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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

Submission date 14/10/2019	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 16/10/2019	**Overall study status** Ongoing	
Last Edited 24/06/2025	**Condition category** Cancer	

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

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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 trail
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 ≥47 years old with screen-detected breast cancer
2. ≤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 ≥ 5 years previously and disease-free)

Previous inclusion criteria as of 02/06/2021:
1. Female aged ≥47 years old with screen-detected breast cancer
2. ≤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 ≥ 5 years previously and disease-free

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Previous inclusion criteria:
1. Female aged ≥ 47 years old with screen-detected breast cancer
2. ≤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 ≥ 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)

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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 (treliske)
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?
Protocol article		08/04/2025	23/04/2025	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes