San Antonio Breast Cancer Symposium - December 9th-12th, 2025

SMALL: Open Surgery versus Minimally invasive vacuum Assisted excision for smaLL screen-detected breast cancer - a phase III randomised trial

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BACKGROUND

- Population breast cancer screening programmes have been shown to reduce breast cancer mortality.
- Mammographic breast screening detects many small tumours with favourable biological features which may not progress during a woman's lifetime.
- Currently all tumours are treated with standard open surgery – usually breast conserving surgery and axillary sentinel lymph node biopsy (SLNB).
- Minimally invasive treatment approaches for such small tumours have been described but there is no prospective randomised evidence to support their use
- Vacuum-assisted excision is in widespread use for the management of benign lesions and lesions of uncertain malignant potential.
- The SMALL trial is designed to determine whether this approach can be used for the treatment of small invasive breast cancers with favourable biological characteristics detected in the UK NHS Breast Screening Programme

AIMS

SMALL is a phase III randomised trial comparing standard surgery to vacuum assisted excision, and seeks to determine:

- Is this approach feasible and acceptable to patients?
- Can it be done with acceptable "re-excision" rates following VAE?
- What are the long-term local recurrence implications of this approach?
- Can SLNB be safely omitted in these patients?

PRIMARY END POINTS

SMALL has co-primary endpoints:

- **Re-excision rates following VAE**
  - *This is a randomised, non-inferiority comparison.*
  - *Re-excision rates are known to be up to 20% following standard surgery for screen—detected breast cancer in the UK.*
- **Local recurrence following VAE**
  - *Local recurrence rates are known to be low following standard surgery and adjuvant radiotherapy: ~1% at 5 years in the UK IMPORT-LOW trial.*
  - *This is a single-arm analysis with an undesirable local recurrence rate of 3% at 5 years following VAE.*

STUDY DESIGN

The study design and key eligibility criteria are summarised in the trial schema (**Figure 1**).

Patients are randomised 2:1 in favour of VAE

In the standard surgery arm, patients are managed according to local protocol, with the requirement for re-excision of margins being determined by local guidelines. Following surgery, radiotherapy and endocrine therapy are given according to local practice (including omission of radiotherapy if this is local practice for low-risk tumours or where patients are entered into a trial of omission of radiotherapy).

Following VAE, completeness of excision is assessed radiologically, based on the operator's impression of completeness of excision during the procedure and on a post-procedure mammogram. Where excision is judged to be incomplete radiologically, patients will undergo standard surgical excision and SLNB, as will patients where histopathological assessment of the VAE specimen shows upgrade of the lesion to grade 3.

Following complete excision at VAE, adjuvant radiotherapy and endocrine therapy are mandated – however these may be given according to local protocol (whole or partial breast radiotherapy).

WHY THIS STUDY DESIGN?

A randomised trial design was considered necessary to provide high quality evidence to change practice should the trial be positive.

Re-excision rates following surgery are consistently around 15-20% in the UK. The requirement for a second procedure to achieve clear margins results in an increase in morbidity and has clear disadvantages for both patients and healthcare providers.

An end-point confirming non-inferiority of VAE for re-excision was consider to have the potential to change practice where local recurrence rates following VAE could be demonstrated to remain low.

Robust historical data demonstrates the risk of local recurrence following standard surgery and radiotherapy to be low – around 1% at 5 years following treatment. Evidence of a risk of local recurrence being higher than expected would indicate a failure of the minimally invasive approach.

Assessing the effectiveness of VAE against a fixed threshold of risk allows us to maintain a precise estimate of treatment benefit while having the advantage of being more efficient than a randomised non-inferiority trial.

In a cohort of low-risk patients such as this, the risk of local failure is expected to be ≤ 3% at 5 years. Should the incidence of local recurrence be > 3% at 5 years, the minimally invasive treatment strategy would not be considered clinically acceptable.

TRIAL SCHEMA

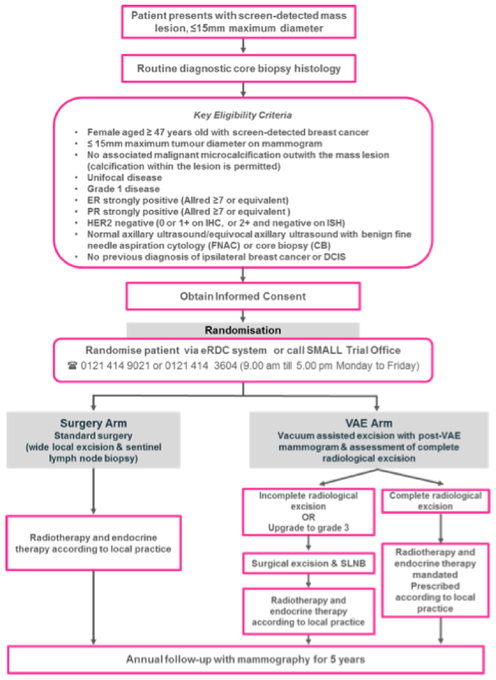


Figure 1: Trial schema

SECONDARY OUTCOME MEASURES

Secondary outcome measures in the trial include:

- Complication rates in both arms
- Time to ipsilateral breast cancer recurrence
- Time to development of contralateral invasive cancer
- Overall survival
- Quality of life
- Cost effectiveness analysis

If you are UK based and are interested in taking part in SMALL at your site, please contact small@trials.bham.ac.uk

STATISTICAL CONSIDERATIONS

The total number of patients to be recruited with an allocation ratio of 2:1 is 800 (533 VAE, 267 surgery).

The total number of patients required for the re-excision comparison is 762 which has been inflated by 5% to allow sufficient patients for the single arm investigation into local recurrence rates and allow for possible drop-outs. To ensure that the trial as a whole only has 5% alpha, the significance level for each co-primary outcome has been set at 2.5% with 90% power. The probability of success in both the surgery arm and the VAE arm is expected to be 80% (20% re-excision). The maximal acceptable difference between the two has been set at 10%.

The total number required for the local recurrence free survival outcome is 511 (VAE). This assumes that the expected survival probability at 5 years is 99% and that an undesirable survival probability for VAE is 97% at 5 years.

QUINTET RECRUITMENT INTERVENTION

Randomised trials of complex interventions such as surgical procedures have historically been proven to be challenging to recruit to. SMALL will therefore employ an embedded QuinteT Recruitment Intervention (QRI) aiming to optimise recruitment and informed consent. The QRI has been developed and refined in a number of RCTs and incorporates qualitative and mixed-methods approaches.

The QRI will proceed in two iterative phases in SMALL:

Phase I – understanding recruitment.

- Mapping recruitment pathways
- Audio-recording of recruitment consultations
- Semi-structured interviews with investigators, clinicians and patients

Phase II – development and implementation of recruitment intervention strategies.

The QRI team, with the CI and TMG, will formulate a 'plan of action' to improve recruitment and information provision, grounded in findings from phase I. Interventions may include 'tips' documents providing suggestions on how to explain the trial design and processes. Supportive feedback will be a core component of the plan of action, with the exact nature and timing of feedback dependent on issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. Group feedback sessions will be aided by displaying anonymised data extracts from interviews and audio-recorded appointments. Individual confidential feedback will also be offered – particularly where recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues.

PATIENT AND PUBLIC INVOLVEMENT

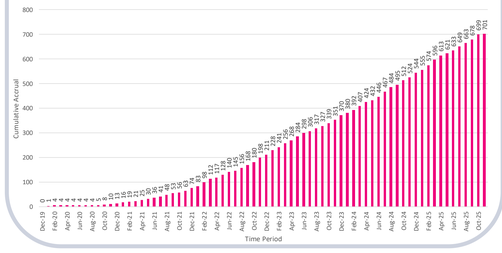
Patient advocates have been involved in the design and development of the SMALL trial since its inception. They have confirmed that the clinical question and the key outcome measures are important to patients and have ongoing input into the study as part of the Trial Management Group. In addition, they will provide input into developing recruitment interventions as part of the QRI.

Patient advocates were involved in determining the acceptable non-inferiority margin of 10% for the re-excision outcome of the study. This wide non-inferiority margin was set in acknowledgement of the fact that this is salvageable by a second procedure and has no survival sequelae. They were also key to setting the 3% unacceptable local recurrence risk for the single arm cohort study, recognising that a very small increase in local recurrence may be acceptable in return for de-escalation of surgical therapy.

RECRUITMENT PROGRESS TO DATE

Recruitment to SMALL was significantly delayed by the Covid-19 pandemic. During the pandemic, the necessary prioritisation of Covid treatment and vaccine studies led to significant delays with site set-up and opening. However, as of 18th November 2025, 50 sites are open to recruitment and have recruited a total of 705 patients. Progress to date with site opening and patient recruitment is shown below.

Examination of trial screening logs has shown that around 46% of patients eligible for study entry who are approached consent to randomisation.



ACKNOWLEDGEMENTS

Grateful thanks to the investigators, site staff, CRCTU staff and the Trial Steering and Data Monitoring Committees. This study/project is funded by the NIHR Health Technology Assessment Programme (reference 17/42/32) . The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. We acknowledge the contribution of the late Professor Adele Francis to the conception of this study.

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