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

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BACKGROUND

Approximately 20% of women with breast cancer will be node-positive at presentation. In the UK, all patients with newly diagnosed breast cancer have axillary staging with an axillary USS +/- biopsy of abnormal/equivocal nodes and currently UK NICE guidelines recommend axillary node clearance (ANC) for ***all*** patients with biopsy proven node positive breast cancer having primary surgery, irrespective of the number of nodes involved. This highly morbid procedure leads to life-long complications in 1 in 3 patients including lymphoedema and chronic pain which dramatically impact quality of life.



ANC aims to reduce locoregional recurrence (LRR) and improve breast cancer survival but there is no evidence to support these benefits for patients with limited nodal involvement (cN0, radiologically detected disease). These patients would meet the criteria for omission of ANC based on eligibility for the ACOSOG Z0011 trial, but this approach has not been adopted in the UK due to concerns regarding false negative sentinel node biopsy (SNB) in node positive patients. Targeted axillary dissection (TAD) which combines removal of the localised biopsy proven involved node(s) in combination with a SNB may offer an alternative to ANC, effectively addressing concerns regarding false negative rates while reducing the risk of life-changing complications

TADPOLE aims to determine if TAD is a clinically & cost-effective alternative to ANC in patients with low volume node positive breast cancer having primary surgery.

STUDY DESIGN AND METHODS

TADPOLE is a multicentre pragmatic phase 3 randomised controlled trial comparing TAD and ANC in breast cancer patients with low volume nodal disease having primary surgery.

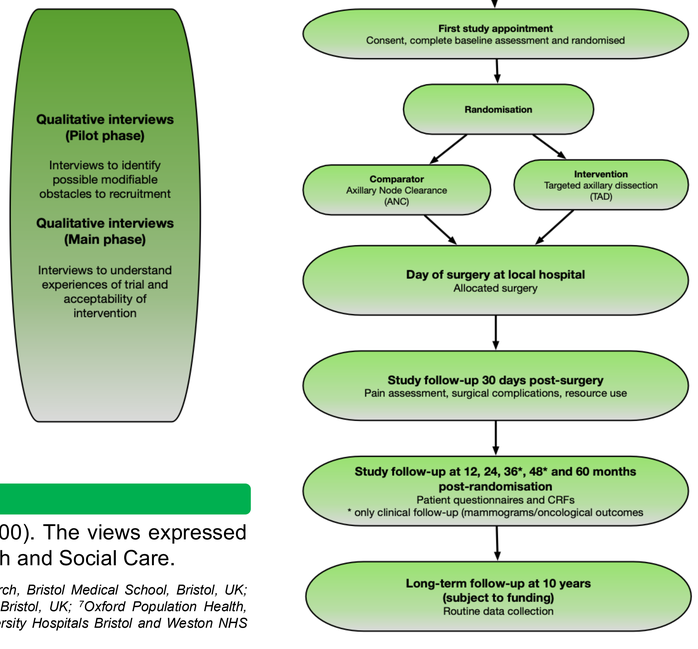
All patients with cN0 biopsy proven low volume axillary nodal disease will be eligible to participate. Excluded will be patients with >3 nodes on USS, those who have recurrent disease, previous axillary surgery or neoadjuvant systemic therapy. Participants will be randomised 2:1 to TAD or ANC.

The **co-primary end-points** are:

1. Patient reported and objective lymphoedema at 12 months
2. Single arm analysis of LRR at 5 years in the TAD cohort.

Recruitment of 390 patients in the TAD arm will be required to detect a 50% reduction in lymphoedema at 12 months with 90% power and a type 1 error of 5% and exclude an undesirable LRR of <5% in the TAD cohort at 5 years with one sided 2.5% alpha and 90% power. Inflating for multiplicity and allowing for 5% dropout and 5% crossover a total of 861 patients (574 TAD:287 ANC) will be required for the trial. 40 UK breast units will recruit to the trial.

TADPOLE Study Schema



Surgical quality assurance (QA) processes will promote standardised introduction of 'primary' TAD in the UK and ensure procedure fidelity within the trial. Participants will have adjuvant therapy as per standard of care but axillary radiotherapy (ART) will be prohibited in the TAD group. Robust radiotherapy quality assurance (RTTQA) will be embedded throughout.

An embedded qualitative study will optimise recruitment and a SWAT (study within a trial) will optimise recruitment of non-English speaking participants.

PROGRESS TO DATE

Consensus work with breast surgeons to agree how to standardise axillary surgery within the trial has been completed and will underpin the surgical QA within TADPOLE.

All regulatory approvals have been obtained. Recruitment will commence late 2025 and include a 9-month internal pilot phase with plans to recruit from a minimum of 40 UK sites over 28 months.

International recruitment is planned.

POTENTIAL IMPACT

TADPOLE will address the top UK breast surgery research priority identified in the James Lind Alliance Priority Setting Process. If TAD causes less lymphoedema and is oncologically safe, TADPOLE will change practice, improving outcomes for thousands of patients with node positive breast cancer each year.

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