response, have a good outcome, regardless of what chemotherapy they receive [22,23]. Therefore, if a patient achieves a pathological complete response, and is otherwise eligible for the study, they may still enter the study regardless of the type and number of cycles of NACT received. This decision should be fully documented by the MDT in the patient's notes, and reason for early discontinuation of NACT should be documented in the CRF. It is the decision of the MDT, in consultation with the patient, whether further adjuvant chemotherapy is suitable. Details of adjuvant chemotherapy should also be documented within the CRF.

6.4.8.2 Radiotherapy

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, supraclavicular fossa and internal mammary irradiation when randomised to no further axillary treatment 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 dissection surgery, no attempt should be made to irradiate the axilla by adjustment of the superior/posterior tangential field margins.

All participants receiving radiotherapy should be treated according to local guidelines. Participants must also be monitored for compliance according to the ATNEC RT QA planning and delivery guidelines (see Section 9 and accompanying RT QA pack for further details).

In summary:
ALL participants may receive radiotherapy to the breast or chest wall.

Experimental arm (no axillary treatment arm): Radiotherapy to the axilla, supra-clavicular fossa (SCF) and internal mammary chain is **not permitted**.

Control arm (axillary treatment arm, if axillary radiotherapy): participants will receive radiotherapy to the axilla (covering at least level 1 & 2). Participants may receive radiotherapy to SCF and internal mammary chain.

6.5. Study assessments

6.5.1. Registration-only participants (not eligible for randomised trial)

For those participants who have registered to the trial, but are not eligible for randomisation, treatment and pathological response data will be collected following the completion of axillary treatment.

Consent will be taken from these registered patients to allow long-term recurrence and survival data to be collected from existing databases via data linkage, using services such as NHS Digital, Public Health England, eDRIS (Public Health Scotland) and cancer registries.

6.5.2. Randomised participants

Primary and secondary outcome data will be collected at randomisation and then annually for at least five years (see Appendix 2- Schedule of Assessments). We are using validated questionnaires for participant reported outcomes that have been used previously. Participant demographics, medical history, tumour characteristics and details of nodal and breast surgery will be collected at randomisation. Details of any adjuvant treatment given will also be collected during follow-up.

The required follow up data will be collected by the research nurse during routine hospital visits for annual mammogram, via hospital records or through telephone follow-up calls with participants. This data will be entered into the online study database. This will ensure high compliance with follow-up, whilst minimising the burden to participants, NHS and funder. Sites are required to report participant follow-up data annually, until all participants have reached at least five years follow-up.

Participant questionnaires with questions on arm morbidity and function, health-related quality of life and health resource use will be completed either in the clinic at randomisation. Follow-up questionnaires will be posted to participants by WCTU and returned directly to WCTU. Non-responders to postal questionnaires will receive up to two reminders by post and will then be contacted by telephone for collection of core outcomes (LBCQ and EQ-5D-5L).

Participants will be consented for collection of long-term follow-up data from existing databases via data linkage, using services such as NHS Digital, Public Health England, eDRIS (Public Health Scotland) and cancer registries; this will enable us to continue to follow-up participants and report long-term recurrence and survival.

6.6. Withdrawal Criteria

Patients are free to stop study participation at any time without giving a reason. In the event of a participant's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the participant wishes to withdraw and record the details on the CRF. For participants withdrawing from all aspects of the trial, the investigator should ascertain from the participant if they continue to consent to collecting routine information from hospital records, and/or data linkage with existing databases e.g NHS Digital and eDRIS, cancer registries and national public health bodies.

Participants may withdraw from the trial intervention only; this may be at the discretion of the investigator due to safety concerns. If a participant is only withdrawn from the intervention, they must be followed-up in accordance with the protocol.

Participants moving away from the region of the local site should not automatically be withdrawn from the trial. Should this occur, please contact the Trial Office with details of the relevant participant, and they will endeavour to assign the participant's follow-up to a hospital site close to their new location. The participant's new contact address for postage of follow-up questionnaires, will also need to be updated with the Trials Office.

Participants who withdraw from the study after randomisation will not be replaced.

6.7. Storage and Analysis of Samples

Further funding is being sought for the storage and translational analysis of patient breast and axillary node tissue, collected routinely as part of standard care. Participants will be asked to consent at trial entry for prospective tissue collection. Any future funded research proposal will seek the necessary ethical approval, prior to commencement.

6.8. End of Study

The end of study will be defined as last data capture for the last participant, allowing three months after the last visit to return CRFs and answer data queries. The CI will notify the Sponsor, participating sites and REC within 90 days of the end of study, or within 15 days if the study is ended prematurely (please see Section 9.6 for the criteria for premature study termination). The clinical study report will be written within 12 months of the end of study.

7. ADVERSE EVENT MANAGEMENT

7.1. Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence in a randomised trial participant and which does not necessarily have a causal relationship with their involvement in the trial.

A Serious Adverse Event (SAE) is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition

For the purposes of this study, the following events do not constitute SAEs:

- Hospitalisations for:
    - Protocol defined treatment

- Pre-planned elective procedures unless the condition worsens
- Treatment for progression of the patient's cancer

- Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the Case Report Form

7.2. Reporting Requirements

7.2.1. Adverse Events

Data about relevant AEs are collected through routine data capture (i.e. on the Annual Follow-up Form and through participant reported outcomes on questionnaires). Recurrence of and/or death from breast cancer and the diagnosis of new cancers in participants are outcome measures of the trial that will be collected via the CRF (the Event Form and Notification of Death Form) and are treated as expected events. Further separate collection of adverse event data is not required for trial analysis.

7.2.2. Serious Adverse Events

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.

For the purpose of this study, the following are regarded as expected SAEs and should not be reported on an SAE Form:

- SAEs relating to neo-adjuvant treatment for breast primary cancer
- Haematoma, wound infection, seroma or other surgical complication of primary breast surgery
- SAEs relating to radiotherapy
- SAEs relating to breast reconstruction
- SAEs relating to adjuvant treatment for breast primary cancer or recurrence
- SAEs relating to lymphoedema events

This is not an exhaustive list and Investigators should only report SAEs which are attributable to the study protocol.

7.2.3. Reporting Procedure

Site

Any SAEs that are deemed related to the study protocol should be reported to WCTU on an SAE form. When completing the form, the Investigator will be asked to confirm the following information:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- grade of severity (categorised using the Common Terminology for Adverse Events (CTCAE) version 4.0)
- causality (i.e. relatedness to intervention), in the opinion of the investigator

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form must be sent by email to the Trial Office as soon as possible and no later than 24 hours after first becoming aware of the event.

To report an SAE, email the SAE form to WCTUQA@warwick.ac.uk

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE form.

Trial Office (WCTU)

On receipt of an SAE Form, the Trial Office will arrange for the Chief Investigator to perform an independent assessment of relatedness. The Chief Investigator will also asses all related SAEs for expectedness. If the event is deemed unexpected (i.e is not defined as an expected event in Section 7.2.2) it will be classified as an Unexpected and Related SAE.

Reporting to the REC

The Trial Office will report all events that are categorised as Unexpected and Related SAEs to the REC within 15 days of receipt. Details of all Unexpected and Related SAEs will also be reported to Principal Investigators at recruiting sites.

DMEC

The independent DMEC will review all reported unexpected SAEs.

7.2.4. Reporting Period

Details of all related SAEs (except those listed in Section 7.2.2) will be documented and reported from randomisation until 12 months post randomisation. This reporting period should be sufficient to capture all SAEs associated with the trial protocol however, if a related SAE is identified after this period, the event should be reported to the Trial Office.

8. DATA HANDLING

8.1. Data Collection Tools

The Case Report Form (CRF) will comprise a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details. This trial will use an electronic data capture (EDC) system which will be used for completion of the CRF. Access to the EDC system will be granted to approved site personnel via the Trial Office. If the use of a paper CRF is required, then original forms should be sent to the co-ordinating team at WCTU and copies retained on site. CRFs are expected to be completed within 4 weeks of their due date.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. Missing and ambiguous data will be queried in line with the WCTU data management plan, which will outline the requirements for CRF completion and return.

Participant reported outcomes will be captured via a series of participant questionnaires (outlined in Section 3.2), combined into one questionnaire booklet. Paper questionnaire booklets will be issued to participants at the required time points by WCTU. Participants will complete their responses within the questionnaire booklet, and return the completed document to WCTU, for entry onto the trial database. Any sensitive disclosures reported via participant questionnaires will be appropriately managed in accordance with the University of Warwick's SOPs.

8.2. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concomitant medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number, not by name.

Investigators should keep records of all participating patients, all original signed informed consent forms and copies of any paper CRFs. It is necessary for investigators to provide access to source document for monitoring and audit purposes to WCTU, Sponsor, any monitoring or regulatory authorities as deemed necessary.

8.3. Data Handling and Record Keeping

The database will be developed and managed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff. The database will meet industry standard security criteria and only be accessible to authorised personnel. Within the database, participants will be identified by the trial participant number only.

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

8.4. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, the WCTU monitoring team, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

8.5. Archiving

At the end of the study, following completion of the end of study report, UHDB and WCTU will securely archive all centrally held study related documentation for a minimum of 10 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of 10 years after the end of study, and in accordance with national legislation. WCTU will notify sites when study documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

9. RADIOTHERAPY QUALITY ASSURANCE

The radiotherapy quality assurance (RT QA) component of the trial will be coordinated by the National Radiotherapy Trials Quality Assurance (RTTQA) Group. The RT QA process will include pre-recruitment and on-trial QA, details of which can be found in the accompanying RT QA planning and delivery guidelines. The RT QA guidelines are to be used in conjunction with the main trial protocol.

All participating sites must undergo the RT QA process and QA approval is required before participant recruitment can begin. Any queries regarding the RT QA process can be directed to the RTTQA team: atnecqa.enh-tr@nhs.net .

10. STATISTICS AND DATA ANALYSIS

A detailed statistical analysis plan (SAP) will be drafted by the trial statistician. The SAP will be finalised and approved by the CI and an independent statistician before the final data analysis.

10.1. Sample Size Calculation

Five-year disease free survival (DFS) for participants with node negative disease after NACT was around 80% based on the pooled analysis published by von MG et al [6]. With advanced drug treatment

and improved outcome over time we would anticipate higher rates of DFS to be seen today and thus the DFS in the control arm was estimated to be 90%. Thus, assuming five years recruitment and minimum of 4.5 years follow-up, recruiting 950 participants in each trial arm (1900 in total) would have the ability to demonstrate non-inferiority of omitting further axillary treatment, defining non-inferiority as 'no worse than 3.5%' below the control arm 5-year DFS with a 5% 1-sided significance level and 85% power, allowing for 7% non-collection of primary outcome data using the POWER procedure within the SAS statistical software.

Lymphoedema is a potential side effect of further axillary treatment and hence is considered as a co-primary endpoint. The AMAROS trial reported five year lymphoedema rates for ALND of 23% (76/328) and 11% (31/286) for ART [24] based on clinical signs of lymphoedema. A meta-analysis reported a lymphoedema rate for sentinel-node biopsy of 6% [3]. A minimum 5% important difference in the proportion of participants with lymphoedema is acceptable as defined by discussions with the clinicians, the PPI group and patient co-investigators. Any differences larger than this would provide stronger evidence and have a bigger impact on clinical practice. Thus assuming similar lymphoedema rates within this trial and the majority of participants randomised to standard axillary treatment had ART (rather than ALND) then a trial of 1900 participants would have 90% power to detect at least a 5% difference between trial arms if the overall lymphoedema rate in the control arm was 11%, with a 2-sided significance level and allowing for 25% dropout. The allowance for attrition is greater as the outcome is participant-reported from questionnaires. The power would be higher to detect the larger differences between trial arms that would be expected with increasing use of ALND in the standard axillary treatment arm (see Table 1).

Table 1: Sample sizes for the proportion of participants self-reporting lymphoedema symptoms at 5 years using a 5% two-sided significance level and 90% power

Proportion in control arm (axillary treatment)	Proportion in no axillary treatment arm	Difference	Sample size in each arm	Total sample size	Allowing for 25% dropout
11	6	5	691	1382	1846
12	6	6	509	1018	1360
13	6	7	395	790	1054
14	6	8	319	638	852
15	6	9	264	528	704

Additionally, the sample size is sufficient to demonstrate non-inferiority of omitting further axillary treatment in the secondary outcome of axillary recurrence free interval (ARFI) with 90% power and a 5% 1-sided significance level, defining non-inferiority as 'no worse than 2%' below the control arm 5-year ARFI of 98% using the POWER procedure within the SAS statistical software.

10.2. Planned Recruitment Rate

ATNEC will randomise 1900 participants from approximately 100 centres across the UK over 5 years. Based on a survey of UK practice, it is anticipated that each hospital will recruit five participants per year. A 50% participant uptake rate of those eligible is assumed.

An 18-month internal feasibility phase has been incorporated into the trial to assess the willingness of clinicians and patients to participate. The criteria for progressing from the internal feasibility phase at 18 months to the main trial are based on site opening, recruitment and compliance to allocated intervention and use a traffic light system of green for continuing to recruit, amber for considering amending the trial to improve recruitment either in terms of relaxing the eligibility, extending the number of sites and red for considering stopping the trial if there are no possible recovery options.

10.3. Statistical Analysis

10.3.1. Stratification

Participants will be stratified by the following factors:

- Institution
- Type of breast surgery (BCS vs mastectomy)
- Receptor status (triple negative vs HER2 positive vs ER status positive or PR status positive and HER2 negative)

10.3.2. Summary of Baseline Data and Flow of Patients

Descriptive statistics will be presented to summarize the distribution of baseline variables across each of the randomisation groups. Continuous baseline variables will be reported with means and 95% confidence intervals (95% CI), if normally distributed, otherwise will be reported with medians and Interquartile Ranges (IQR). Categorical variables will be reported with frequencies and percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients/ participants:

- Assessed for eligibility or confirmed as eligible,
- Excluded before randomisation (and the frequency of each reason for exclusion),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated intervention,
- That did not receive each allocated intervention,
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each randomisation group,
- Analysed for each randomisation group,
- Not analysed (and the frequency of each reason for not being analysed) for each randomisation group.

10.3.3. Statistical Methods

Time to event outcomes, including the co-primary outcome of DFS, will be assessed using Kaplan-Meier curves and compared using Cox proportional hazards models. Hazard ratio (forest) plots will be constructed for the stratification variables and important prognostic factors. A sensitivity analysis will be carried out adjusting for stratification variables (institution, type of breast surgery, receptor status). Exploratory subgroup analyses will be performed for those having ALND or ART.

The proportion of patients experiencing lymphoedema at five years will be compared across trial arms using a chi-squared test and a logistic regression model used to adjust for stratification variables. Arm morbidity, arm function and QoL will be scored using the appropriate manuals and assessed using a longitudinal mixed model regression analysis if model assumptions valid or a standardised area-under-the-curve analysis. Consideration will be given to any missing data in the form of a sensitivity analysis to determine the degree to which the conclusions may change with different missing data assumptions and mechanism models.

All analyses will be carried out on an intention-to-treat basis to preserve randomisation, avoid bias from exclusions and preserve statistical power. Thus, all subjects randomised into the study regardless of whether they receive the study intervention will be analysed unless they withdrew consent for further follow-up. The success of no axillary treatment relies on the confirmation of both non-inferiority in DFS and at least a 5% reduction in the proportion of participants with lymphoedema. No adjustment for multiple testing has been incorporated.

A Statistical Analysis Plan (SAP) will be developed to provide full details of the planned analysis.

10.4. Economic analysis

All methods and assumptions used in the economic evaluation will be pre-specified in a comprehensive Health Economic Analysis Plan (HEAP), which will be authored by the study economist, agreed by the grant holders, and finalised before the database is closed for the final analysis. As the HEAP relates to the economic outcomes only, which are a subset of the trial outcomes dealt with in the Statistical Analysis Plan (SAP), the HEAP will be developed to be consistent with the SAP.

The economic evaluation will take the take the perspective of the NHS, personal social services, but in a sensitivity analysis, a wider perspective incorporating costs to participants and their families will be taken. A within trial analysis will estimate costs, effects, and cost-effectiveness over the five-year follow-up and a model-based analysis will extrapolate the trial findings over the longer-term. Costs will be based upon the costs of the randomised interventions received (ALND or ART) and on the use of subsequent care and services.

Data on axillary treatment will be reported on a CRF; use of subsequent primary and secondary healthcare resources will be collected using a health service utilisation questionnaire, administered at baseline and 12, 24, 36, 48, and 60 months post-randomisation. Participant costs (time away from employment and any out-of-pocket expenses) will also be collected via the health utilisation questionnaire. Time and travel costs associated with the intervention will be estimated based on study estimates, including postcodes, and previous studies to reduce the burden on participants. Costs of the interventions will be estimated based on study estimates and costs from previous studies which will be inflated to the current price year, where applicable [25, 26]. All unit costs for subsequent healthcare resource use will be derived from routine sources or study specific estimates [27]. Data on resource use will be combined with the unit costs to produce a total cost for each trial participant. From which the mean cost to the NHS per participant per randomised group will be estimated. This work will be replicated in order to estimate a mean cost per participant per randomised group that incorporates participant costs. Costs and outcomes will be discounted at UK recommended rates [28]. Sub-group analyses will account for equity issues to examine if socio-economic status has an impact on costs and cost-effectiveness. The index of multiple deprivation, based on participants' postcodes, will be used to describe each participants' socio-economic status. Information on participant characteristics such as: marital status, employment status, education, and ethnicity will be presented as descriptive statistics.

1) Cost-effectiveness analysis. Two cost-effectiveness analyses will be conducted. These two analyses will be based on the incremental cost to avoid an incidence of the two co-primary outcomes, disease free survival and lymphoedema. Mean costs for each randomised group will be calculated alongside the frequency of disease recurrence and lymphoedema, these will then be presented as point estimates of mean incremental costs and effects (frequency of disease recurrence and lymphoedema) and the incremental cost per disease free interval and the incremental cost per lymphoedema avoided at five years.

2) Cost-utility analysis, based on incremental cost per QALY gained. QALYs will be based on the area under the curve approach [29] using health state utilities based on responses to the EQ-5D-5L administered at baseline, 12, 24, 36, 46, and 60 months [30]. Both mean cost and QALYs will be presented for each randomised group as point estimates of mean incremental costs and QALYs and the incremental cost per QALY gained over five years.

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.

3) Model-based analysis, based on incremental cost per QALY gained. An economic model will be used to estimate costs and effects at 5 years (to mirror the within trial analysis) and over a patient lifetime time horizon to determine the long-term impact of axillary treatment on outcomes. It is likely the economic model will take the form of a micro-simulation model informed from reviews of existing breast cancer models, but the precise form of model used will be determined as part of the research project [25, 31-33]. Trial data, clinical opinion, and existing literature will be used to inform the model parameters and estimate the incremental cost per QALY over the lifetime of a woman with early stage breast cancer.

Probabilistic sensitivity analysis (PSA) will conducted to address any uncertainty in the model-based analysis using the Monte Carlo simulation. PSA allows you to vary all of the model parameters simultaneously to determine the effect they have on the over probability of one treatment being cost-effective relative to another. Distributions will be attached to all parameters, and the shape and type of distribution will depend on the data available and recommendations for good practice in modelling. Deterministic sensitivity analysis will also be conducted to explore uncertainties (e.g. the impact of using trial data or estimates from the individual data meta-analysis). The results of this analysis are presented in a similar fashion to those from the within trial stochastic results.

10.5. Qualitative methods and analysis

Qualitative research, referred to as the Patient Experience sub-study, has been embedded within the recruitment phase to identify and investigate recruitment issues and develop effective and realistic strategies to ensure success of the trial. This is a key component of the pilot phase but will be continued as new sites are set up.

A multi-faceted, flexible approach will be adopted, that will include using one or more of the following methods, depending on recruitment:

1. Audio-recording appointments where researchers discuss the trial with potential participants
2. Semi-structured interviews or focus groups with researchers and patients
3. Assessment of screening logs

10.5.1. Study 1: Audio-recording appointments where researchers discuss the trial with potential participants

Aim: The aim will be to help the research team to understand recruitment issues and develop effective and realistic strategies to ensure success of the main trial. Recordings and transcripts may be used as teaching material to help boost recruitment at sites which struggle to recruit.

Method: Researchers will be invited to take part in this qualitative part of the study. They will be trained in the processes needed in order to record discussions with patients regarding possible participation in the ATNEC study. This will include giving consent to be part of the study (researcher consent) and obtaining patient consent for recording the consultations (patient consent).

Identified sites will be provided with a digital recorder, patient and recruiter information sheets, consent forms and standard operating procedures for securely transferring the recordings to the qualitative researcher.

Analysis: Interviews will be recorded, transcribed and analysed using a Framework Approach. Computer software will be used to organise the data for analysis (e.g. NVivo). Analysis will be a collaborative process between the interviewer and the qualitative researcher. Sites with high recruitment rates and low recruitment rates will be assessed to identify similarities and differences in communication and develop strategies to improve recruitment.

10.5.2. Study 2: Interviews with researchers and patients

10.5.2.1 Interviews with researchers

Aim: The qualitative researcher will carry out interviews with Health Professionals seeking to recruit patients to the study. The aim will be to help the research team to understand recruitment issues and develop effective and realistic strategies to ensure success of the main trial.

Method: Interviews with health professionals will be conducted and audio recorded to explore the views and experiences of the MDT (e.g. surgeons, oncologists, breast care nurses, radiologists) regarding treatment of the axilla. Interview topic guides will be established to ensure similarity across interviews, asking about their equipoise for the trial, recruitment pathways, how they explain the trial and its processes. Health professionals from approximately 10 sites at different geographical locations in the UK will be interviewed initially but this may be extended if it is felt that a saturation of themes has not been reached.

Interviews will be conducted face to face or by telephone or video call, whichever is most suitable and convenient for the researcher. Interviews will be semi-structured and audio-recorded. They will then be transcribed and stored on the university's shared drive. All interviewees will remain anonymous.

Interviews will be conducted at a range of sites including the more successful sites as well as sites with low recruitment in to order to identify lessons learnt and provide hints and tips for successful recruitment.

Analysis: Interviews will be recorded, transcribed and analysed using a Framework Approach. Computer software will be used to organise the data for analysis (e.g. NVivo).

10.5.2.2 Interviews with participants

Aim: The qualitative researcher will carry out interviews with study participants to help the research team to; 1) find out more about participants' views on reduced axillary treatment; 2) to understand recruitment issues; and 3) develop effective and realistic strategies to ensure success of the main trial.

Method: On recruitment to ATNEC, participants will be invited to take part in the Patient Experience sub-study. If a participant agrees to take part, they will be asked to consent to being contacted directly by the researcher in order to arrange the interview.

We aim to interview around 10-15 patients from each of the trial arms (standard axillary treatment; no further axillary treatment). Purposive sampling will be utilised to strive for a mix according to age and socio-demographic characteristics.

Interviews will be conducted face to face or by telephone or video call, whichever is most suitable and convenient for the participant. Interviews will be semi-structured, and audio recorded. They will then be transcribed and stored on the university's shared drive. All interviewees will remain anonymous.

Analysis: Interviews will be recorded, transcribed and analysed using a Framework Approach. Computer software will be used to organise the data for analysis (e.g. NVivo).

10.5.3. Study 3: Assessment of screening logs

All centres will be asked to provide screening logs which should include number of patients screened, reasons for refusal and any issues at randomisation. Recruitment rates will be regularly checked to see if any additional training or interventions are required to improve rates at poorly recruiting sites, and to share best practice from the top recruiting sites.

Screening logs of eligible patients will be assembled using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment processes.

10.6. Interim Analysis and Criteria for the Premature Termination of the Study

A formal interim analysis is planned when 33% of the required primary outcome events have been reported, which is anticipated to occur prior to recruitment closure. An overall 5% one-sided Type I error rate for testing non-inferiority will be controlled using an O'Brien-Fleming-like alpha-spending rule set at p = (0.01, 0.046) for the interim and final analysis respectively.

With a 5 year recruitment period, a minimum follow-up of 4.5 years, a 5 year estimated disease free survival of 90% in the control arm and 85% power, it is estimated that 282 DFS events are required for the final analysis; thus the formal interim analysis is planned when 93 DFS events have been reported. At this formal interim analysis, the trial may be stopped on the grounds of futility (i.e. conclude that it is not reasonably possible to show non-inferiority) if the obtained hazard ratio from the interim analysis is above the hazard ratio limit of 1.62 using a one-sided p-value of 0.01.

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants or serious repeated deviations from the protocol/ regulations). If this occurs the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

11. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the Research Ethics Committee (REC) or regulatory authority inspectors. Authorised representatives of the Sponsor may visit the participating sites to conduct audits/ inspections.

Monitoring and source data verification will be conducted by the Sponsor or delegated authority according to the Trial Monitoring Plan, which will be developed by the TMG. The extent and nature of monitoring will be determined based on the trial risk assessment.

All forms will be checked for completeness and consistency and any anomalies will be queried with the site. The trial staff will maintain regular communication with sites through routine calls, mailings and meetings. In the event of persistent issues with the quality and /or quantity of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. A representative from the Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and to determine the site's future participation in the trial.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Assessment and Management of Risk

A full risk assessment has been conducted identifying risks, their likelihood, impact and detectability in order to determine mitigation strategies. Such mitigation strategies will be implemented in trial documentation including the WCTU risk assessment and monitoring plan.

12.2. Peer review

This study has been peer reviewed as part of the NIHR's HTA application process.

12.3. Public and Patient Involvement

PPI has been key from the conception of the study including discussions with representatives from Independent Cancer Patients' Voice (ICPV), the NCRI dragon's den consumer forum and a Macmillan focus group. A Macmillan patient focus group was conducted with the help of Research and Design Service. The proceedings were recorded and analysed by an independent research fellow to obtain feedback from breast cancer survivors and to inform the study design. The trial had full support from these patients, but they stressed the importance of clear communication about the risks and benefits of armpit treatment.

Our PPI co-applicants and lay study team members include Janice Rose (consumer member – NCRI Breast CSG) and Helen Teresa Edwards (consumer member – ICPV). They will contribute to developing the patient pathway, information leaflet and study-related communication aids.

12.4. Research Ethics Committee (REC) & Regulatory Considerations

The study will be conducted in compliance with the approved protocol, GCP, the Declaration of Helsinki and the University of Warwick's SOPs. The protocol and all related documentation (e.g. ICF, PIS, and questionnaires) have been reviewed and received approval by a REC. The investigator will not begin any participant activities until approval from the HRA and REC has been obtained and documented. All documentation and correspondence must be retained in the trial master file/investigator site file. Substantial amendments that require HRA and REC (where applicable) review will not be implemented until the HRA and REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

It is the responsibility of the CI to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The CI is also responsible for notifying the REC of the end of study within 90 days. Within one year of the end of study, the CI will submit a final report with the results, including any publications/abstracts to the REC.

The CI is also responsible for ensuring any publicly available database (e.g. ISRCTN or clinicaltrials.gov) are updated with the results of the trial.

Before any site can enrol a participant into the study confirmation of capacity must be sought from the site's research and development (R&D) department. In addition, for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is ongoing.

12.5. Protocol Compliance

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations may happen and as such these must be reported immediately to the trial's office via a protocol deviation form, in accordance with the University of Warwick's SOP. Protocol non-compliances will be documented and reviewed regularly by the TMG to identify any trends. Corrective and preventative actions will be identified and actioned.

12.6. Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or
(b) The scientific value of the study.

If a serious breach is confirmed by clear and unequivocal evidence, the study Sponsor must notify the REC within 7 days of the matter coming to their attention. The Corrective and Preventative Actions Report template, supplied by WCTU, may be used for this purpose.

12.7. Data Protection and Patient Confidentiality

The study will be conducted in accordance with the General Data Protection Regulation (GDPR). The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. Participants will be identified on all study specific documents (except for the informed consent form and enrolment log) by only the participants study specific identifier (and initials if deemed necessary). This identifier will be recorded on documents, biological samples and the database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

All documents will be stored securely with access restricted to study staff and authorised personnel.

To preserve the participants' anonymity, only their allocated trial number and initials will be required on the CRFs. With the participant's permission, their date of birth and health service (NHS) number/Community Health Index (CHI) number will be collected at randomisation to allow flagging with the Office of National Statistics. Participant' name and address will be collected for sending out questionnaires from the WCTU to achieve higher data completeness. Personal data will be stored securely and separately from the main database and security roles would be applied to ensure only those people who require access to participant identifying data are granted access. Participants should be assured that their confidentiality will be respected at all times

UHDB and the University of Warwick will act as joint data controllers of the data generated in the study.

12.8. Financial and Other Competing Interests

At the time of protocol writing, there are no known financial or other competing interests of the Chief Investigator or their team. The membership of the TSC and DMEC will be asked to review the specific charter for their committee, which requests that they declare any competing interests.

12.9. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

12.10. Amendments

Changes to the protocol will be documented in written protocol amendments; the Sponsor is responsible for deciding if an amendment should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendments will only be implemented after approval and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

12.11. Access to Final Study Dataset

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

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 WCTU representatives.

12.12. Data Sharing Statement

Participant data is stored on a secure server at WCTU where each participant has been assigned a de-identified trial number. Any requests for access to the trial data should be sent to the CI who will inform the data custodians and agreement will be made through the data access committee which will comprise of the principal investigators from the trial management group. For each data sharing request, it is essential that a proforma is completed which will describe the purpose, scope, data items requested, analysis plan and acknowledgment of the trial management team. Requestors who are granted access to the data will be required to complete a data sharing agreement which will be signed by the requester, sponsor and principal investigator(s). We anticipate that data sharing will be possible after the publication of the primary endpoint of the trial.

13. DISSEMINATION POLICY

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 least 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 and Breast Cancer Now.

13.1. Policy for Publication and Authorship

Authors and Contributors will be defined as per The International Committee of Medical Journal Editors (ICJME) recommendations. 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.

Citable collaborators: Citable collaborators will have made a considerable contribution to the study but will not have met the ICMJE criteria for authorship (non-author contributors). These will include leads at each site and other team members who have randomised at least 20 participants to the study. All citable collaborators will be listed at the end of the paper and their roles identified.

Acknowledged collaborators: Acknowledged collaborators will include team members and trainees who have made a lesser contribution to patient recruitment and data collection than that required for citable collaborator status. Trainees who are acknowledged contributors will also receive a certificate of participation for inclusion in their portfolios.

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

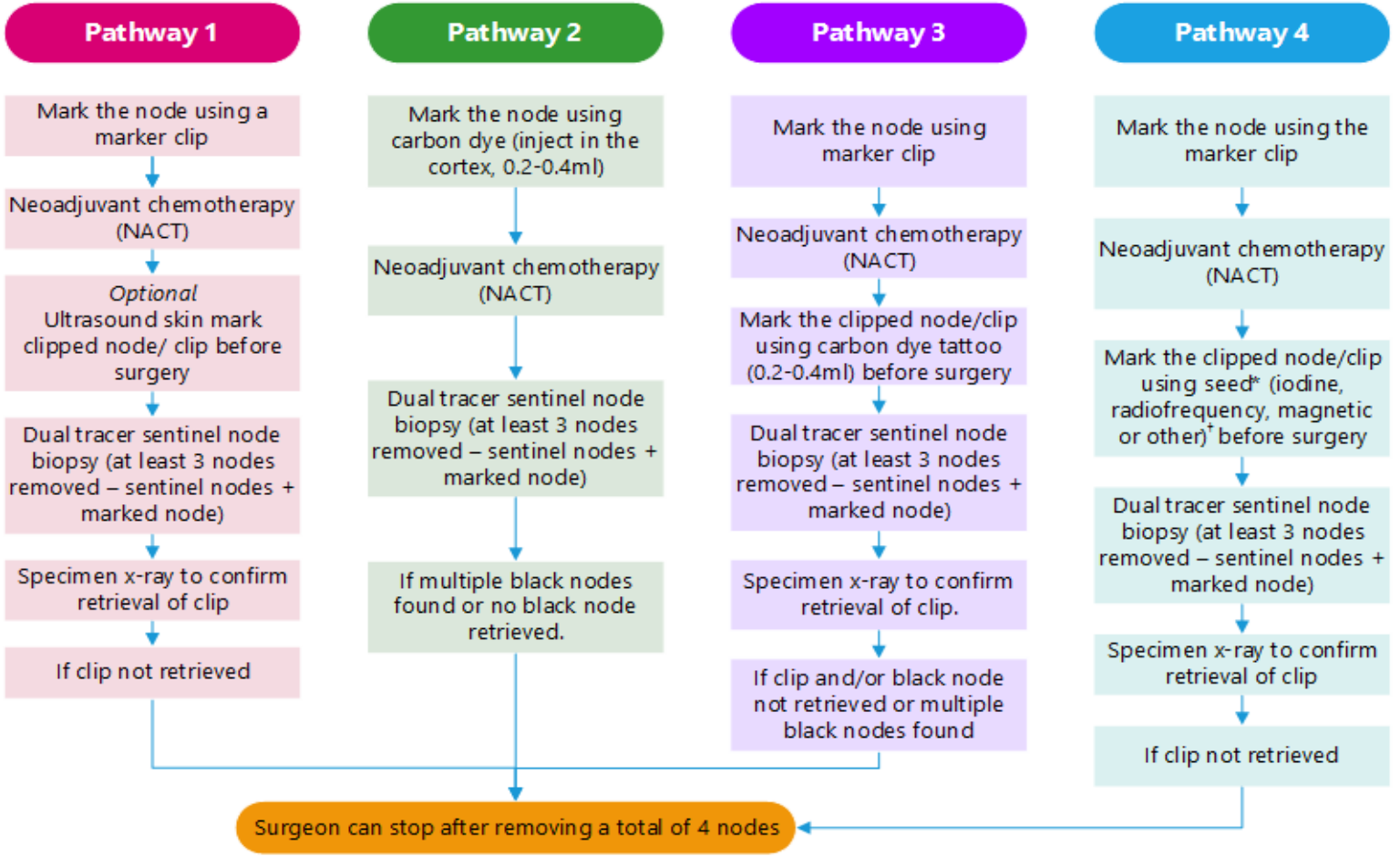
14. REFERENCES

1. NICE guideline [NG101]. Early and locally advanced breast cancer: diagnosis and management. 2018; Available from: https://www nice org uk/guidance/ng101.
2. Mansel RE, F.L., Kissin M, Goyal A, Newcombe RG, Dixon JM, Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst, 2006. **98**(9): p. 599-609.
3. DiSipio T, R.S., Newman B, Hayes S, Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013. **14**(6): p. 500-515.
4. Fu MR, R.S., Hu SH, Stewart BR, Cormier JN, Armer JM, Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. Psychooncology, 2013. **22**(7): p. 1466-1484.
5. Barron AU, H.T., Day CN, Hwang ES, Kuerer HM, Boughey JC, Association of Low Nodal Positivity Rate Among Patients With ERBB2-Positive or Triple-Negative Breast Cancer and Breast Pathologic Complete Response to Neoadjuvant Chemotherapy. JAMA Surg 2018.
6. von MG, U.M., Blohmer JU, Costa SD, Eidtmann H, Fasching PA Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012. **30**(15): p. 1796-1804.
7. Tee SR, D.L., Evoy D, Rothwell J, Geraghty J, Prichard RS, Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg 2018. **105**(12): p. 1541-1552.
8. Boughey JC, S.V., Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013. **310**(14): p. 1455-1461.
9. Kuehn T, B.I., Fehm T, Fleige B, Hausschild M, Helms G, Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013. **14**(7): p. 609-618.
10. Caudle AS, Y.W., Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol, 2016. **34**(10): p. 1072-1078.
11. Choy N, L.J., Porter C, Ozawa M, Kieryn A, Pal S, Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. Ann Surg Oncol, 2015. **22**(2): p. 377-382.
12. Boughey JC, B.K., Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). Ann Surg Oncol, 2016. **263**(4): p. 802-807.
13. Simons JM, v.N.T., van der Pol CC, Luiten EJT, Koppert LB, Smidt ML, Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Meta-analysis. Ann Surg Oncol, 2019. **269**(3): p. 432-442.
14. NCRI The UK Top living with and beyond cancer research priorities. 2018; Available from: https://www ncri org uk/lwbc/all-questions/
15. Cutress RI, M.S., Potter S, Goyal A, Kirwan CC, Harvey J, Opportunities and priorities for breast surgical research. Lancet Oncol, 2018. **19**(10): p. e521-e533.
16. Gandhi A, C.C., Makris A, Provenzano E, Goyal A, Maxwell AJ, Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology. Clin Oncol (R Coll Radiol) 2019. **31**: p. 664-668.
17. Bulley C, G.S., Coutts F, Blyth C, Jack W, Chetty U, Comparison of breast cancer-related lymphedema (upper limb swelling) prevalence estimated using objective and subjective criteria and relationship with quality of life. Biomed Res Int, 2013. **2013:807569.**
18. Armer JM, S.B., Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. Lymphology, 2010. **43**(3): p. 118-127.
19. Armer JM, R.M., Porock D, Culbertson SD, Predicting breast cancer-related lymphedema using self-reported symptoms. Nurs Res, 2003. **52**(6): p. 370-379.

20. Kennedy CA, B.D., Smith P, Van ED, Tang K, Inrig T, Measurement properties of the QuickDASH (Disabilities of the Arm, Shoulder and Hand) outcome measure and cross-cultural adaptations of the QuickDASH: a systematic review. Qual Life Res 2013.
21. Provenzano E, B.V., Viale G, Cameron D, Badve S, Denkert C, MacGrogan G, Penault-Llorca F, Boughey J, Curigliano G, Dixon JM, Esserman L, Fastner G, Kuehn T, Peintinger F, von Minckwitz G, White J, Yang W, Symmans WF, Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Mod Pathol, 2015. **28**(9): p. 1185-1201.
22. Campbell J.I, Yau, C., Krass, P., Moore, D., Carey, L.A., Au, A., Chhieng, D., Giri, D., Livasy, C., Mies, C., Rabban, J., Sarode, V.R., Singh, B., Esserman, L., Chien, Y.Y., Comparison of Residual Cancer Burden, American Joint Committee on Cancer Staging and Pathologic Complete Response in Breast Cancer After Neoadjuvant Chemotherapy: Results from the I-SPY 1 Trial (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res. Treat. 2017. 165(1): p.181-191
23. Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J.P., Wolmark, N. *et al.* Pathological Complete Response and Long-Term Clinical Benefit in Breast Cancer: the CTNeoBC Pooled Analysis. The Lancet. 2014. 384(9938): p. 164-172
24. Donker M, v.T., Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014. **15**(12): p. 1303-1310.
25. Huxley N, J.-H.T., Coelho H, Snowsill T, Cooper C, Meng Y, A systematic review and economic evaluation of intraoperative tests [RD-100i one-step nucleic acid amplification (OSNA) system and Metasin test] for detecting sentinel lymph node metastases in breast cancer. Health Technol Assess 2015. **19**(2): p. v-215.
26. Prescott RJ, K.I., Williams LJ, King CC, Jack W, van der Pol M A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technol Assess, 2007. **11**(31): p. 1-iv.
27. Curtis L, B.A., Unit Costs of Health and Social Care 2018. Personal Social Services Research Unit, University of Kent, Canterbury 2018.
28. NICE. National Institute for Health and Care Excellence (NICE): Guide to the methods of technology appraisal 2013. 2013; Available from: https://www nice org uk/article/pmg9.
29. Matthews JN, A.D., Campbell MJ, Royston P, Analysis of serial measurements in medical research. BMJ 1990. **300**(6719): p. 230-235.
30. van HB, J.M., Feng YS, Kohlmann T, Busschbach J, Golicki D, Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health, 2012. **15**(5): p. 708-715.
31. Mandrik O, Z.N., Meheus F, Severens JLH, Guha N, Herrero AR, Systematic reviews as a 'lens of evidence': Determinants of benefits and harms of breast cancer screening. Int J Cance, 2019.
32. Schiller-Fruhwirth IC, J.B., Arvandi M, Siebert U, Cost-Effectiveness Models in Breast Cancer Screening in the General Population: A Systematic Review. Appl Health Econ Health Policy, 2017. **15**(3): p. 333-351.
33. van den Broek JJ, v.R.N., Mandelblatt JS, Cevik M, Schechter CB, Lee SJ, Comparing CISNET Breast Cancer Models Using the Maximum Clinical Incidence Reduction Methodology. Med Decis Making, 2018. **38**( ): p. 112S-125S.

15. APPENDICES

15.1. Appendix 1 – Node marking pathways



N.B Sites can adapt the pathways to their local preference. The node may be marked at the time of the needle biopsy or at a separate visit.
*Seed may be inserted in the node before the start of NACT. †Subject to CE marking.
If marked node not retrieved, patient is **ELIGIBLE** if at least 3 nodes removed and histology report shows evidence of down staging with complete pathological response in at least one node e.g fibrosis or scarring.

15.2. Appendix 2 – Schedule of Assessments

15.2.1. Trial Entry

		Pathway One		Pathway Two	
		Pre-NACT	Post-Surgery and SNB	Pre-NACT	Post-Surgery and SNB
Trial Entry	Trial Entry Criteria Satisfied	X			X
	Informed Consent Obtained	X			X
	Registered to Trial	X			X
	Nodal Status Eligibility Confirmed		X		X
	Randomised to Trial		X		X

15.2.2. Trial Data Collection

Study Assessments	Registration	Randomisation	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72	Month 84	Month 96	Month 108	Month 120
Participant Demographics	X											
Medical History	X											
Tumour Characteristics	X	X[1]										
Nodal Information	X	X[1]										
Treatment Details		X[1]										
ATNEC Questionnaire Booklet		X	X	X	X	X	X					
Annual Follow-Up			X	X	X	X	X	X	X	X	X	X
Long-term health status follow-up via data linkage eg. using NHS Digital maintained by Public Health England.												X

[1] For those participants who have been registered to the study but are not eligible for randomisation due to positive nodal status, treatment and response data will be collected following the completion of axillary treatment.