Targeted Axillary Dissection versus axillary node clearance in patients with POsitive axillary Lymph nodes in Early breast cancer: A multicentre, pragmatic, phase III randomised controlled trial

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AMENDMENTS TO PROTOCOL

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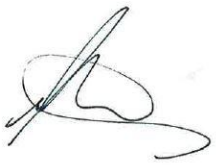
PROTOCOL SIGN OFF

Signed (Chief Investigator):  Date: 17/04/2025

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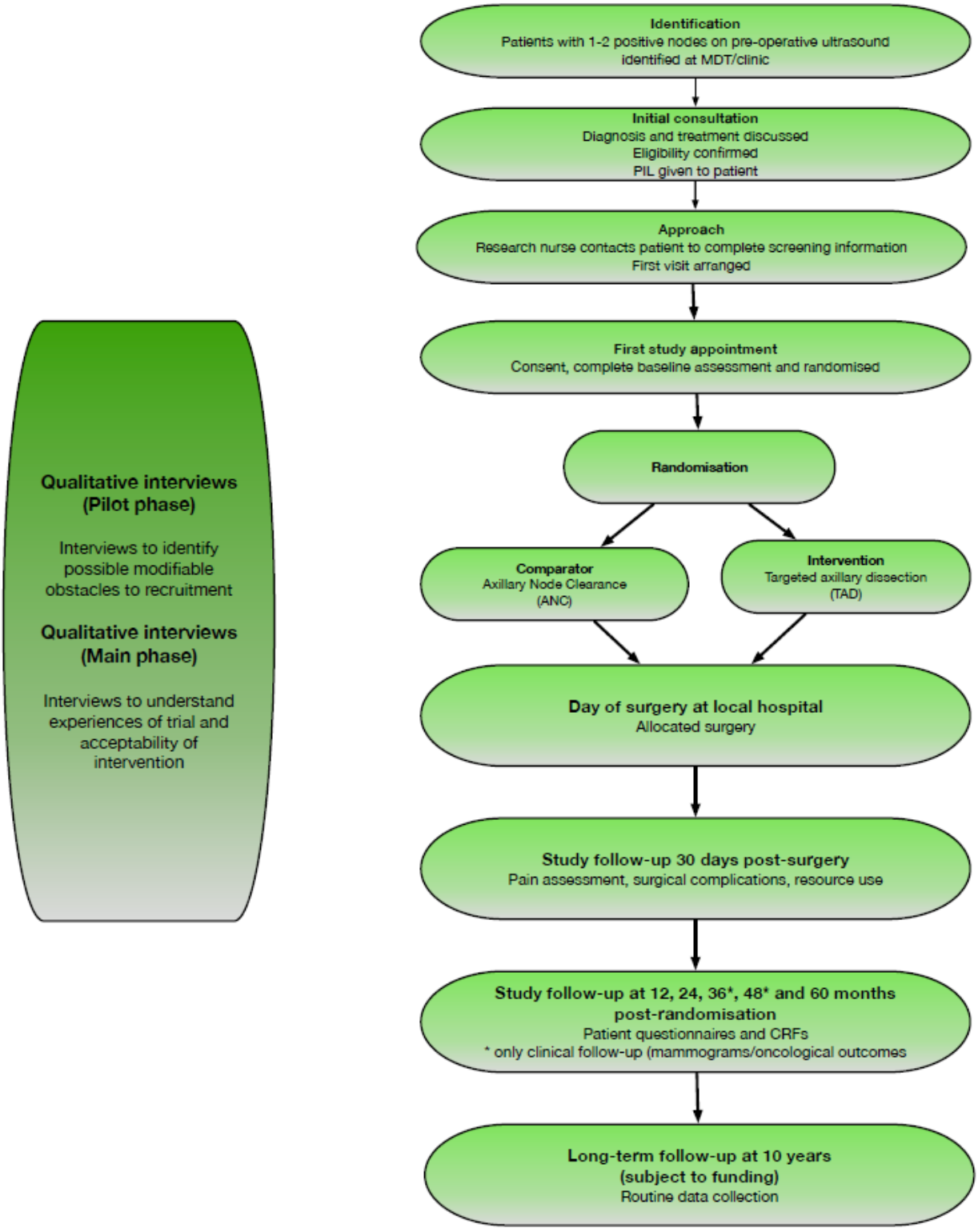
TADPOLE TRIAL SYNPOSIS

Title	**TADPOLE**: Targeted Axillary Dissection versus axillary node clearance in patients with POsitive axillary Lymph nodes in Early breast cancer: A multicentre, pragmatic, phase III randomised controlled trial
Chief Investigator	Professor Shelley Potter
Sponsor	North Bristol NHS Trust
ISRCTN Number	TBC
Trial design	Multicentre pragmatic phase 3 randomised controlled trial (RCT) with a 9-month internal pilot, embedded qualitative work and surgical quality assurance (QA); two parallel groups with 2:1 randomisation to TAD vs ANC and co-primary endpoints, integrated study within a trial (SWAT) to optimise recruitment of minority ethnic groups; patient follow up for 60 months and a trial-based economic evaluation with development of an economic model to estimate the long-term cost-effectiveness of TAD vs ANC. Tissue sample collection will take place for future ethically approved translational research.
Intervention	Targeted axillary dissection (TAD)
Comparator	Axillary node clearance (ANC)
Primary Objectives	To establish whether, in early breast cancer patients with biopsy-confirmed low volume axillary nodal disease having primary surgery, TAD is superior to ANC in terms of reducing lymphoedema at 12 months while maintaining acceptable rates of locoregional recurrence at 5 years.
Secondary objectives	1. To estimate the difference between groups with respect to a range of patient-reported, clinical and oncological secondary outcomes 2. To estimate the short and long-term cost-effectiveness of TAD compared with ANC by combining data from this trial with other published data.
Primary outcomes	i. Lymphoedema at 12 months ii. Locoregional recurrence at 5 years
Secondary outcomes	i. Surgical complications at 1 month post-last axillary surgery ii. Surgical and oncological outcomes at 1-month post-last axillary surgery iii. Patient-reported lymphoedema at 12, 24 and 60 months assessed using two questions from the LBCQ questionnaire iv. Objective assessment of lymphoedema at 12 months using measurement of arm circumference v. Arm and shoulder morbidity using the QuickDASH (51) at 12, 24 and 60 months vi. Pain at 1 and 12 months using the Numerical Pain Rating Scale (NPRS) vii. Overall and disease-free survival at 60 months viii. Health-related quality of life using the EQ-5D-5L, FACT-B+4 and LYMPH-Q at 12, 24, 60 months ix. Resource use to estimate costs at 12, 24, 60 months and modelled beyond the end of the trial
Patient population	Adults ≥18 with primary unilateral breast cancer and low volume axillary nodal disease, defined as clinically normal (cN0), radiologically detected, biopsy-proven, nodal involvement with <=2 involved nodes on ultrasound scan (USS) having primary surgery
Sample size	861 patients

Eligibility criteria	**Inclusion criteria** 1. Adults (≥18 years of age) 2. Primary T1-2 breast cancer of any grade (multifocal/multicentric disease is permitted) 3. Low volume N1 axillary nodal disease confirmed on core biopsy or fine needle aspiration cytology, defined as: a. clinically normal(cN0) b. radiologically detected nodal involvement c. with <=2 involved nodes on USS 4. Able and willing to provide written informed consent 5. Willing, fit and able to undergo primary surgical treatment **Exclusion criteria** 1. ≥3 suspicious nodes on USS or clinically abnormal (cN1) 2. T3 or T4 disease by clinical or radiological assessment 3. Pure invasive lobular carcinoma 4. Bilateral breast cancer 5. Previous ipsilateral breast cancer or ductal carcinoma in situ 6. Received neoadjuvant systemic anticancer therapy (neoSACT) 7. Received neoadjuvant endocrine therapy (defined as >4 weeks of treatment) 8. Previous axillary surgery (sentinel node biopsy, axillary node clearance or axillary sample) 9. Other invasive cancers unless a) Disease free for 5 years or b) Previous basal cell carcinoma, cervical carcinoma in situ; non-muscle invasive urothelial carcinoma 10. High risk group for developing breast cancer as defined by NICE guidance 11. Pregnant or breast feeding 12. Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process. 13. Prisoners

TRIAL FLOWCHART



SCHEDULE OF EVENTS

ASSESSMENT	Screening	Trial entry	Before surgery	Intra-operative	Post-operative MDT meeting	Further surgical intervention if indicated	Post completion of surgery	Months since last axillary surgery					
								1	12	24	36	48	60
Diagnostic biopsy of breast & axilla + core biopsy or FNA of suspicious/abnormal axillary lymph nodes	x												
Molecular markers – ER/HER2	x												
Multidisciplinary team decision for primary surgery	x												
Medical history	x												
Clinical examination of breast and axilla	x												
Informed consent for trial entry		x											
Height/Weight		x											
WHO performance status		x											
Measurement of arm circumference		x							x				
Completion of PRO questionnaires[a]		x							x	x			x
Eligibility assessment and randomisation		x											
Ultrasound scan to localise involved node			x										
Marking of most abnormal/biopsied node (TAD only)			x										
Sentinel Node Localisation (TAD only – day before **or** day of surgery)			x	x									
Surgery – Breast surgery and ANC or TAD				x									
Intraoperative confirmation of excision of the clipped/localised node (e.g. specimen radiograph)				x									
Post-operative histology review					x								
Further breast/axillary surgery as per MDT recommendation[b]						x							
Tissue collection							x						
Adjuvant therapy as recommended by MDT[c]							x						
Pain assessment telephone call								x	x				
Collection of surgical complication data								x					
Collection of adjuvant therapy data									x				
Mammogram									x	x	x	x	x
Assessment of oncological outcomes – notes review/CRF & Phone call									x	x	x	x	x
Resource use from medical notes									x				x
Resource use from patient questionnaires									x	x			
Qualitative decliner interviews (timings are approximates)		x	x										
Qualitative interviews (timings are approximates)		x	x					x	x				
Safety recording/reporting procedures		x	x	x	x	x	x	x	x				

a At baseline: 2 questions from LBCQ, FACT-B+4, EQ-5D-5L, Quick-DASH; At 12, 24 and 60 months: 2 questions from LBCQ, FACT-B+4, EQ-5D-5L, LYMPH-Q, Quick-DASH; [b]if involved margins post BCS OR at least one involved node cannot be identified in the axillary surgical specimen OR pN2 disease in TAD group and MDT recommend completion axillary clearance; [c]axillary radiotherapy is prohibited in the TAD arm unless T3 or N2 disease on post-operative histology and nodal RT recommended by MDT; ANC – axillary node clearance; MDT – multidisciplinary team; TAD – targeted axillary dissection

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GLOSSARY OF ABBREVIATIONS

AE	Adverse event
AI	Artificial Intelligence
ANC	Axillary node clearance
AR	Adverse reaction
BTC	Bristol Trials Centre
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
DFS	Disease free survival
DMSC	Data Monitoring and Safety Committee
EDI	Equality Diversity and Inclusion
GCP	Good Clinical Practice
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ITT	Intention to treat
LPLV	Last patient last visit
LRR	Locoregional recurrence
MRC	Medical Research Council
NBT	North Bristol NHS Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health & Care Research
OS	Overall survival
PIL	Patient Information Leaflet
PI	Principal Investigator
PPIE	Patient and Public Involvement and Engagement
PROM	Patient reported outcome measure
QALYs	Quality adjusted life years
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SWAT	Study Within A Trial
TAD	Targeted axillary dissection
TMF	Trial Master File
TMG	Trial management group
TSC	Trial steering committee
UoB	University of Bristol

1. BACKGROUND AND RATIONALE

1.1 Background

Breast cancer affects approximately 56,000 patients in the UK every year (1), the majority of whom have surgery as their first treatment ('primary surgery'). This surgery usually has two components: an operation to the breast to remove the cancer and an axillary procedure (2). The type of operation performed to the axilla currently depends on whether the cancer has spread to the axillary lymph nodes at diagnosis (2).

Current management of patients with node positive breast cancer in the UK

In the UK, patients with newly diagnosed breast cancer have an ultrasound scan (USS) of their axilla with a needle biopsy of any abnormal nodes to determine if the cancer has spread (2). NICE guidelines state that all patients with biopsy-proven node-positive breast cancer should be offered an axillary node clearance (ANC) (2), a radical operation removing all lymph nodes in the axilla. This operation is recommended even if patients have only one or two radiologically detected positive nodes: so-called 'low volume' nodal disease.

However, ANC is a highly morbid procedure with one in three patients experiencing life-changing, life-long complications that can significantly impact long-term quality of life - such as lymphoedema (20%)(3) and chronic pain (20%)(4). These require ongoing management which is costly for the NHS.

ANC was traditionally performed to reduce the risk of locoregional recurrence (LRR) and improve survival but there is no evidence that it improves breast cancer outcomes for patients with low volume nodal disease (5-14). Subsequently, ~3,800-4,000 patients ***every year*** in England alone may be having unnecessary and potentially harmful surgery.

Targeted axillary dissection (TAD)

Targeted axillary dissection (TAD), which combines a sentinel node biopsy (SNB) with targeted removal of involved node(s) which are localised pre-operatively, may offer an effective alternative to ANC. This targeted approach is feasible (15), is associated with significantly fewer surgical complications than ANC (16) and leads to more accurate identification and removal of involved nodes than SNB alone (17, 18) whilst providing accurate staging and prognostic information for planning adjuvant therapy.

TAD is becoming increasingly popular. It is already standard of care in node-positive patients with a complete response to neoadjuvant chemotherapy (19) and the TADPOLE national practice survey suggests that 15% of units are already using TAD routinely or selectively in node-positive patients having primary surgery (20). However, 84% of breast units believe there is uncertainty regarding optimal surgical management of low volume nodal disease, and 74% (30/42) would be willing to randomise such patients to a randomised controlled trial (RCT) comparing TAD and ANC.

Currently there is equipoise and enthusiasm to conduct the TADPOLE RCT in the UK (20). Failure to robustly evaluate TAD in a well-designed pragmatic RCT is likely to lead to haphazard adoption, with the risk of significant avoidable patient harm and the unwelcome perpetuation of existing variation in axillary management in the UK.

A search of clinicaltrials.gov has been undertaken to identify any trials that are ongoing or in set up evaluating TAD in node positive patients having primary surgery and only two trials; TADEN and TAXIS were identified. TADEN (NCT04671511) is a Canadian cohort study assessing the technical feasibility of TAD in the primary surgical setting. TAXIS (NCT03513614) is a multicentre

international RCT comparing ANC and TAD + axillary radiotherapy (ART) in all node-positive patients, not specifically those with low-volume disease. All patients having TAD in TAXIS will receive axillary radiotherapy, which would represent overtreatment for this patient group. Neither trial will address the question of whether TAD alone is sufficient local treatment for low volume nodal disease.

TADPOLE will therefore be unique in comparing TAD and ANC in the setting of primary surgery for low volume nodal disease. If TAD significantly reduces surgical complications without adversely impacting oncological outcomes, this trial will change clinical practice improving outcomes for thousands of breast cancer patients each year.

1.2 Trial rationale

Although ANC is currently standard of care for patients with node-positive breast cancer having primary surgery in the UK (2), there is no evidence that this radical axillary surgery improves overall survival, disease free survival (DFS) or significantly reduces locoregional recurrence (LRR) in patients with low volume nodal disease (5-14).

Indeed, it is increasingly recognised that ANC represents overtreatment in this group. The US ACOSOG-Z0011 trial (7-10) and recent meta-analyses (11-13) have shown no benefit in either breast cancer specific survival or LRR when ANC is performed in clinically node negative T1 – T2 (cN0) breast cancers found to have low volume nodal disease (defined as <=2 involved lymph nodes) after surgical staging with sentinel node biopsy (SNB). Several confirmatory trials including the HTA-funded UK POSNOC trial (21) are ongoing.

Z0011 findings have been adopted into US breast cancer guidelines (22) leading to de-escalation of axillary surgery in cN0 patients with <=2 positive sentinel nodes in North America (23), and decreasing use of ANC worldwide (24, 25). Our 2022 survey of 54 UK breast units, however, shows that in line with NICE guidelines (2), ANC remains standard of care for UK patients with node-positive breast cancer (20).

Z0011 has not led to ANC being replaced with SNB in patients with low volume nodal disease in the UK for two main reasons. Firstly, patients in whom nodal involvement is diagnosed pre-operatively by USS staging have been shown to have a much higher burden of axillary disease than those detected by surgical staging, so the patient group in Z0011 is not comparable to the patients under discussion here (26). Secondly, SNB is less accurate in patients with positive nodes so it cannot be relied upon for accurate axillary staging in the context of known nodal disease seen on imaging (27-29). There therefore remains an urgent need to identify a safe and effective alternative to ANC in patients with biopsy confirmed T1-T2 tumours with low volume axillary nodal disease to address axillary overtreatment in this group.

1.2.1 Design justifications

TADPOLE includes a randomised comparison of lymphoedema rates between the surgical techniques (TAD and ANC) at 12 months and is powered to exclude an unacceptable rate of LRR at 5 years in the TAD group. This design has been carefully chosen to evaluate TAD rapidly and efficiently in patients with low volume disease having primary surgery while also generating sufficient data to demonstrate acceptable levels of locoregional disease control.

Patients will be randomised in a 2:1 ratio to TAD vs ANC to test the superiority of TAD in terms of reducing lymphoedema rates compared with the current standard of care (ANC). Randomisation is necessary to minimise bias when comparing two surgical techniques. This is a pragmatic RCT designed to reflect real world practice with embedded surgical and radiotherapy quality assurance to maximise external validity. The 2:1 randomisation has been chosen to optimise recruitment and ensure inclusion of sufficient numbers of patients in the TAD arm to demonstrate acceptable oncological safety.

Oncological safety will be demonstrated if LRR at 5 years does not exceed 5% in the TAD group. This design is appropriate as the LRR rate in breast cancer patients with low volume axillary nodal disease having primary surgery is very low (1-4%) (8, 13, 30-33). This extremely low event rate means that a randomised non-inferiority comparison of LRR between TAD and ANC would not be appropriate due to the prohibitively large numbers of patients required. However, for TADPOLE to potentially change practice, it is necessary to demonstrate acceptable levels of locoregional control. Demonstrating oncological safety will be essential to support widespread adoption of TAD in patients with low volume nodal disease having primary surgery if the trial is positive. The embedded controls provided by the randomised comparison arm for the lymphoedema outcome within this design limits the risk of selection bias associated with single arm trials and provides a group of patients receiving contemporaneous standard of care to aid interpretation of the single group data. The LRR in both the TAD and ANC arms will be carefully monitored by the DMSC throughout the trial to ensure estimates are correct and an exploratory comparative analysis of LRR in the TAD and ANC arms will be performed at 5 years.

The NIHR HTA funded SMALL trial (34) has an identical hybrid design with co-primary surgical and oncological endpoints and includes a randomised comparison of re-excision rates in the vacuum-assisted excision (VAE) and surgical groups and a single cohort analysis of LRR at 3 years in the VAE arm which must not exceed a pre-specified unacceptable rate of 3%. Other precedents where a single arm interventional cohort design has been used in breast cancer treatment de-escalation studies include the successful PRIMETIME avoidance of radiotherapy study (35) and the ongoing NIHR HTA funded HER2-RADiCAL study (ISRCTN81408940), both of which have strong patient advocate support.

TADPOLE will include robust surgical and radiotherapy quality assurance (see Section 5 and 6, 6.12) to ensure the fidelity of the intervention; maximise external validity and ensure the results are accepted and will be implemented by the breast cancer community if the trial is positive. Lack of Radiotherapy Quality Assurance (RTQA) has been a major criticism of previous axillary surgery de-escalation trials (36).

2. AIMS AND OBJECTIVES

2.1 Aim

To compare the clinical and cost-effectiveness of TAD compared with ANC in patients with low volume node positive breast cancer having primary surgery and test the hypothesis that TAD is superior to ANC in terms of reducing rates of lymphoedema without adversely affecting long-term locoregional recurrence (LRR).

2.2 Primary objective

To determine whether, in breast cancer patients with biopsy-confirmed low volume axillary nodal disease having primary surgery, TAD is superior to ANC in terms of reducing lymphoedema at 12 months while maintaining acceptable rates of locoregional recurrence at 5 years.

2.3 Secondary objectives

1. The difference between groups with respect to a range of patient-reported, clinical and oncological secondary outcomes

2. The short and long-term cost-effectiveness of TAD compared with ANC by combining trial data with data from the literature.

2.4 Primary and secondary outcomes

2.4.1 Co-primary outcomes

i. ***Lymphoedema*** at 12 months post-last axillary surgery defined as BOTH an objective increase in arm circumference of >2cm from baseline (37, 38) and using two items from the validated Lymphoedema and Breast Cancer Questionnaire (LBCQ) (39) for patients to self-report lymphoedema symptoms defined as a response of 'yes' to both: arm "swelling now" and arm "heaviness in the past year" from. A composite endpoint combining objective and patient-reported outcomes was considered important to minimise potential bias in the trial.

ii. ***Locoregional recurrence (LRR)*** at 5 years defined as pathologically and/or radiologically confirmed recurrent tumour in the ipsilateral breast after breast conserving surgery or the skin or soft tissues of the chest wall within the anatomical boundaries of the breast after mastectomy; ipsilateral axilla, infraclavicular, supraclavicular fossa, interpectoral area or ipsilateral internal mammary chain. Date of locoregional recurrence will be the date on the imaging or pathology report, whichever comes first.

2.4.2 Secondary outcomes

Data will be collected on the following secondary outcomes (all timepoints are measured from post-last axillary surgery):

i. Surgical complications at 1-month post-last axillary surgery
ii. Surgical and oncological outcomes at 1-month post-last axillary surgery
iii. Patient-reported lymphoedema at baseline,12, 24 and 60 months assessed using two questions from the LBCQ questionnaire (as per primary outcome)
iv. Objective assessment of lymphoedema at baseline and 12 months using measurement of arm circumference
v. Arm and shoulder morbidity using the QuickDASH (40) at baseline, 12, 24 and 60 months
vi. Pain at 1 and 12 months using the Numerical Pain Rating Scale (NPRS)
vii. Overall and disease-free survival at 60 months
viii. Health-related quality of life using the EQ-5D-5L, FACT-B+4 at baseline, 12, 24, 60 months and LYMPH-Q at 12, 24, 60 months
ix. Resource use to estimate costs at 12, 24, 60 months and modelled beyond the end of the trial

Table 1: Trial Outcomes

Objective	Outcome	Collection timepoints (post-last axillary surgery)	Data Source
Primary Objectives			
1	Lymphoedema	Baseline & 12 months – **in-person visit**	**PROM** LBCQ **CRF completion**: Measuring arm circumference
	Locoregional recurrence (LRR)	12, 24, 36, 48 & 60 months	**CRF completion**: Mammogram outcome and oncological assessment via phone call with participant and medical notes review
Secondary Objectives			
1	Surgical complications	1 month post-last axillary surgery	**CRF completion**: Phone call with participant and medical notes review
	Surgical and oncological outcomes	1 month post-last axillary surgery	**CRF completion:** Surgical CRF – from medical notes Post-op/MDT final pathology – from medical notes
	Lymphoedema	Baseline, 12, 24 & 60 months	**PROM:** LBCQ
	Arm and shoulder morbidity	Baseline, 12, 24 & 60 months	**PROM** Quick-DASH
	Pain	1 & 12 months	**PROM** NPRS
	Overall disease free survival	12, 24, 36, 48 & 60 months	**CRF completion**: Mammogram outcome and oncological assessment via phone call with participant and medical notes review

Objective	Outcome	Collection timepoints (post-last axillary surgery)	Data Source
	Health related quality of life	Baseline, 12, 24 & 60 months	**PROM** EQ-5D-5L, FACT-B+4
		12, 24 & 60 months	LYMPH-Q
2	Resource use	12 & 24 months 12 & 60 months	**PROM:** MODRUM and questions on productivity loss **CRF completion:** Medical notes review

3. TRIAL DESIGN AND SETTING

TADPOLE is a multicentre pragmatic phase 3 randomised controlled trial (RCT) with a 9-month internal pilot, embedded qualitative work, surgical and radiotherapy quality assurance (QA), an integrated Study Within A Trial (SWAT) and co-primary outcomes. It aims to assess whether in patients with breast cancer and low volume axillary nodal disease having primary surgery, compared with the current standard of care (ANC), TAD leads to significantly less lymphoedema at 12 months following their last axillary surgery without leading to unacceptable rates of LRR at 5 years and is cost-effective.

The internal pilot will continue for 9 months. If the progression criteria are met (see below), the main trial recruitment will continue for a further 19 months (total recruitment 28 months) at a minimum of 40 UK sites. If the main trial proceeds, patients from the internal pilot will be included in the final analysis. All participants will be followed up for 5 years post-surgery. Consent will be obtained for long term (10- and 20-year) follow up via linkage to routinely collected data, (subject to funding).

Please see Trial Flowchart on page 8.

3.1 Setting

Patients will be recruited from at least 40 secondary and tertiary care NHS hospitals across England, Wales, Scotland and Northern Ireland.

3.2 Trial population

Adults with primary breast cancer and biopsy-proven low volume axillary nodal disease defined as having clinically normal (cN0), radiologically detected nodal involvement with <=2 involved nodes on USS (22, 26) having primary surgery.

3.3 Internal pilot phase

The aim of the internal pilot phase is to demonstrate that sufficient numbers of eligible patients can be identified, recruited and will adhere to their allocated treatment over the course of the main trial to robustly answer the trial questions. This will be evaluated after 9 months of active recruitment from the following factors:

i) The number of sites opened
ii) Recruitment rates (number of patients randomised overall)
iii) Adherence to allocated intervention.

Criteria for progression from pilot to main trial are outlined in **Table 1**.

An embedded qualitative study will explore and address potential recruitment challenges (See Section 10). Participant demographics will also be monitored for diversity using an abbreviated version of DISTINCT demographics question set. All sites will be encouraged to aim for a black/ black British target of 5- 8% and no less than 25% from the two lowest deprivation quintiles.

Table 1: Progression criteria after 9 months of active recruitment

Progression criteria	Red	Amber	Green
% Threshold	<50%	50-99%	100%
Number of sites opened	<14	14-27	28
Recruitment of participants	<60	60-119	120
Adherence to allocated intervention	<90%	90-94%	95%

4. ELIGIBILITY CRITERIA

4.1 Inclusion criteria

ALL of the following must apply:

1. Adults (≥18 years of age)
2. Primary T1-2 breast cancer of any grade (multifocal/multicentric disease is permitted)
3. Low volume N1 axillary nodal disease confirmed on core biopsy or fine needle aspiration cytology, defined as:
    a. clinically normal (cN0)
    b. radiologically detected nodal involvement
    c. with <=2 involved nodes on USS
4. Able and willing to provide written informed consent
5. Willing, fit and able to undergo primary surgical treatment

4.2 Exclusion criteria

Participant may not enter the study if ANY of the following apply

1. ≥3 suspicious nodes on USS or clinically abnormal (cN1)
2. T3 or T4 disease by clinical or radiological assessment
3. Pure invasive lobular carcinoma
4. Bilateral breast cancer
5. Previous ipsilateral breast cancer or ductal carcinoma in situ
6. Received neoadjuvant systemic anticancer therapy (neoSACT)
7. Received neoadjuvant endocrine therapy (defined as >4 weeks of treatment)
8. Previous axillary surgery (sentinel node biopsy, axillary node clearance or axillary sample)
9. Other invasive cancers unless
    a. Disease free for 5 years or
    b. Previous basal cell carcinoma, cervical carcinoma in situ; non-muscle invasive urothelial carcinoma
10. High risk group for developing breast cancer as defined by NICE guidance
11. Pregnant or breast feeding
12. Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process.
13. Prisoners

5. TRIAL INTERVENTIONS

TADPOLE will compare the outcomes of targeted axillary dissection (TAD; intervention) and axillary node clearance (ANC; control), the current standard of care in patient with low volume nodal disease having primary surgery.

All interventions will be delivered under the care of a consultant breast surgeon. All participating surgeons will deliver both trial treatments. Surgical QA processes (41, 42) will be embedded within the trial. They will balance the need to minimise performance bias whilst maximising generalisability and accounting for the pragmatic nature of the study. It is expected that patients will have surgery within 31 days of randomisation.

5.1 Targeted axillary dissection

Targeted axillary dissection is defined as the combination of a sentinel node biopsy (SNB) with targeted removal of the biopsy-proven involved node that is localised prior to surgery.

The sentinel node biopsy is the operation to remove the sentinel nodes. The sentinel nodes need to be localised prior to the SNB. This is called sentinel node localisation. The sentinel node localisation will be according to local unit practice but *may* involve a technetium 99 radioactive tracer (this may not always use radioisotope) injected subcutaneously into the breast. It is done before the patient is anaesthetised either the same day as surgery or the day before depending on local unit practice. The localisation is an essential part of the sentinel node biopsy procedure.

The prohibited, mandatory and flexible steps for a primary TAD procedure will be agreed using consensus methods with the breast surgical community prior to the start of the trial as part of surgical quality assurance (SQA).

5.2 Axillary node clearance

Axillary node clearance defined as removal of all level 1 and 2 axillary lymph nodes, will be performed as per standard of care. Further details can be found in the Surgical Manual.

Adherence to the treatment allocation will be monitored through operative case report forms (CRFs) and numbers of lymph nodes removed in each group as part of the surgical QA process.

5.3 Site and surgeon eligibility

Surgeons participating in TADPOLE will be required to have experience in performing TAD. This procedure is now the established standard of care in patients post neoadjuvant chemotherapy (19) so it is anticipated that most UK surgeons will already have the necessary skills to participate.

Training resources including videos and webinars focusing on the key components of primary TAD will be developed to support participating surgeons. TAD Champions will promote dissemination of good practice. This will form an important part of the surgical QA; promote ‘buy in’ and engagement in the breast surgical community; ensure the results of the trial are accepted and promote rapid and effective implementation of TAD in patients having primary surgery if the trial is positive

Requirements for surgeon credentialing will be agreed by the surgical community and monitored as part of the SQA consensus process.

6. TRIAL METHODS

6.1 Site selection

We will engage with Research Delivery Networks (RDNs) in England and other relevant networks in the devolved nations to promote the trial at relevant sites. We will aim to select sites from geographically diverse areas of the UK to ensure our trial population is representative. We will also engage with breast surgical trainees and promote the Associate Principal Investigator (API) Scheme to optimise recruitment at participating sites.

It is possible that radiotherapy services may not be available within the recruiting site where surgery occurs. Where radiotherapy will be delivered at another hospital, a local arrangement (i.e. Service Level Agreement) must be in place with the TADPOLE recruiting site.

6.2 Participant screening and identification

Patients presenting via either the symptomatic or screening pathway will be eligible to participate. These potential participants will be screened prior to multidisciplinary team (MDT) meetings where diagnosis and decision-making occurs. Demographics of patients will be collected at screening to ensure those being screened and approached at sites are representative of the population.

If agreed at the MDT meeting that the patient is suitable for primary surgery, a member of the direct care clinical team will arrange a consultation to discuss the patients' diagnosis and treatment plan. At this appointment the clinical team will also introduce the study to the patient and they will be provided with a study information pack as part of a layered approach. This information pack will comprise of an invitation letter/text and a patient information leaflet (PIL). The PIL will contain a link and QR code to the trial website where patients can access a short video to supplement the information they have received in the PIL, and additional written information (Supplementary Participant Information). The Supplementary Participant Information will also be available on paper for those who request it. A member of the local team, trained in the trial protocol, will then follow-up with a conversation/phone call/video call to discuss the study further, answer any questions they may have, and arrange a baseline visit if the patient wishes to participate.

At the baseline visit any further questions can be answered prior to consent. Where possible, patient-facing study documentation will be translated into different languages depending on the sites' population demographic. Where possible, recruitment videos will contain subtitles and captions to improve the accessibility for all potential trial participants. Interpreters can be provided at sites for those patients whose first language is not English to support recruitment and facilitate data collection when required.

Patients who are contacted and do not want to find out more about the study will be asked if they would be willing to briefly give their reasons. Some sociodemographic data (age, sex, ethnicity and postcode for deprivation index) on non-participants will be collected to monitor inclusivity. The postcode will be entered onto the trial database to identify the deprivation index and then will be removed from view of the research teams (it will be available only in the database audit logs).

6.3 Eligibility

Eligibility will be confirmed by the local Principal Investigator or suitably medically trained delegate prior to baseline visit.

6.4 Pregnancy and breastfeeding

Sites will follow their local process for checking whether the patient is pregnant and testing appropriately is part of routine clinical care before surgery and follow up mammograms. Should a patient be pregnant or be breast feeding, clinical advice will be provided accordingly. Patients

who are pregnant at diagnosis or who wish to continue to breast feed will be excluded from taking part in TADPOLE.

6.5 Baseline visit

Where possible, the baseline visit will take place on the same day as other existing hospital appointments to reduce patient burden of travelling. At the baseline visit patients will be consented before completing baseline assessments. Patients who are willing to participate will be asked to provide informed, written consent, either electronically (eConsent) or on paper. Where possible, reasons for declining participation will be recorded on the patient electronic case report form (eCRF) and will inform any changes to recruitment procedures if needed.

Where an eConsent form is used, the original consent form will be stored on the trial database and two copies of the consent form will be required: (1) to be provided to the participant; (2) to be filed with a copy of the PIL in the participant's medical records. If the consent form is not completed electronically, as well as the two copies above, a copy of the paper form should also be scanned and uploaded to the trial database and the original paper copy stored in the Investigator Site File.

A baseline CRF will be used to collect clinical information on all participants and all participants will be required to complete baseline questionnaires and have their baseline arm (corresponding to the side surgery is expected) circumference measured. Randomisation can proceed once these have been completed.

6.6 Randomisation

Participant eligibility must be confirmed before randomisation can take place. Randomisation will be undertaken by the Research Nurse at the baseline visit after consent and the baseline questionnaire and CRFs have been completed. This is to allow time for participants allocated to TAD to have an axillary USS after randomisation to mark the biopsied positive lymph node prior to their surgery (see 6.8 below), and allow for theatre scheduling for the appropriate procedure as the duration is different between the two.

Patients will be randomised in a 2:1 ratio to TAD vs ANC stratified by centre and minimised on the type of breast cancer surgery performed (breast conservation vs. mastectomy). The randomisation sequence will be generated by Sealed Envelope™ using their secure online randomisation system and will also have allocation concealment. It is expected that patients will have surgery within 31 days of randomisation.

The participant's GP will be informed that they are taking part in the TADPOLE study, and a request will be made that their participation is noted on their electronic medical record.

6.7 Sample size calculation

The sample size is based on the co-primary endpoints of lymphoedema (at 12 months) and LRR (at 5 years) to include:

i) A randomised superiority comparison of lymphoedema at 12 months in the TAD and ANC groups
ii) Exclusion of a predefined unacceptable rate of LRR at 5 years in the TAD cohort

Assuming lymphoedema at 12 months will be observed for 20% of the ANC arm and 10% in the TAD arm (3), a randomisation ratio of 2:1, 90% power and 5% significance will require a total sample size of 585 (390 TAD, 195 ANC). For the co-primary outcome, 390 patients in the TAD group will be sufficient to exclude an undesirable LRR of <5% at 5 years with one-sided 2.5% alpha and 90% power, assuming an expected rate of LRR of 2% (31). To allow for multiplicity and provide 90% power overall, assuming no correlation between these outcomes (most conservative estimate), the sample sizes will be elevated to 490 in the TAD group (power for lymphoedema at

12 months 95.1%; power for LRR at 5 years 94.6%). Inflating the sample size to allow for 5% crossovers and 5% lost to follow-ups consistent with other breast cancer trials (21), a total sample size of 861 patients (574 in the TAD group and 287 patients in the ANC group) will be required for the study.

Given that the rate of LRR in the study population is expected to be extremely low (~2-3%)(43), oncological safety of TAD will be demonstrated if LRR is <5% in the TAD cohort. This threshold has been agreed in collaboration with our patient group and the wider breast cancer community through engagement with Independent Cancer Patients' Voice (ICPV). Patient advocates felt that a small increase in LRR would be an acceptable trade-off for a 50% reduction in the risk of lymphoedema given that LRR is not life threatening and can be salvaged with further surgery whereas lymphoedema has permanent lifelong impacts on quality of life. The recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis (13) demonstrates that reducing the extent of axillary surgery does not affect LRR, distant recurrence or breast cancer mortality but LRR in both the TAD and ANC arms will be carefully monitored by the Data Monitoring and Safety Committee (DMSC) throughout the trial to ensure the estimates are correct. Exploratory comparative analysis of LRR in the TAD and ANC groups will be performed at 5 years.

6.8 Blinding

It will not be possible to blind patients or surgeons due to the nature of the intervention. Participants and their treating clinical teams will be informed of the treatment allocation to allow appropriate theatre list planning, organisation of nodal localisation in the TAD group, preoperative informed consent and counselling. Research Nurses at local sites will also be unblinded from the point of randomisation onwards. Baseline data will be collected blind.

Risk of bias within the trial will, however, be minimised by including objective measures of both co-primary endpoints. Lymphoedema will be a composite endpoint that includes both an objective measurement of arm circumference at baseline and 12 months, together with a validated patient reported outcome measure (LBCQ) as the latter was the most important outcome for patients. LRR is an objective outcome that will be confirmed by biopsy. Where possible and feasible, sites will be asked if they have capacity to have a separate member of the local research team who can complete follow-ups and remain blinded from the recruiting member of the team.

Within the TMG and BTC groups, the majority of the team will be blinded and will review aggregate information about the 2 groups to monitor overall progress of the trial and response rates of PROMs, for example. It will not be possible for some of the operations team to remain blinded as they will have access to the database for monitoring purposes and for answering site/participant queries where appropriate. The Lead Statistician will be blinded along with the rest of the TMG and the Trial Statistician will be unblinded for their role of producing reports for the DMSC and they will also be undertaking the main analysis of the trial data.

6.9 Prior to surgery

All participants will meet with their clinical teams to discuss their surgery in more detail and will be counselled about the associated surgical risks including lymphoedema and strategies to mitigate against this including physiotherapy referral as per standard local practice.

Participants randomised to TAD will have a further axillary USS after randomisation to mark the biopsied positive lymph node. The time of marking will be according to local practice but MUST be before surgery. At least one node should be marked as part of the trial. Marking of the node will be as per local practice (clip, carbon dye, radiofrequency, magnetic or other seed subject to CE marking) but use of wireless localisation technologies (i.e. seeds) will be encouraged as these can be localised by the surgeon in theatre without the need for a further axillary USS to localise the involved node with a guide wire on the day of surgery. Further details of the process of ultrasound localisation of the involved nodes can be found in the Radiology Manual.

6.10 Day of surgery

Participants will undergo surgery under general anaesthetic to remove their breast cancer (breast conserving surgery or mastectomy +/- immediate breast reconstruction) as agreed with their surgical team at the same time as their allocated axillary procedure (TAD or ANC). ANC will be performed according to local practice. TAD will be performed according to the mandatory/prohibited steps agreed as part of the surgical quality assurance process (see study specific Surgical Manual). Successful completion of TAD will include confirmation of removal of the involved localised node (e.g., specimen radiograph). Further details can be found in the surgical manual. Surgical data will be recorded on CRFs.

Participants will receive standard post-operative care and will be discharged from hospital as per local practice.

6.11 Post-operative visit at 1 month

Participants will receive a phone call at **1-month post-last axillary surgery** to collect information about their pain (Numerical Pain Rating Scale; NPRS) and any surgical complications they have experienced. Further information will be collected from their notes about any resource use.

6.12 Post-operative multidisciplinary meeting and histology review

All participants will have their post-operative histology reviewed at their local multidisciplinary team meeting (MDT) as per local standard of care, usually within 1 month of surgery. Review will include pathological confirmation of pT1-2 pN1 disease and subsequent planning of adjuvant treatment as per MDT recommendations. This information will be recorded on CRFs by sites.

Further axillary treatment **IS PERMITTED** in the following circumstances **ONLY IF**

i. Absence of at least one involved (metastatic) lymph node in the axillary excision specimen for both TAD and ANC groups (i.e. the biopsy proven involved node has NOT been removed)
ii. pN2 disease of histological assessment (4 or more involved axillary nodes) in the TAD GROUP

Further surgery will NOT be permitted in TAD patients who are found to have <=3 involved nodes on histological assessment to determine eligibility for further adjuvant therapies. Additional axillary surgery following TAD has not been shown to inform recommendations for systemic therapy (44), and indeed the morbidity of additional axillary surgery has been demonstrated to far outweigh the benefits of additional treatment (45). Further details will be in the surgical manual.

6.12.1 No evidence of nodal involvement in axillary excision specimen

Patients in whom no involved (metastatic) nodes can be identified in the axillary excision specimen will require further assessment and intervention. This may include an axillary USS and further targeted excision of any abnormal nodes or an axillary node clearance a per local MDT guidance and patient preference.

6.12.2 pN2 disease on histological assessment

Patients in the TAD arm who are found to have pN2 disease (4 or more involved nodes) on surgical histology will require further axillary treatment. This may be an axillary node clearance or axillary radiotherapy as per local MDT recommendation and patient preference.

Both the absence of involved nodes and post-operative diagnoses of more extensive nodal involvement (pN2 disease) will be monitored as part of the QA processes and monitored by DMEC.

6.12.3 Adjuvant treatment

Main adjuvant treatment recommended within the first 12 months post-surgery will be recorded on CRFs. This will be reviewed annually for any on-going/new treatments.

6.12.4 Chemotherapy

Adjuvant systemic anticancer treatment (SACT) will be given as per standard of care, as agreed by the local MDT. No additional visits will be required for the purposes of the trial.

6.12.5 Radiotherapy

It is expected that all patients will receive radiotherapy to the whole breast or (if required) chest wall only. Level 1 and 2 axillary irradiation will not be permitted in the either trial arm (with the exception of the volume of level 1 included in standard breast or chest wall tangential fields).

However, in the circumstances that regional nodal radiotherapy (i.e. radiotherapy to the supraclavicular fossa (SCF) +/- internal mammary chain (IMC)) is recommended by the multidisciplinary team on the basis of post-operative histology, irradiation of the undissected axilla will be permitted in both trial arms and these patients will be retained in the trial.

Further details can be found in RTTQA Manual.

6.12.5.1 Radiotherapy quality assurance (RT QA)

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. All participating sites will undergo the RT QA process and QA approval will be required before participant recruitment starts. This approach has been used successfully in the HTA funded POSNOC (21) and ATNEC studies. A streamlined approach will be used in centres already recruiting to the HTA funded ATNEC study. Details of RTTQA can be found in RTTQA Manual.

6.12.6 Endocrine therapy and other treatments

Participants will receive endocrine therapy and additional treatments (including CDK4/6 inhibitors) as per local MDT recommendation.

6.13 Annual Follow up – for 60 months/5 years post-surgery

6.13.1 Mammography

Participants will be invited to attend annual mammograms for 5 years as per standard of care. Mammograms should be performed annually (+/- 2 months) of the patients' surgery anniversary. Follow-up beyond 5 years will be in accordance with local guidelines. In the majority of cases, it is anticipated that this will be through the NHS Breast Screening Programme.

As per standard care, following annual mammography, participants should be informed of the outcome of their mammogram as soon as possible and ideally within two weeks of the mammogram being carried out. For the trial, the outcome of the mammogram will be recorded in a CRF collected from either the participant's notes or directly from the participant during the annual follow-up phone call.

If a patient fails to attend for a mammogram appointment the site research team must make every effort to ensure that patient contact details are up to date for appointments to be re-scheduled. The site team will have annual phone calls with participants so this can be checked during these contacts.

6.13.2 Research contacts

All participants will have a face to face 12-month (+/- 1 month) research visit to complete PROMS (NPRS, EQ-5D-5L, FACT-B+4, LYMPH-Q, Quick-DASH and LBCQ), and an objective

assessment of lymphoedema (see Appendix 1). This will be timed to coincide with participants' year 1 mammogram appointment wherever possible to minimise participant burden.

After the 12-month visit, research follow up visits for the trial will be completed via a phone call to collect oncological outcome data.

6.14 Recurrence or new primary breast cancer

Any patient presenting with suspected locoregional, or distant breast cancer recurrence should be investigated and treated as per local practice. This data along with other oncological outcomes will be collected annually via notes review, CRFs and annual participant phone call.

Any additional clinical follow up will be as per local standard of care.

6.15 Deaths

Upon being made aware, sites should report patient deaths by completing the Death Form immediately. Every effort should be made to obtain a date and cause of death (see section 7 for reporting details).

6.16 Data collection at 12, 24 and 60 months post-last axillary surgery

6.16.1 Patient questionnaires

Participants will complete subjective measure of lymphoedema, quality of life and resource use questionnaires either electronically or on paper at 12, 24 and 60 months after their last axillary surgery.

Subjective assessment of lymphoedema (Lymphoedema and Breast Cancer Questionnaire (LBCQ). See Appendix 1) will be completed at 12 months as per 6.12.2. For 24 and 60 months this will be completed alongside the other PROMs at these timepoints.

The HRQoL objectives will be to compare patient-reported arm problems after TAD vs ANC in the short- (after 12 months), intermediate- (after 24 months), and long-term (60 months) using three validated measures: the EQ-5D-5L, FACT-B+4 and LYMPH-Q.

The validated Quick-DASH (Disabilities of the Arm, Shoulder and Hand) (42) questionnaire will be used to measure arm function at 12, 24 and 60 months. It consists of 11 items scored 1-5 where higher scores indicate greater disability. The Quick-DASH has been used to assess arm function in other NIHR HTA funded breast cancer studies (21).

Reminders will be sent up to 3 times and contact for reminders may be done be by any reasonable means (phone call, text, post and/or emails). Where possible, patient questionnaires translated into different languages will be provided for sites, otherwise/ or in addition, the use of interpreters will be encouraged to facilitate the collection of patient reported outcomes from those whose first language isn't English.

6.16.2 Notes review

Sites will complete CRFs from notes to collect data on resource use and clinical outcomes.

6.17 Long-term follow up

Written consent will be obtained to allow long-term recurrence and survival data to be collected from existing national databases via data linkage, using the flagging resource within the National Disease Registration Service (NDRS). Separate funding will be sought for 10 and 20-year follow up of the TADPOLE cohort.

6.18 Participant withdrawal

At each follow up point, research staff will confirm that the participants are happy for ongoing trial participation. All participants are free to withdraw from study treatment or active follow-up at any time. The PI can also decide to withdraw participants based on clinical opinion at any time during the trial. Although it is the participant's right to withdraw without giving a reason, it is a GCP requirement that a reason be sought and recorded, if given.

If a participant withdraws from the study, data collected up to the point of withdrawal will be kept and utilised in the analyses. All withdrawals, including reasons (where given), will be recorded. Data collection from medical records will continue unless the participant expresses they do not want this to be collected further. For participants which withdraw, their demographics will be linked to monitor any withdrawals related to possible inclusion barriers.

6.19 Loss of capacity

In the unlikely event that a participant loses capacity during the study they will be withdrawn. Any information already collected about them will be used.

6.20 Germline mutation carriers

Known germline mutation carriers (e.g. BRCA1/2) who are at high genetic risk will be excluded from the study but some participants will have genetic testing as part of their breast cancer management. These results are unlikely to be known at the point of enrolment. Any participants who are found to be germline mutation carriers after randomisation carriers will be retained in the study and managed as clinically appropriate by their local MDT.

6.21 Likely loss to follow up

Loss to follow up in breast cancer studies is generally low (<5%)(21). In the event of loss to follow-up, information on disease recurrence and death will be extracted from routine sources. If a participant does not wish to continue with active trial follow-up (e.g., questionnaire completion), all data collected up to that point will still be included in the analyses, and the participant will be asked if data collection from their medical records can continue. Participants' demographics will be linked to those who are lost to follow-up and reported to monitor for any possible inclusion barriers.

6.22 Concurrent studies

Investigators wishing to enrol patients into another interventional trial should contact the TADPOLE Trial Office in the first instance. The TADPOLE Trial Management Group (TMG) will consider the enrolment of TADPOLE patients into other trials that do not interfere with the analysis of the primary outcome or introduce bias. Examples may include trials of imaging or supportive treatment. The TADPOLE Trial Office will maintain a contemporary record of trials approved by the TMG. Where a trial has not been considered, the TADPOLE Trial Chief Investigator will provide advice based on the above principles.

6.23 Data collection

The schedule of data collection is outlined in the Schedule of Events (page 9). Data will be captured using a secure online database. Sites will be encouraged to use direct data entry into the database, and participants will be encouraged to use electronic questionnaires. This will allow real time validation and monitoring of data quality and completeness. Paper data collection methods will be provided to sites as a back-up, and to participants who are unable (i.e due to language barriers) or do not wish to complete online questionnaires. Detailed screening data will also be collected to allow ongoing review of recruitment rates and identify problems and barriers, and to populate the CONSORT diagram, which is a requirement of reporting clinical trials. Other data includes transcriptions of audio recordings of interviews as part of the qualitative work.

6.24 Definition of end of trial

Active data collection will continue up to 5-years post-last axillary surgery. The participant's active involvement in the trial will end at this point. Data collection for the whole trial will be complete when the final randomised participant has completed the 5-year post-surgical assessments. The end of the trial will be when the database is closed and all the data queries have been answered and statistical analysis completed.

7. SAFETY REPORTING

Serious and other adverse events will be recorded and reported in accordance with Good Clinical Practice (GCP) guidelines and the Sponsor's SOP (see Figure 1 below for flowchart for recording/reporting requirements).

Table 3 Definitions

Term	Definition
Adverse Event (AE)	An AE can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the research procedure, whether or not considered related. AEs require continuous assessment.
Adverse Reaction (AR)	The distinguishing feature between an AR and AE is whether there is evidence to suggest there is a causal relationship between the event and the research procedure.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • results in death • is life-threatening[a] • requires inpatient hospitalisation or prolongation of existing hospitalisation[b] • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. [a] "*Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.* [b] *"Hospitalisation" is defined as an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Emergency Department would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.*
Serious Adverse Reaction (SAR)	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is expected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is unexpected.

7.1 Serious adverse events

The reporting framework for SAEs is presented in Figure 1 and described in Table 4. SAEs will primarily be detected via the follow-up questionnaires, 1-month and 12-month research contacts post-last axillary surgery and from medical records.

SAE forms for expedited reporting will be completed by the local site team. The local PI will confirm relatedness and expectedness with input from CI as required. Sites will report SAEs to the BTC within 24hrs of the study team becoming aware of the event. If it is confirmed the SAE falls within expedited reporting procedures, this will be reported to the sponsor within 24 hours of the form being sent to BTC.

7.2 Expected Events

The following adverse events may occur for procedures related to the intervention (TAD and marking the node prior to surgery):

- Bleeding/Haematoma
- Wound infection
- Seroma
- Skin necrosis
- Altered sensation of upper inner arm
- Damage to nerves in armpit
- Shoulder stiffness/reduced mobility
- Lymphoedema
- Anaphylaxis reaction to sentinel node agents (blue dye reactions)
- Anaesthesia related complications
- Deep vein thrombosis/pulmonary embolism
- Chest infection
- Unable to localise and/or remove marked involved lymph node
- Further axillary surgery/treatment (possible if 4+ nodes or no involved node identified at pathology)

7.3 Anticipated events

The following adverse events occur frequently in patients undergoing surgery and treatment for breast cancer, and therefore will be considered anticipated:

- Hospitalisation for additional planned breast and axillary surgery (e.g. re-excision of margins)
- Complications from breast and axillary surgery
    - Bleeding/haematoma
    - Wound infection
    - Wound breakdown or dehiscence
    - Seroma
    - Poor cosmetic outcome
    - Altered sensation to the breast/chest wall
    - Altered sensation to the upper inner arm
    - Damage to the blood vessels/nerves in the axilla
    - Shoulder stiffness/reduced mobility/weakness of movement
    - Scarring
    - Skin necrosis
    - Re-excision surgery for close/involved margins
    - Inability to localised/remove breast cancer and/or pre-cancerous disease
    - Lymphoedema

    - Chest infection
    - Deep vein thrombosis/pulmonary embolism
    - Chest infection
    - Anaesthesia related complications
- Complications related to breast reconstruction surgery
    - Seroma (breast/donor site)
    - Haematoma (breast/donor site)
    - Wound infection (breast/donor site)
    - Mastectomy skin flap necrosis Nipple necrosis
    - Wound dehiscence
    - Implant loss
    - Donor site skin necrosis
    - Impaired flap perfusion requiring return to theatre for exploration/revision of anastomosis (flap salvage)
    - Partial flap necrosis requiring return to theatre for debridement.
    - Total flap necrosis requiring removal of flap
    - Other reconstruction related issues
- Toxicities relating to adjuvant treatment for primary breast cancer
- Events that are related to recurrence of the patient's cancer and/or its treatment
- Death from cancer or from a pre-existing medical condition.

7.4 Reporting adverse events

Data on both anticipated and expected adverse events and all deaths collected on CRFs during the trial will be reported regularly to the trial DMSC and to the Sponsor for review.

Events that listed as expected or anticipated will not require **expedited reporting** to the Sponsor, unless they **result in death and** are deemed by the Principal Investigator (or delegated individual) to be possibly, probably or definitely **related** to the intervention.

Any adverse events that may be expected after TAD (including those related to localisation of the involved node) will be collected on the study case report forms (CRFs) for the period from randomisation until 1 month after the last axillary surgery.

Adverse Events (AEs) will be graded in severity in accordance with the Common Terminology Criteria for Adverse Events v5.0 (CTCAE), which is a set of criteria for the standardized classification of adverse events in cancer studies.

7.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

If an SAE is detected that is deemed to be unexpected, that is not listed in the protocol or events of a severity that is not consistent with clinical experience of an expected event between randomisation and 12 months post-surgery, will require expedited reporting to the sponsor. If it is confirmed as possibly, probably or definitely related to the ANC/TAD, this will require onward reporting to the REC and DMEC.

BTC will report SUSARs to regulatory authorities and copy all reports to the sponsor within the expected time frames.

If the event is ongoing, there is no mandatory requirement regarding the frequency which follow-up reports should be submitted. As a minimum, a report should be submitted when the event resolves/ends.

7.6 Monitoring safety data

The Trial Management Group (TMG) will regularly review blinded safety data, and an independent Data Monitoring and Safety Committee (DMSC) will be convened to review safety data including monitoring locoregional recurrence rates and may request unblinded data by group. Safety secondary outcomes such as surgical complications and overall survival (OS) and disease-free survival (DFS) will be described and reported in the results manuscript.

7.7 Period for recording serious adverse events

Data on non-serious **adverse events** will be collected from randomisation to 1 month following the last axillary surgical procedure.

All **serious adverse events** (SAEs) will be collected from consent up to 12 months after the last axillary surgery.

All unexpected and un-anticipated events, regardless of relatedness, will be subject to expedited reporting to the Sponsor up to 1 month after the last axillary surgery as per the timings described in 7.1.

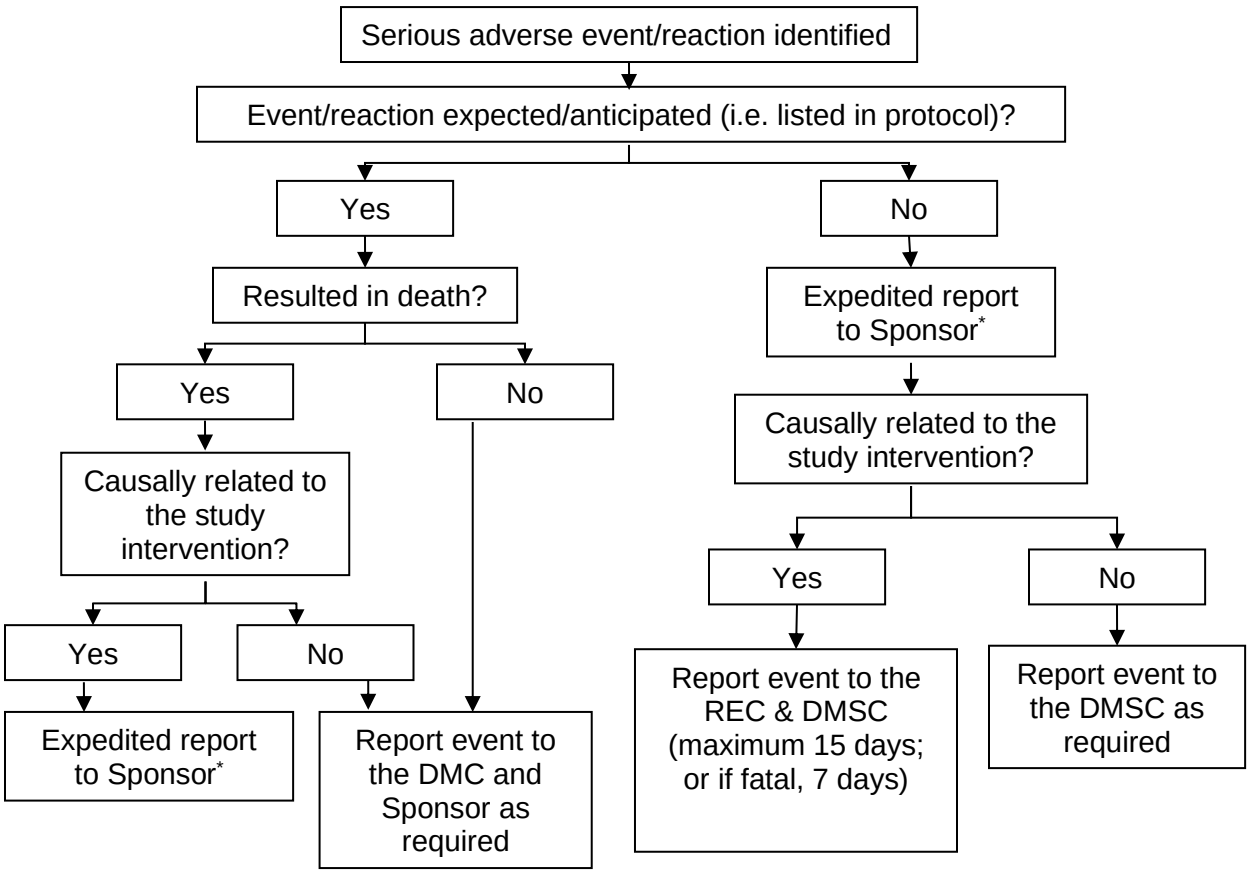
Thereafter, only unexpected and related SAEs will be subject to expedited reporting to the Sponsor up to 12 months after the last axillary surgery and all other SAEs will be reported to the Sponsor in periodic aggregated reports.

Table 4 Reporting overview

	1 month post last axillary surgery	**2-12 months post last axillary surgery**
Expected Adverse Event (expected of the intervention - TAD)	• Record in CRF only • Record CTCAE severity • Record if event fulfilled seriousness criteria • Record relatedness to the intervention (TAD) • Record how the event was treated	If event fulfils the seriousness criteria **AND** is related to the intervention (TAD) record and report on an SAE form within 24 hours of becoming aware of the event
Anticipated Adverse Event (anticipated of the disease **OR** of surgery)	• Record in CRF only • Record CTCAE severity • Record if event fulfilled seriousness criteria • Record reason for seriousness • Record if resulted in death • Record onset date	Anticipated events of the disease or of surgery should not, by default, be related to the intervention. Therefore, serious adverse events anticipated of the disease or of surgery do not need to be recorded or reported.

'Other' Adverse Events (any events that don't fall under the list of expected or anticipated events)	• Record in CRF • Record CTCAE severity • Record if event fulfilled seriousness criteria • Record onset date • If the event fulfils the seriousness criteria, record and report it to BTC on an SAE form within 24 hours of becoming aware of the event (regardless of relatedness)	If event fulfils the seriousness criteria **AND** is related to the intervention (TAD) record and report on an SAE form to BTC within 24 hours of becoming aware of the event

Figure 1 Serious adverse event reporting flow chart



** All unexpected and un-anticipated regardless of relatedness events will be subject to expedited reporting to the Sponsor up to 1 month after the last axillary surgery. Unexpected and related SAEs will be subject to expedited reporting to the Sponsor up to 12 months after the last axillary surgery.*

8. DATA ANALYSIS

8.1 Primary analysis

Primary analyses will follow CONSORT reporting guidelines for superiority trials and will include intention to treat (ITT) analysis. Binary outcomes will be compared using a generalised linear model, risk differences and relative risk will be reported along with 95% confidence intervals. Time-to-event outcomes will be compared using Cox's proportional hazards; in the presence of one or more competing risks, outcomes will be compared using competing-risks survival. If the assumptions of the Cox proportional hazard model are violated e.g. the proportional hazards assumption is not met, alternative methods such as parametric models will be used as appropriate. The exact partial-likelihood method will be used to account for tied times where necessary. EQ-5D-5L, pain, arm morbidity and other health-related quality of life (HRQL) scores will be compared using a mixed model with repeated measures as appropriate. Interactions between treatment and time will be examined and if significant at the 10% level, results will be reported separately for post-intervention time points; otherwise overall treatment effects will be reported. Analyses will be adjusted for type of breast cancer surgery (breast conservation vs. mastectomy) fitted as a fixed effect and site fitted as a random effect, and baseline values where measured. Adverse events will be described and reported as a rate of follow up time. The point estimate for LRR at 5 years will be calculated with 2-sided 95% confidence interval using the Kaplan-Meier method.

Participants will consent for linkage to routinely collected data sources to allow for long-term follow up at 10- and 20-years (subject to funding).

Full details of statistical analyses will be pre-specified in a publicly available Statistical Analysis Plan (SAP) in accordance with the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (46).

8.2 Subgroup analyses

No subgroup analyses are planned

8.3 Frequency of analyses

Analysis for the first co-primary endpoint (lymphoedema) will take place when 12-month follow-up is complete for all recruited patients, i.e., at 1 year post surgery.

Analysis for the second co-primary endpoint will take place when all participants have been followed up for 5 years, i.e. at 5 years post-surgery. No interim analysis of outcomes is planned.

Safety data will be reported to the DMSC at a frequency agreed by the committee, together with any additional analyses the committee request.

8.4 Economic evaluation alongside the clinical trial

An ITT trial-based cost-effectiveness analysis will be performed to establish if TAD is a more cost-effective alternative to ANC at 12 months after surgery.

The trial-based analysis will take place at 12 months aligning with the first co-primary outcome. The primary analysis will be performed by the National Health Service plus Personal Social Services (NHS+PSS) perspective and report costs and outcomes for those who are disease free, have developed locoregional or distant recurrence or died at 12 months, overall, and per group. The secondary analysis will take a societal perspective, including private expenses, informal care, and productivity losses.

The base case scenario will include multiple imputation with chained equations of missing cost and outcome data, adjusting for socio-economic and baseline characteristics (47). Costs and QALYs at 12 months (48), and jointly estimated using seemingly unrelated regressions and adjusted for stratification variables (e.g., centre), pre-specified variables as in the statistical analysis of clinical outcomes and baseline utility for QALYs. Bootstrapped incremental net monetary benefit (INMB) statistics at 12 months will be derived for willingness to pay thresholds of £20,000 and £30,000/QALY. If no arm is dominant, the incremental cost-effectiveness ratios at 12 months will be estimated. The probability of TAD being the most cost-effective procedure (vs ANC) will be depicted for a range of willingness to pay thresholds using cost-effectiveness acceptability curves (49). Sensitivity analyses will be performed (e.g., varying costing assumptions, mapping FACT-B responses to utilities, per protocol/complete case analysis) to address uncertainty around results and decision to adopt. Full details of economic analyses will be pre-specified in a publicly available health economics analysis plan.

Healthcare resource use will be collected using multiple sources from randomisation to last follow-up on hospital outpatient and inpatient visits, diagnostic tests, and therapies received. These will include surgery with TAD/ANC, subsequent care to treat complications, adjuvant treatments and additional cancer hospital care if patients develop recurrence. Data on breast cancer related hospital admissions and outpatients visits will be collected in the CRFs at 12 and 60 months

Participants will complete a questionnaire at questionnaire at 12 and 24 months to complement medical record review by providing information on loss of productivity (time-off work and daily activities), social care use and informal care (ModRUM (modular resource-use measure) questionnaire blocks) (50) related to breast cancer treatment or complications. Those who developed lymphoedema will fill in further ModRUM modules for primary care and community care utilisation related to lymphoedema, aids and dressings used and out-of-pocket expenditures related to lymphoedema care.

Resource use related to the administration of adjuvant therapy, complications or recurrence will be valued using national unit costs for health and social care and local sources when necessary (50, 51). Systemic therapy will be costed using the British National Formulary for medications. Informal care, productivity losses and lost income will be valued using Office of National Statistics weekly median earnings estimates in a human capital approach or micro-costed when appropriate, for example, to value TAD surgery.

8.5 Long-term cost-effectiveness

The trial findings will be extrapolated to the remainder of the patients' life using an economic decision model, most likely a discrete Markov model with 1-year cycles. The model will involve a simulated cohort of patients with early breast cancer with baseline characteristics similar to patients involved in the TADPOLE trial. The model will consist of discrete health states and movements that follow standard breast cancer pathways and current practice standards. Possible model states are disease-free, LRR, distant metastasis, cancer related death and non-cancer related death (52). The model structure and cycle length will be refined based on patient/public advisory group (PAG) and clinician input and the trial results. For example, disease-free health state after recurrence may be added, and/or the cancer-/non-cancer related death states merged. Cycle length may be shortened if data are available to increase granularity of results. Each health state will be assigned a cost estimate and a HRQL score, or utility weight for patients spending time in that health-state.

8.5.1 Economic model inputs

The initial distribution of patients within model states will be calibrated from the trial data at 1 year post-surgery for both treatment arms. Trial data will be used to inform costs and utilities attached

to model states and transition probabilities up to 5years. Transition probabilities beyond 5 years will be obtained from the literature. Non-cancer related death rates will be derived from UK mortality data for women with a median age of trial participants.

The probability of experiencing lymphoedema in the initial model states will be estimated from the trial patients in the TAD/ANC groups. It will be assumed that the proportion of lymphoedema patients in each health state will not change over time (i.e., lymphoedema patients cannot recover, and lymphedema does not affect DFS/OS), and that incremental costs and disutility related to lymphoedema are constant over time.

Costs will be estimated from the NHS+PSS perspective and will include additional patient-level data for trial patients who recur within the 5 years of the trial follow-up. Utilities will be informed from HRQL scores of trial patients who recur in the follow-up period up to 5 years, and the literature. An annual discount rate of 3.5% will be applied to all future costs and outcomes (48).

8.5.2 Economic data analysis

A probabilistic analysis approach will be applied, which reflects parameter uncertainty in the sampled distributions, and simulating at least 10,000 iterations. Cost-effectiveness will be estimated using the mean INMB statistic for TAD compared to ANC, at the NICE willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY. The probability of TAD being the most cost-effective procedure will be depicted on cost-effectiveness acceptability curves for various willingness-to-pay thresholds.

Sensitivity analyses will be undertaken to assess the robustness of the results to changes in key parameters and assumptions. These may include varying the model structure, and data input sources for transition probabilities, costs and QALYs of model states. Full details of economic analyses will be pre-specified in a publicly available health economics analysis plan.

9. INTEGRATED QUALITATIVE STUDY

The TADPOLE integrated qualitative study will be led by researchers from within BTC. The study will have two aims:

1. To identify modifiable obstacles to recruitment in order to support and optimise delivery of the trial (pilot phase)
2. To understand the acceptability of the intervention and experiences of participants in both trial arms (main trial phase)

9.1 Pilot phase

The qualitative work will be essential to optimise recruitment, retention, and trial acceptability. It is anticipated that equipoise amongst clinicians and conveying equipoise to potential trial participants may be an issue. It will be crucial to address this to optimise the success of the trial.

Semi-structured interviews will be conducted with around 15-20 clinicians involved in participant recruitment to TADPOLE, and 15-20 patients (including those who have consented to participate and those who decline or withdraw). Meetings between sites and the research team (e.g., site initiation visits) will be observed. Observation templates and interview topic guides will be developed with input from our patient/public advisory group (PAG) to focus on views of the trial including equipoise, ways of presenting the trial to patients, concerns, and reasons for (not) taking part. Data will be analysed rapidly using a framework approach (53) alongside data collection to facilitate rapid implementation of suggested changes. If relevant, equipoise training will be provided to site staff.

9.2 Main Trial phase

Semi-structured interviews with up to 30 trial participants from both trial arms will be conducted. Reflexive thematic analysis (54) informed by the theoretical framework of acceptability (55) will be used. This will provide important understanding and comparisons of the lived experience of the different types of surgery. For example, patients' attitudes to TAD; views of de-escalating breast cancer treatment, and how fears about risks of recurrence differ between the study groups. Understanding patients' views will have further relevance if TADPOLE is positive; supporting shared decision-making and development of patient-centred resources and allowing barriers to implementation to be overcome.

9.3 Data collection

All interviews will be conducted either in-person or remotely (telephone or video call) using a flexible topic guide developed in collaboration with our PAG. To reduce burden on the participants, verbal consent will be audio-recorded at the start of each interview and reflected on the database that consent has been given verbally for interviews. Researchers will read out the consent clauses and the participant states that they understand and agree. This is after we have had a conversation with them to check their understanding of the PIL and reiterate key topics like recording, withdrawal, anonymisation etc. All interviews will be audio-recorded and transcribed verbatim (including consent discussion) with identifiable information removed. The consent transcript will be saved separately from the main interview transcript and recording. Regular meetings amongst the team to reflect on the interviews will inform subsequent data collection and analysis. The sample sizes have been estimated based on our expectation of achieving saturation, where enough data has been gathered to understand each of the evolving categories and themes, rather than that there is 'nothing new' to be found (56, 57).

9.4 Sampling and recruitment

Purposive sampling will be used to achieve diversity in terms of role and site (clinicians), and age, ethnicity, trial arm, and site (patients). As data collection progresses, other relevant characteristics for sampling may be identified, e.g. site recruitment rate. It is likely that all participants who decline the trial but agree to an interview will be sampled for an interview, as the pool may be small. However, if the pool is large, participants will be purposively sampled using study site.

Clinician interviewees will be identified and approached using delegation logs, or e.g. following observations of meetings. TADPOLE participants can indicate at the point of entering the trial their willingness to be approached about the qualitative study, and these potential interviewees will be identified using the study database. Patients who decline to participate in TADPOLE will be asked gently and sensitively by recruiting staff if they would be willing to speak to a researcher about their decision-making. They will be reassured that this is unrelated to their care, and that the interview is not intended to persuade them to take part but to help us document and understand reasons that people do not want to take part in the trial. The details of those who agree to be approached will be shared securely with the qualitative researcher.

All potential participants will be approached by the qualitative research team via telephone or email, provided with the appropriate PIL, and given time and opportunity to consider participating and to ask questions. Before starting the recorder, the interviewer will recap the main points in the information sheet including consent, withdrawing, and pseudonymisation. After starting the recorder, the researcher will read out the statements and ask the participant to confirm verbally they agree. Consent will be considered a process continuing throughout the interview, and the interviewer will endeavour to ensure participants feel comfortable answering the questions during and at the end of the interview.

9.5 Data analysis

In the pilot phase, qualitative data will be analysed rapidly using a framework approach (53) alongside data collection. A framework will be developed in Excel, to be completed for each interview, capturing the pre-determined areas of interest but also enabling the addition of new emergent topics. This will be reviewed alongside data collection to enable rapid implementation of any potential improvements or changes to facilitate recruitment.

In the main phase, thematic analysis will be used, using software such as NVivo to aid data management. This will involve familiarisation (reading and re-reading of transcripts), initial coding (coding transcripts inductively), theme development (analyse the codes to identify patterns in the data), reviewing (examining these themes against the data to develop a coherent interpretation), and finalising the thematic analysis (naming the themes and defining the subthemes)(58).The developing analysis will be discussed regularly between the qualitative team.

10. SWAT: Implementation of translation and interpretation services to facilitate recruitment of low level-English speaking participants from ethnic minority groups in the TADPOLE surgical trial

One of the recommendations from the INCLUDE Ethnicity Framework (59) and Trial Forge guidance 3 (60) is to 'ensure trial materials are developed with inclusion in mind' comprising of translated study materials and offering verbal interpretation when needed. Verbal interpretation can enable those individuals with low literacy (in English or in their own language) or those who simply prefer to speak to someone in their own language to consider trial participation.

Whilst the framework and associated guidance may be a useful tool for researchers, there is little robust evidence to help researchers consider which recruitment strategies are most effective in increasing recruitment of ethnic minority groups in trials (61). As such, this study within a trial (SWAT) aims to evaluate the use of translated study materials and an interpreting service at sites to facilitate the recruitment of ethnic minority groups with low levels of English.

Both resource use and costs of the translation and interpretation services will be collected and qualitative interviews with participants/patients (both recruited and decliners respectively), research staff at sites and the study team will be used to explore the implementation of the strategy at sites. The SWAT interviews with participants/patients will be combined into the interviews detailed in section 9, to reduce patient burden. Therefore, the qualitative researcher will be asking SWAT specific questions as part of their interview. SWAT data will be monitored and used to further refine the implementation of the SWAT intervention if required. We will ensure our diverse PPIE PAG provides input on the delivery of the SWAT and dissemination of the findings.

10.1 Interventions and comparators

Intervention: Translation and interpretation services provided for each site when required. The use of the translation and interpreting services will be discussed with sites at their Site Initiation Visits (SIVs) and its use encouraged throughout the duration of the trial period by the trial team.

10.2 Method for allocating to intervention or comparator

Not applicable, all sites to receive the intervention.

10.3 Outcome measures

Primary: Proportion of potential participants and participants from ethnic minority backgrounds using translation and interpretation services (resource use) and cost spent in total for the services to calculate cost per ethnic minority participant recruited.

Secondary: Acceptability, facilitators and barriers of the translation and interpretation services used at sites from the perspectives of participants/ patients, research staff and the study team.

10.4 Analysis plans

Analyses will be descriptive. The number and proportion of potential participants and participants using the translation and interpretation services at each site will be reported on screening logs and baseline case report forms. Cost per participant recruited from an ethnic minority background will also be calculated by collecting total costs utilised for the translation and interpretation services and the total number of participants recruited from an ethnic minority background in the TADPOLE surgical trial. Total number of participants screened, eligible, approached and recruited from an ethnic minority background will be collected and reported from the participant screening logs following the SEAR framework (62).

This study will also involve individual, semi-structured interviews (up to 45 minutes), mainly by virtual methods, which will be digitally recorded and transcribed verbatim by a University of Bristol approved supplier, coded, and analysed thematically using Framework analysis (53) to understand contrasting perspectives, context, and barriers/ facilitators to the implementation of the translation/ interpretation services. To not interfere with the main trial, research staff at sites will not be approached until the site has been open for recruitment for at least 6 months and the interviews will be conducted at a time which is most convenient for them. We will pay all participants £10 for taking part. A maximum of 10 research staff at sites, 10 participants/patients (recruited and decliners), and three members of the study team will be interviewed. We will use a purposeful sampling strategy to interview 'information-rich' participants (63) who represent the key groups involved in recruitment at sites. Two researchers (qualitative researcher and lead) will independently code a proportion of the data, discuss discrepancies, and develop a coding frame based on anticipated and new themes. The qualitative researcher will then apply the framework to the whole dataset and ensure that newer themes identified are compared against previously coded transcripts. We will pay particular attention to dissonant data (or negative data, i.e., data that differs from the main themes and helps revise and refine those themes) (63).

11. TRANSLATIONAL STUDY

Biobanking tumour samples during the study will provide a valuable future resource to allow development of appropriate diagnostic and prognostic biomarkers. Linkage to long-term outcomes will offer the potential for identification of putative biomarkers of local treatment failure and late relapse in this population of node positive patients. In TADPOLE, we are collecting and storing formalin fixed paraffin embedded tissue from both surgically resected primary tumour and nodal disease. With separate funding, these samples will then be used for genomic and transcriptomic analyses which will allow future (separately funded) biomarker discovery and validation studies. Appropriate consent will be sought for trial participants.

Samples will be handled, stored, used and disposed of in accordance with the Human Tissue Act 2004 (and any amendments thereto) and in accordance with good laboratory practice and the highest standards of care and skill. Sites will be supplied with a study manual with further details about collecting samples.

11.1 Sample collection

The samples will be collected by the surgical team as part of standard care (i.e. collection of these samples would happen normally, even if the participant wasn't in the study). A proportion of the sample collected will be sent to an external laboratory (Northern Ireland Biobank at Queen's University Belfast) for storage and future analysis subject to separate funding.

The samples will be identified only by the study ID and, therefore, only research staff at the Bristol Trials Unit will have access to the linked identifiable information related to the samples. Researchers and scientists conducting analyses on the samples will not be able to identify participants or have access to files linking the samples with identifiable information.

11.2 Sample transportation

QUB on behalf of the Northern Ireland Biobank (NIB) will receive formalin fixed paraffin embedded (FFPE) tissue samples from trial participants directly from the participating sites via post. The Royal Mail Safeboxes will be arranged by the Sponsor. The NIB will process the material appropriately and store it. FFPE tissue samples will be retrieved from pathology departments directly by the staff at each Participating Site. The Participating site will arrange for the samples to be sent to the Biobank at QUB via Royal Mail Safeboxes.

The samples will remain in the control of the Sponsor but will be stored by the NIB once the TADPOLE trial is completed until directed by the Sponsor to destroy or transfer samples to another organisation or until a further agreement is put in place to cover the use of the samples.

Should QUB wish to use the material in any analyses beyond those set out in the TADPOLE research then the permission of the Sponsor and Chief Investigator must be sought.

12. DATA MANAGEMENT

12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

12.2 Data handling

Full details will be provided in the data management plan, which will also define how personal identifiable and non-identifiable patient information is used in the study.

Data will be entered into a purpose-designed REDCap database hosted on the University of Bristol network. Database access will be password-controlled and restricted to TADPOLE trial staff at the participating site and the co-ordinating centre.

Any information capable of identifying individuals will be held on a secure University of Bristol server. TADPOLE trial staff at the coordinating centre will have access to this identifiable information.

The processing of personal data of participants will be minimised by making use of a unique participant trial number on trial documents and the study database, with the exception of signed consent forms and the screening log.

The database, randomisation system (see section 6.6) and text messaging service will be designed to protect participant information in line with data protection legislation. Trial staff will ensure that the participant's confidentiality is maintained through secure handling and storage of participant information at participating sites and in accordance with ethics approval. The Chief Investigator will preserve the confidentiality of participants taking part in the study and is the data custodian

Data will be entered promptly with data validation and cleaning to be carried out throughout the trial. The trial manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained.

If participants opt for text reminders this is managed within the REDCap database. Only the content of the text and the participant phone number is shared with the text messaging service (Voodoo). Participants will consent to this.

12.3 Data collection

12.3.1 Data sources

A full list of source data and location will be maintained in the Data Management Plan (DMP). The complete details of the DMP will be reviewed, agreed and approved by the sponsor. Hospital records will also form part of the source data for this trial.

Data will be collected using electronic case report forms (eCRFs). Direct data entry to eCRFs will be done using REDCap, if paper CRFs are used these will be entered into the database as soon as possible.

Participant questionnaires will either be completed on paper (with data entered into the REDCap database by trial staff) or through an email link sent to the participant (data saved directly to the REDCap database).

12.3.2 Data System

REDCap will be used to capture and store study data for the trial. REDCap is a web-based electronic central data management system which is built and supplied by Vanderbilt.

The BTC systems team have standard operating procedures (SOPs) to ensure there is a structured approach to designing, building, testing and validating the database prior to release.

Access to the trial REDCap database is managed at an individual level via delegation logs and requires a password that must meet the minimum format requirements.

Participant personal identifiers will be stored securely. Participants will be informed of data storage and security processes in the Participant Information Leaflet.

The database contains audit trails to record all changes to the data and who actioned the changes, user permissions and when access was granted and revoked. The database is held on UoB servers that are automatically backed up daily by UoB IT and stored securely.

In the event of a study amendment, updates to the study database will be coordinated through changes to the relevant specification documents. Specification updates will be discussed between the study team (including the statistician) and the CI.

12.3.3 Data quality

Throughout the trial, data integrity, accuracy and completeness of data collection will be monitored and reported in compliance with good clinical practice (GCP) guidelines. This may include source data verification, use of automated data validation rules, data cleaning, training and risk-based monitoring. Periodic data reviews will be carried out and audit trails will be maintained.

12.3.4 Essential document storage and security

Essential documentation, as specified by the sponsor, will be stored in an eTMF and eISF. Read only access to the relevant systems can be provided for inspection purposes.

Access to the eTMF and eISF will be restricted and access will be approved and monitored by the BTC trial team. All systems where essential documentation is held are automatically backed up daily by UoB IT teams and stored securely.

12.3.5 Essential document archiving

Essential documentation, as specified by the sponsor, and source data (including REDCap database) will be kept for at least 5 years after the end of the trial. Documents will be kept at the University of Bristol and/or participating sites for this time. At the end of the archiving period, documents will be destroyed by confidential means. All non-essential documentation will be destroyed securely prior to archiving.

Where source data are documented in paper medical records, these records will be identified by a label bearing the name and duration of the trial and clearly stating the ‘do not destroy before’ date. Where electronic records are in use, local site policy will be followed.

Participant personal identifiers will be archived where they form part of the essential documentation and will be destroyed at the end of the archiving period.

A study archiving plan will be developed, to include the TMF and ISF, in accordance with the BTC archiving procedure which require sponsor and CI oversight. This archiving plan will be

undertaken in-line with sponsor archiving policy. Sites will retain access to their ISF throughout the archiving period and the trial archive will be available for inspection purposes.

Data held at the University of Bristol will conform to the University of Bristol Data Security Policy and be held in compliance with the UK General Data Protection Regulation (GDPR), tailored by the Data Protection Act 2018.

12.3.6 Database lock and exports

At the point of data lock all user access to the database will be changed to read-only to prevent any changes to the data. A final data extract will be produced for analysis and a copy archived with restricted access to authorised individuals only. At the end of the study all sites will be provided with a copy of their site data, or read-only access to their site data, for the archiving period.

12.3.7 Database archiving

The database export created at the point of database lock will be stored on secure UoB servers for the duration of the archive period. The REDCap database will then be archived following REDCap standard procedures. The BTC systems team have protocols in place to retrieve the database from archive for inspection purposes, if required.

12.3.8 Data sharing

Members of the TMG will develop a data sharing policy for the below consistent with UoB policy.

Final anonymised datasets generated and analysed during the study will be made available on the University of Bristol's data.bris Research Data Repository. In accordance with University of Bristol Policy for datasets involving sensitive information, access is restricted to bona fide researchers subject to data access agreements to ensure compliance with ethical and legal considerations. All data sharing will comply with the consent provided by participants and adheres to data protection legislation.

12.3.9 Qualitative data management

Audio-recordings will be transcribed by University of Bristol employees or University approved transcription services (Bristol Transcription and Translation Services https://www.bristoltts.co.uk/). Transcripts will be labelled with a study-assigned participant number, edited to ensure pseudonymisation of respondents and stored securely adhering to the University's data storage policies. Transcripts will be retained by the University of Bristol where anonymised quotations may be used by the University for training, teaching, research and publication purposes for this and future studies. Anonymised transcripts may be made available to other researchers (including those outside of the University) by controlled access if they secure the necessary approvals for purposes not related to this study, subject to individual verbal informed consent from participants.

Interviews conducted remotely will be audio-recorded using the Teams recording function (telephone or video call) and downloaded and saved securely to the University of Bristol as soon as possible from Microsoft Stream, and then deleted from the online platform. Video files will be converted to audio files and the video file deleted. For in-person interviews, an encrypted digital audio-recorder will be used, and the audio files transferred securely as soon as possible. In both scenarios (video and in-person), the recording of verbal consent at the beginning of the interview will be separated from the main interview recording. They will be transcribed as separate recordings and produce two separate transcriptions (consent and interview, respectively). All audio files will be stored securely adhering to the University's data storage policies and will be destroyed when researchers have completed their analysis. A key to link the pseudonyms with

the patients will be kept securely and destroyed in-line with other identifiable data collected during the trial (5 years). No identifiable data will be documented from the pilot phase observations.

13. TRIAL MANAGEMENT

13.1 Day-to-day management

The trial will be managed by the Bristol Trials Centre (BTC). The BTC is a fully registered UK Clinical Research Collaboration (UKCRC) Unit. North Bristol NHS Trust will act as Sponsor. Day-to-day management of the trial will be overseen by the Chief Investigator (CI) and BTC staff. The CI and BTC team will work with the co-applicants to prepare the final protocol and submissions for regulatory approvals; REC and HRA. The BTC will prepare all trial documentation and data collection forms, and design and implement the data management systems.

The Trial Manager will be the contact point to provide support and guidance to the participating sites throughout the trial.

13.2 Trial Management Group (TMG)

The trial will be managed by a trial management group (TMG), which will meet approximately every 6-8 weeks for the duration of the study. The TMG will comprise of all investigators, including the PPI co-applicants. Other members of the research team will be invited to attend as required. The TMG will have responsibility for the day-to-day management of the trial and will report to the Trial Steering Committee (TSC).

13.3 Data Monitoring and Safety Committee (DMSC)

An independent DMSC will be established to review safety data during the trial and will advise on any interim analyses if appropriate. Membership, responsibilities, and reporting mechanisms of the DMSC will be formalised in a DMSC charter. The DMSC will usually meet jointly with the TSC before recruitment in the trial begins and then approximately every six months or as agreed with the DMSC during the course of the trial. It is anticipated that the DMSC will comprise of independent members including a Chairperson, Statistician and expert in the clinical and/or academic field of this research. The CI, Trial Manager, Lead Statistician and any other TMG members agreed by the DMSC chair will attend the open session only and <insert trial members who will attend the open and close sessions> will attend both open and closed sessions. The DMSC will usually meet prior to the TSC and will provide their recommendations to the TSC Chairperson.

13.4 Trial Steering Committee (TSC)

A TSC will be established, in line with funder requirements, to oversee the conduct of the trial. Membership, responsibilities, and reporting mechanisms of the TSC will be formalised in a TSC Terms of Reference. The TSC will make recommendations during the trial to the TMG and will advise on key decisions. Meeting minutes will be sent to the funder. It is anticipated that the TSC will comprise of independent members including a Chairperson, Statistician, relevant experts in the clinical and academic field of this research, Health Economist (if applicable), and PPI representative(s). The CI, Trial Manager and Lead Statistician will represent the TMG as observers, the attendance of any other TMG members will be agreed by the TSC chair. Anyone not directly involved in the study team but from the same institution may attend as non-independent members, with the agreement of the TSC Chair. The TSC will meet before recruitment to the trial begins and then approximately every six months or as agreed with the TSC during the trial.

13.5 Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator (CI), Regulatory Authority, or Funder, based on new safety information or for other reasons provided by the Data Monitoring and Safety Committee (DMSC) or TSC, regulatory authority, or ethics committee.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder. If the trial is prematurely discontinued, no new participants will be recruited and a decision on data collection for active participants will be made in discussion with the Funder, TSC, DMSC and Sponsor.

14. PATIENT AND PUBLIC INVOLVEMENT & ENGAGEMENT (PPIE)

People with lived experience of under arm (axillary) surgery for breast cancer will be involved in every phase of the research trial. We will convene a Patient and Public Advisory Group (PAG), comprising a diverse range of patient and public contributors to ensure representation from a wide range of views (including, for example, different ages, geographical locations, ethnicities, and genders), and together will co-develop and deliver our PPIE strategy. PPIE will include, for example, group meetings, patient/public contributor roles on the TMG, review of the protocol and participant information, consent and data collection forms, reviewing and considering optimal recruitment practices and trial progress, and informing dissemination of the research findings to participants and wider public.

We will observe the principles set out in the UK Standards for Public Involvement (64). We will:

- Use plain language for well-timed and relevant communications, including meetings involving patient/public contributors, avoid jargon, and provide a glossary of definitions for commonly used terms.
- Value all contributions, building and sustaining relationships. Terms of reference will be agreed during trial set-up and activities that support this will be reviewed in an on-going manner. We will also offer training opportunities, so members can build their skills and hence confidence to contribute.
- Involve patient/public contributors in research governance, management and decision making, identifying and sharing the difference this makes to our research: Our previous experience is that good PPIE often ameliorates problems and reassures the relevant regulatory authorities (Sponsor, ethics committee, etc.) about the design and acceptability of clinical trials. We will prospectively record how PPIE influences decisions and actions and report these at the end, using the GRIPP2 checklist (65) .
- Communicate with a wider audience about PPIE and research, using a broad range of approaches that are accessible and appealing.

15. MONITORING, AUDIT & INSPECTION

15.1 Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by the Sponsor, the relevant REC and other licensing bodies.

A Trial Monitoring Plan will be developed by the Sponsor based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.

The central research team routinely conduct auditing of the study data, which will be shared during Sponsor monitoring processes. The central research team will ensure the following:

- Written informed consent has been properly documented
- Data collected adhere to the trial protocol
- CRFs are only completed by authorised persons
- SAE recording and reporting procedures are being followed correctly
- Key data are recorded
- Data is valid
- A review is undertaken of recruitment rates, withdrawals and losses to follow up

On a regular basis we will monitor the proportion of people that meet the eligibility criteria and report the proportion of participants who give consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMSC if requested, preliminary data on adverse event and dropout rates observed in the trial population.

15.2 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol breaches will be documented and reported to the Trial Manager, the CI and Sponsor. Information about protocol breaches will also be included in routine reports to the TMG, TSC and DMSC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, Sponsor, TSC, DMSC and the TMG.

All protocol breaches will be reported to the Sponsor. The Sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Governance and legislation

This trial will be conducted in accordance with:

- Good Clinical Practice (GCP)
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation
- Human Tissue Act 2004

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability (or equivalent organisation approval) for each site in-line with HRA processes along with other documentation required for the Sponsor to grant sites with a greenlight letter.

For all amendments, the CI or designee will confirm with the Sponsor and relevant RDNs that permissions are ongoing prior to implementation.

This research trial will be run in accordance with GCP guidance. GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

16.2 Radiation assurance

Due to the inclusion of mammograms of this population and using information from those along with the possibility of some sites using radioactive isotopes when identifying lymph nodes in the TAD arm, radiation assurance will be sought. This will need to be completed before submitting for regulatory approvals.

16.3 Review by an NHS Research Ethics Committee

HRA and ethics review of the protocol for the trial and other trial related participant facing documents (e.g., consent form) will be carried out by a UK NHS Research Ethics Committee (REC) and Health Research Authority (HRA). The trial will comply with the necessary regulations and will gain Sponsor and HRA approval. The trial will not commence until favourable REC opinion and HRA approval have been provided, and sponsorship is issued. All correspondence with the REC or HRA will be retained in the Trial Master File (TMF).

16.4 Administration of Radioactive Substances Advisory Committee (ARSAC)

In parallel to the REC submission, TADPOLE will also require an ARSAC license. This may occur after REC approval is received. However, no research activity will commence until all approvals and sponsorship are in place. All correspondence relating to ARSAC will be retained in the Trial Master File (TMF).

16.5 Amendments

Any amendments to the protocol or other trial related participant facing documents will be approved by the Sponsor before being submitted to the REC/HRA for approval prior to implementation.

It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC, in accordance with the legislation and HRA processes. All amendments will be documented on the HRA amendment tool regardless of substantiality.

16.6 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA application process, which includes independent expert and lay reviewers.

16.7 Data quality

The quality of the trial data will be monitored throughout the trial (see section 15) and data completeness will be reported to the DMSC and TSC. Any cause for concern over data quality will be highlighted and an action plan put in place.

16.8 Financial and other competing interests

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

16.9 Indemnity

The necessary trial insurance is provided by the Sponsor. This is an NHS-sponsored research study. For NHS sponsored research HSG (96) 48 reference no. 2 is applicable. The PIL provides a statement regarding indemnity.

For UoB staff involved in the conduct of the trial, there is separate indemnity in place.

Patient information documents will include a joint statement regarding insurance and compensation for participants which will cover both Sponsor and UoB should a complaint be raised against the responsible organisation.

17. DISSEMINATION

A publication policy will be developed following the BTC template, with authorship models agreed in advance with the TMG.

All publications (including poster presentations and annual reports) must be submitted to the Sponsor for review and acknowledgement before submitting for publication.

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available. This will include consideration of sharing findings with patients and the public from different community groups and use of social media to engage the wider population.

Participants may opt to receive a summary of the qualitative findings (main study interviews), a copy of their contact details will be held securely for this purpose

Where possible, information will be disseminated to participating sites and participants in line with timelines for academic audiences (i.e. participant and sites being informed of the study results on or shortly after the date the academic paper is published). Before dissemination materials are drafted, PPI members should be consulted on the proposed methods for dissemination to non-academic audiences.

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APPENDIX 1

Primary outcome measures

Lymphoedema at 12 months following surgery - Co-primary outcome

A participant will be considered to have developed lymphoedema if ***BOTH*** patient-reported and objective lymphoedema criteria are fulfilled.

Patient-reported lymphoedema will be defined as 'yes' to two items from the validated Lymphoedema and Breast Cancer Questionnaire (LBCQ) (arm "swelling now" and arm "heaviness in the past year").

Lymphoedema will be assessed objectively using the change in the ipsilateral upper limb circumference from baseline to 12 months corrected for any change in the contralateral upper limb using the formula:

$$L= (I_{12m}-I_{base}) - (C_{12m}-C_{base}).$$

where 'I' indicates the ipsilateral upper limb, 'C' indicates the contralateral upper limb, 'base' indicates baseline measurement and '12m' indicates measurement at 12 months follow up. Measurements will be obtained 10 cm above and 5 cm below the olecranon process from both the ipsilateral and contralateral upper limbs. Lymphoedema will be defined as present if L is >2cm for either location at 12 months. These criteria have been successfully used in other axillary surgery trials (66).

Objective and patient-reported lymphoedema at 12 months will individually be key secondary outcomes.

Patient reported lymphoedema will also be assessed at 24 and 60 months using the two aforementioned questions from the LBCQ questionnaire.

Locoregional recurrence (LRR) at 5 years - Co-primary outcome

Locoregional recurrence was selected as the most important oncological endpoint for the trial as this is the outcomes most likely to be impacted by reducing the extent of axillary surgery (a component of locoregional treatment). Locoregional endpoints are established primary outcomes for use in axillary de-escalation trials internationally (67, 68) and LRR was considered the most important primary outcome by the UK clinical breast cancer community (20).

LRR will be defined as pathologically and/or radiologically confirmed recurrent tumour in:

i) The ipsilateral breast after breast conserving surgery
ii) The skin or soft tissues of the chest wall within the anatomical boundaries of the breast after mastectomy.
iii) The ipsilateral axilla, infraclavicular, supraclavicular fossa, interpectoral area or ipsilateral internal mammary chain.

Date of locoregional recurrence will be the date on the imaging or pathology report, whichever comes first.