

# A study for women who have small breast cancers found by screening, comparing removal of the cancer by standard surgery with a smaller procedure, which is more like a biopsy

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<b>Registration date</b> 16/10/2019	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 24/06/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/this-trial-is-looking-at-vacuum-assisted-excision-for-breast-cancers-small>

## Contact information

### Type(s)

Scientific

### Contact name

Dr Jessica Foster

### Contact details

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## Additional identifiers

### Clinical Trials Information System (CTIS)

Nil known

## **Integrated Research Application System (IRAS)**

254892

## **ClinicalTrials.gov (NCT)**

Nil known

## **Protocol serial number**

RG\_18-180; CPMS 40111

# **Study information**

## **Scientific Title**

SMALL: A Phase III, randomised, multi-centre trial addressing overtreatment of small screen-detected breast cancer by comparing standard surgery versus minimally invasive vacuum-assisted excision

## **Acronym**

SMALL

## **Study objectives**

The aim of the main trial is to determine whether the extent of surgical treatment can be reduced in the context of standard adjuvant radiotherapy and endocrine therapy

## **Ethics approval required**

Ethics approval required

## **Ethics approval(s)**

approved 07/08/2019, HSC REC A (Office for Research Ethics Committees Northern Ireland (ORECNI), Customer Care and Performance Directorate, Unit 4, Lissue Industrial Estate West, Rathdown Walk, Moira Road, Lisburn, BT28 2RF, United Kingdom; +44 (0)28 9536 1400; reca@hscni.net), ref: 19/NI/0126

## **Study design**

Randomized controlled study

## **Primary study design**

Interventional

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Breast Cancer

## **Interventions**

### **STUDY DESIGN & JUSTIFICATION**

The SMALL trial is a prospective, randomised, two-arm, multicentre trial. The recruitment target is 800 patients. It is anticipated that 70 U.K. sites will be opened to recruitment. Patients will be randomised in a 1:2 ratio to undergo either standard surgery +/- sentinel lymph node biopsy or

vacuum-assisted excision (VAE), and it is expected that this will take place within 31 days of randomisation. All patients will be followed up via the recruiting site for 5 years post-randomisation. Further long-term follow-up data may be collected by the data linkage services.

This study aims to address the issue of possible over-treatment of small screen-detected breast cancers by assessing whether such cancers can be treated with minimally invasive vacuum excision, in the context of a randomised clinical trial. To be practice changing, it will be necessary to demonstrate that not only is there an acceptable local recurrence risk associated with VAE followed by radiotherapy and endocrine therapy, but also that there is not an excess requirement for additional procedures in the VAE arm, in case of radiologically-determined incomplete excision.

The total number of patients to be recruited with the 1:2 allocation ratio in favor of VAE is 800 (267 surgery, 533 VAE). The total number required for the re-excision comparison was 762, and this has been inflated by 5%. This will ensure that we have sufficient patients for the single arm investigation of local recurrence rates with VAE, and allow for possible drop-outs.

No formal interim analysis is planned. The final analysis following the initial procedure will be conducted 3 months following the completion of recruitment. This will ensure that all patients have undergone their randomised procedure and been assessed for re-excision. The analysis of complications arising from surgery or VAE will also be conducted at this point. Analysis of the local recurrence free survival and all remaining secondary outcomes will be conducted 3 months after all patients have completed 3 years of annual mammography following randomisation.

#### PATIENT PATHWAY

Patients enrolling in the trial will recently have attended their local NHS Breast Screening Unit following recall for assessment of a mammographic abnormality identified on their routine screening mammograms. At this time, where possible, the local screening unit will supply potentially eligible patients with a copy of the brief introductory Patient Information Leaflet (PIL), and this will be given either with the invitation to attend for assessment or at the clinic appointment. This PIL aims to provide information to prepare patients for a possible invitation to participate in a research study at an early stage in their pathway. They will also receive information regarding the Information Study (the optional recruitment intervention) at this stage.

The subsequent patient pathway will be as follows:

1. Eligible patients will attend clinic to receive the results of their biopsy
2. They will be invited to take part in the optional Information Study
3. Patients will complete and sign the optional Information Study Informed Consent Form, if applicable
4. If the patient consents to participate in the Information Study, the subsequent trial discussion may be audio-recorded
5. Patients agreeing to participate in SMALL will complete and sign the Informed Consent Form for the main trial
6. Patients will complete baseline Quality of Life questionnaires
7. Randomisation by the research team
8. Patient attends for either standard surgery or VAE according to randomised allocation
9. Patients in the VAE arm will have post-procedure mammography on the same day as their procedure
10. After treatment, patient results including histopathology and post-procedure imaging will be discussed in the local MDT
11. Patients will be seen in the clinic to discuss histopathology results, any requirement for an

- additional procedure and subsequent radiotherapy and endocrine therapy discussed
12. In order to obtain accurate follow-up information, patients will need to attend the hospital every year for mammograms for 5 years. Patients will be informed of the results of these as soon as possible after these have been carried out (usually within 2 weeks)
  13. The Trial Office will send Quality of Life questionnaires to complete at 6 months after surgery /VAE, and subsequently annually until year 5
  14. The hospital research team provide follow-up information on patients for up to 5 years
  15. If there is enough tissue available, the trial will collect tissue samples from the diagnostic biopsy and from any future breast investigations or surgery, for research

## Interventions

### Surgery arm:

- Standard surgical treatment as deemed appropriate by local MDT, +/- axillary sentinel lymph node biopsy
- Adjuvant radiotherapy/endocrine therapy as per local treatment guidelines

### VAE arm:

- Image-guided vacuum excision of breast cancer
- No axillary surgery
- Adjuvant radiotherapy to breast
- Adjuvant endocrine therapy

Sites will randomise patients into the trial using a bespoke electronic Remote Data Capture system, or via completion of a Randomisation Form followed by a telephone call the SMALL Trial Office. Patients will be randomised at a ratio of 1:2 in favour of the VAE arm using computerised minimisation technique

## Intervention Type

Other

## Phase

Phase III

## Primary outcome(s)

1. Re-excision following initial procedure at 3 months following the end of the recruitment period
2. Local recurrence-free survival time for VAE at 3 months after all patients have completed 3 years of annual mammography following randomisation

## Key secondary outcome(s)

1. Complications arising from surgery or VAE at 3 months following the end of the recruitment period
2. Time to ipsilateral breast cancer recurrence at 3 months after all patients have completed 3 years of annual mammography following randomisation
3. Time to development of contralateral invasive breast cancer at 3 months after all patients have completed 3 years of annual mammography following randomisation
4. Overall survival time at 3 months after all patients have completed 3 years of annual mammography following randomisation
5. Quality-adjusted life year (QALY) at 3 months after all patients have completed 3 years of annual mammography following randomisation
6. Quality of life: will be assessed using the following tools: EORTC QLQ-C30 and BR23, EuroQoL EQ-5D, BREAST-Q (breast conserving therapy module). The Quality of Life questionnaires will be

completed by patients prior to randomisation at baseline, all other questionnaires will be distributed directly to the patients' home address by the SMALL Trial office at 6, 12, 24, 36, 48 and 60 months post-randomisation

## Completion date

30/06/2029

## Eligibility

### Key inclusion criteria

Current inclusion criteria as of 24/06/2025:

1. Female aged  $\geq 47$  years old with screen-detected breast cancer
2.  $\leq 15$  mm maximum tumour diameter on mammogram and ultrasound
3. No associated malignant microcalcification outwith the mass lesion (calcification within the lesion is permitted)
4. Unifocal disease
5. Grade 1 disease on diagnostic core biopsy
6. ER strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in  $>66\%$  of tumour cell nuclei)
7. PR strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in  $>66\%$  of tumour cell nuclei)
8. HER2 negative (0 or 1+ by immunohistochemistry, or 2+ and negative by in situ hybridisation techniques (FISH or DISH))
9. Normal axillary ultrasound axillary, or equivocal ultrasound with benign fine needle aspiration cytology (FNAC) or core biopsy (CB)
10. Must be a technically appropriate candidate for VAE as determined by local MDT
11. Willing to be randomised
12. Able to provide written informed consent
13. Willing and able to undergo standard surgical treatment
14. Willing and able to undergo radiotherapy
15. Willing and able to take standard endocrine therapy
16. No previous diagnosis of ipsilateral breast cancer or DCIS (contralateral DCIS or invasive disease permitted if surgically treated  $\geq 5$  years previously and disease-free)

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Previous inclusion criteria as of 02/06/2021:

1. Female aged  $\geq 47$  years old with screen-detected breast cancer
2.  $\leq 15$  mm maximum tumour diameter on mammogram and ultrasound
3. No associated malignant microcalcification outwith the mass lesion (calcification within the lesion is permitted)
4. Unifocal disease
5. Grade 1 disease on diagnostic core biopsy
6. ER strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in  $>66\%$  of tumour cell nuclei)
7. PR strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in  $>66\%$  of tumour cell nuclei)
8. HER2 negative (0 or 1+ by immunohistochemistry, or 2+ and negative by in situ hybridisation techniques (FISH or DISH))
9. Normal axillary ultrasound axillary, or equivocal ultrasound with benign fine needle aspiration cytology (FNAC) or core biopsy (CB)

10. Willing to be randomised
11. Able to provide written informed consent
12. Willing and able to undergo standard surgical treatment
13. Willing and able to undergo radiotherapy
14. Willing and able to take standard endocrine therapy
15. No previous diagnosis of ipsilateral breast cancer or DCIS (contralateral DCIS or invasive disease permitted if surgically treated  $\geq$  5 years previously and disease-free)

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Previous inclusion criteria:

1. Female aged  $\geq$  47 years old with screen-detected breast cancer
2.  $\leq$ 15mm maximum tumour diameter on mammogram and ultrasound
3. No associated indeterminate, suspicious or malignant mammographic microcalcification associated with the lesion or extending beyond it
4. Unifocal disease
5. Grade 1 disease on diagnostic core biopsy
6. ER strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in  $>$ 66% of tumour cell nuclei)
7. PR strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in  $>$ 66% of tumour cell nuclei)
8. HER2 negative (0 or 1+ by immunohistochemistry, or 2+ and negative by in situ hybridisation techniques (FISH or DISH))
9. Normal axillary ultrasound axillary, or equivocal ultrasound with benign fine needle aspiration cytology (FNAC) or core biopsy (CB)
10. Willing to be randomised
11. Able to provide written informed consent
12. Willing and able to undergo standard surgical treatment
13. Willing and able to undergo radiotherapy
14. Willing and able to take standard endocrine therapy
15. No previous diagnosis of ipsilateral breast cancer or DCIS (contralateral DCIS or invasive disease permitted if surgically treated  $\geq$  5 years previously and disease-free)

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

47 years

**Sex**

Female

**Key exclusion criteria**

Current exclusion criteria as of 24/06/2025:

1. Associated malignant microcalcification outwith the lesion

2. Bilateral breast cancer
  3. Pure invasive lobular cancer
  4. Grade 2 or grade 3 on core biopsy assessment
  5. Not strongly ER or PR positive (Allred score of <7, or equivalent, e.g. <66% positivity of tumour cell nuclei) or HER2 positive tumour
  6. Neoadjuvant endocrine therapy (any duration)
  7. Unable to provide informed consent
  8. Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process
  9. Unfit or unwilling to undergo standard surgical treatment
  10. Contra-indications to standard adjuvant therapies (radiotherapy, endocrine therapy)
  11. Previous ipsilateral invasive breast cancer or DCIS
  12. Other invasive malignancy unless:
    - 12.1. Disease free for 5 years, or
    - 12.2. Previous basal cell carcinoma, cervical carcinoma in-situ, superficial bladder tumour
  13. High-risk group for developing breast cancer (as defined by NICE guidance, women undergoing screening more frequently than 3 yearly in the population screening programme)
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Previous exclusion criteria as of 02/06/2021:

1. Associated malignant microcalcification outwith the lesion
  2. Bilateral breast cancer
  3. Invasive lobular cancer
  4. Grade 2 or grade 3 on core biopsy assessment
  5. Not strongly ER or PR positive (Allred score of <7, or equivalent, e.g. <66% positivity of tumour cell nuclei) or HER2 positive tumour
  6. Unable to provide informed consent
  7. Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process
  8. Unfit or unwilling to undergo standard surgical treatment
  9. Contra-indications to standard adjuvant therapies (radiotherapy, endocrine therapy)
  10. Previous ipsilateral invasive breast cancer or DCIS
  11. Other invasive malignancy unless:
    - Disease free for 5 years, or
    - Previous basal cell carcinoma, cervical carcinoma in-situ, superficial bladder tumour
  12. High-risk group for developing breast cancer (as defined by NICE guidance)
- 

Previous exclusion criteria:

1. Lesions with associated mammographic microcalcification outwith the lesion
2. Bilateral breast cancer
3. Invasive lobular cancer
4. Grade 2 or grade 3 on core biopsy assessment
5. ER or PR negative or HER2 positive tumour
6. Unable to provide informed consent
7. Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process
8. Unfit or unwilling to undergo standard surgical treatment
9. Contra-indications to standard adjuvant therapies (radiotherapy, endocrine therapy)
10. Previous ipsilateral invasive breast cancer or DCIS

11. Other invasive malignancy treated within the last 5 years
12. High-risk group for developing breast cancer (as defined by NICE guidance)

**Date of first enrolment**

15/11/2019

**Date of final enrolment**

30/06/2025

## **Locations**

**Countries of recruitment**

United Kingdom

England

Northern Ireland

Scotland

Wales

**Study participating centre**

**Belfast City Hospital**

51 Lisburn Road

Belfast

United Kingdom

BT8 8BH

**Study participating centre**

**Southmead Hospital**

Southmead Road

Westbury-On-Trym

Bristol

United Kingdom

BS10 5NB

**Study participating centre**

**Addenbrookes Hospital**

Hills Road

Cambridge

United Kingdom

CB2 0QQ

**Study participating centre**  
**Aberdeen Royal Infirmary**  
Foresterhill Road  
Aberdeen  
United Kingdom  
AB25 2ZN

**Study participating centre**  
**Altnagelvin Area Hospital**  
Glenshane Road  
Londonderry  
United Kingdom  
BT47 6SB

**Study participating centre**  
**Edgware Community Hospital**  
Edgware Community Hospital  
Burnt Oak Broadway  
Edgware  
United Kingdom  
HA8 0AD

**Study participating centre**  
**Poole Hospital**  
Longfleet Road  
Poole  
United Kingdom  
BH15 2JB

**Study participating centre**  
**The Royal Marsden Hospital (surrey)**  
Downs Road  
Sutton  
United Kingdom  
SM2 5PT

**Study participating centre**  
**The Royal Victoria Infirmary**  
Queen Victoria Road  
Newcastle upon Tyne

United Kingdom  
NE1 4LP

**Study participating centre**  
**Thomas Linacre Centre**  
Parson's Walk  
Wigan  
United Kingdom  
WN1 1RU

**Study participating centre**  
**Churchill Hospital**  
Churchill Hospital  
Old Road  
Headington  
Oxford  
United Kingdom  
OX3 7LE

**Study participating centre**  
**Craigavon Area Hospital**  
Lurgan Rd  
Craigavon  
United Kingdom  
BT63 5QQ

**Study participating centre**  
**Doncaster Royal Infirmary**  
Armthorpe Road  
Doncaster  
United Kingdom  
DN2 5LT

**Study participating centre**  
**Ipswich Hospital**  
Heath Road  
Ipswich  
United Kingdom  
IP4 5PD

**Study participating centre**  
**Norfolk and Norwich University Hospital**  
Colney Lane  
Colney  
Norwich  
United Kingdom  
NR4 7UY

**Study participating centre**  
**Gateshead - Queen Elizabeth Hospital**  
Queen Elizabeth Hospital  
Sherriff Hill  
Gateshead  
United Kingdom  
NE9 6SX

**Study participating centre**  
**Liverpool University Hospitals NHS Foundation Trust**  
Royal Liverpool University Hospital  
Prescot Street  
Liverpool  
United Kingdom  
L7 8XP

**Study participating centre**  
**The Royal Marsden Hospital (london)**  
Fulham Road  
London  
United Kingdom  
SW3 6JJ

**Study participating centre**  
**Southend Hospital**  
Prittlewell Chase  
Westcliff-on-sea  
United Kingdom  
SS0 0RY

**Study participating centre**

**Leeds Teaching Hospitals NHS Trust**  
St. James's University Hospital  
Beckett Street  
Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**  
**North Tees General Hospital**  
Hardwick Road  
Stockton-on-tees  
United Kingdom  
TS19 8PE

**Study participating centre**  
**York Hospital**  
Wigginton Road  
York  
United Kingdom  
YO31 8HE

**Study participating centre**  
**Alexandra Hospital**  
Woodrow Drive  
Redditch  
United Kingdom  
B98 7UB

**Study participating centre**  
**Royal Bournemouth General Hospital**  
Castle Lane East  
Bournemouth  
United Kingdom  
BH7 7DW

**Study participating centre**  
**Royal Cornwall Hospital (treliste)**  
Treliske  
Truro  
United Kingdom  
TR1 3LJ

**Study participating centre**  
**Royal Devon and Exeter Hospital**  
Barrack Road  
Exeter  
United Kingdom  
EX2 5DW

**Study participating centre**  
**Southampton General Hospital**  
Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**  
**Wycombe General Hospital**  
Queen Alexandra Road  
High Wycombe  
United Kingdom  
HP11 2TT

**Study participating centre**  
**Wythenshawe Hospital**  
Southmoor Road  
Wythenshawe  
Manchester  
United Kingdom  
M23 9LT

**Study participating centre**  
**Castle Hill Hospital**  
Castle Road  
Cottingham  
United Kingdom  
HU16 5JQ

**Study participating centre**

**Cheltenham General Hospital**

Sandford Road  
Cheltenham  
United Kingdom  
GL53 7AN

**Study participating centre**

**Clatterbridge Hospital**

Clatterbridge Rd  
Bebington  
Wirral  
United Kingdom  
CH63 4JY

**Study participating centre**

**Cumberland Infirmary - Carlisle**

Cumberland Infirmary  
Newtown Road  
Carlisle  
United Kingdom  
CA2 7HY

**Study participating centre**

**Kingston Hospital**

Galsworthy Road  
Kingston upon Thames  
United Kingdom  
KT2 7QB

**Study participating centre**

**Luton and Dunstable University Hospital**

Lewsey Road  
Luton  
United Kingdom  
LU4 0DZ

**Study participating centre**

**Queen Elizabeth Hospital**

Edgbaston

Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**

**Bolton Royal Hospital**

Minerva Road  
Farnworth  
Bolton  
United Kingdom  
BL4 0JR

**Study participating centre**

**Worcestershire Royal Hospital**

Charles Hastings Way  
Worcester  
United Kingdom  
WR5 1DD

**Study participating centre**

**Macclesfield District General Hospital**

Macclesfield District Hospital  
Victoria Road  
Macclesfield  
United Kingdom  
SK10 3BL

**Study participating centre**

**Gartnavel General Hospital**

1053 Great Western Road  
Glasgow  
United Kingdom  
G12 0YN

**Study participating centre**

**Leighton Hospital**

Leighton  
Crewe  
United Kingdom  
CW1 4QJ

**Study participating centre**  
**Forth Valley Royal Hospital**  
Stirling Road  
Larbert  
United Kingdom  
FK5 4WR

**Study participating centre**  
**Kings College Hospital**  
Mapother House  
De Crespigny Park  
Denmark Hill  
London  
United Kingdom  
SE5 8AB

**Study participating centre**  
**Royal United Hospital**  
Combe Park  
Bath  
United Kingdom  
BA1 3NG

**Study participating centre**  
**Milton Keynes University Hospital**  
Standing Way  
Eaglestone  
Milton Keynes  
United Kingdom  
MK6 5LD

**Study participating centre**  
**University College London Hospitals NHS Foundation Trust**  
250 Euston Road  
London  
United Kingdom  
NW1 2PG

**Study participating centre**

**Western General Hospital**  
Crewe Road South  
Edinburgh  
Lothian  
United Kingdom  
EH4 2XU

**Study participating centre**  
**Broomfield Hospital**  
Court Road  
Broomfield  
Chelmsford  
United Kingdom  
CM1 7ET

## Sponsor information

**Organisation**  
University of Birmingham

**ROR**  
<https://ror.org/03angcq70>

## Funder(s)

**Funder type**  
Government

**Funder Name**  
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 17/42/32

## Results and Publications

### Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

### IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Protocol article</a>		08/04/2025	23/04/2025	Yes	No
<a href="#">HRA research summary</a>			26/07/2023	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes