ISRCTN11896599 https://doi.org/10.1186/ISRCTN11896599

Does the timing and order of breast surgery and hormone treatment affect the quality of life and the amount of surgery required in post-menopausal women with breast cancer? The EndoNET study

Submission date
02/04/2022

Recruitment status
Recruiting

Registration date
04/05/2022

Overall study status
Ongoing

Last Edited
12/05/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
50,000 women develop breast cancer each year in the United Kingdom, mostly women after menopause and of a type known as oestrogen-receptor positive (ER+), HER-2 (human epidermal receptor-2) negative. The current usual standard treatment is surgery within a month of diagnosis, followed by radiotherapy for some where required, and anti-hormone therapy (known as endocrine therapy; ET) for 5-10 years. Most post-menopausal women with early breast cancer will not require chemotherapy. Almost one half will be treated by surgical removal of the breast (mastectomy). For others, lumpectomy (breast conservation surgery), enables a more limited amount of breast tissue to be removed and breast preservation. ET after surgery is very effective in the long-term treatment of breast cancer; it is however currently unknown whether it is also beneficial to start this same ET before surgery, known as neoadjuvant endocrine therapy (NET). This study is to determine whether giving some of the ET before surgery will shrink the tumour before operating. This could increase the rates of breast preservation by reducing the number of mastectomies for some women and the extent of surgery for others (removing less tissue leaves less defect). After mastectomy, many women do not want or are unsuitable for breast reconstruction. Even if received, this may not always fully compensate for breast removal. If it is shown that NET reduces the amount of breast tissue that has to be removed and increases the rates of breast preservation, this would be anticipated to improve cosmetic outcomes, leading to a better quality of life. This study therefore compares the traditional order of surgery within a month, to a period of pre-surgical ET followed by surgery.

Who can participate?
Post-menopausal women with breast cancer who do not require chemotherapy

What does the study involve?
Participants start their endocrine treatment on trial entry. Surgery is required in both arms of

the trial, but it is the timing that differs. The surgery will be within the standard NHS treatment target of 2-4 weeks in the comparator arm (standard of care; up to 8 weeks permitted for trial purposes), or at 6 +/- 1 months in the NET arm. The surgical operation performed will be decided by the patient and treating clinical team in the usual way. Patients in both arms will complete quality-of-life questionnaires at intervals during their 15-month participation and rates of lumpectomy (breast conservation surgery) will be documented.

What are the possible benefits and risks of participating?
This treatment is normally given and its risks and side effects are well documented and should be no different for participants taking these treatments within the trial compared to those outside of the trial. Both arms of the trial therefore constitute treatment strategies consistent with current NICE guidance. The risks relating to the surgery itself will be discussed with the participant in detail as part of the standard, routine consent for an operation. The researchers do not think that being part of this study will change any of the risks of the operation but this is one of the things they will be studying. The trial endpoints include measures to determine if the intervention approach (NET) reduces the burden of surgery and so improves quality of life. Patients in the NET group will be monitored closely with an early clinic visit at 6 weeks, and then further clinical reviews with ultrasound monitoring at 3 and 5 months. In the unlikely event that the clinical team feel the tumour is not responding to the NET as anticipated, this will enable cross-over to early surgery with minimal delay.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
June 2021 to February 2027

Who is funding the study?
NIHR Health Technology Assessment Programme (UK)

Who is the main contact?
Prof. Michael Douek
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Study website
https://www.endonettrial.org/

Contact information

Type(s)
Scientific

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Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
2022-000582-40

IRAS number
1005155

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
PID15899, IRAS 1005155, CPMS 52372

Study information

Scientific Title
Randomised controlled trial evaluating effectiveness of neoadjuvant endocrine treatment in post-menopausal women

Acronym
EndoNET

Study objectives
Current study hypothesis as of 04/10/2024:
Neoadjuvant endocrine therapy (NET) reduces breast cancer size prior to surgery, reducing surgical burden, and resulting in a higher proportion of breast conservation surgery (BCS).

Current study hypothesis as of 12/10/2022 to 04/10/2024:
Neoadjuvant endocrine therapy (NET) reduces breast cancer size prior to surgery, reducing surgical burden leading to better HRQoL and higher rates of breast conservation surgery (BCS).

Previous study hypothesis:
The overall aim is to evaluate whether 6 (+/-1) months of neoadjuvant endocrine therapy (NET) reduces surgical burden resulting in better health-related quality of life (HRQoL) over 15 months and higher rates of breast conservation surgery (BCS) for post-menopausal women with >T1, strongly ER+, HER2- invasive breast cancer who do not require chemotherapy.

1. Evaluate tumour response rates following NET
2. Compare invasive tumour size, histological grade and lymph node status (including the number of involved nodes)
3. Compare the HRQoL related to body image and surgery (FACT-B with ES and +4, Breast Q, EQ-5D-5L, Hopwood Body Image Scale)
4. Provide an estimate of the risk of relapse and measure of endocrine sensitivity in NET arm
5. Compare post-surgical complications and AI side effects
6. Assess treatment compliance (MARS-5)
7. Evaluate the prognostic significance of Ki67
8. Assess surgical management of the breast
9. Assess surgical management of the axilla
10. Compare rates of local and distant recurrence
11. Compare breast cancer specific survival and overall survival
12. Assess the cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with current practice of surgery followed by adjuvant ET for a reduction in mastectomy
13. Compare the accuracy of USS and MRI
14. Compare requirements for adjuvant chemotherapy

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/05/2022, East Midlands - Nottingham 2 Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8169; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0086

Study design
Randomized controlled open parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Newly diagnosed strongly ER-positive negative breast cancer

Interventions
Patients will be randomised 1:1 upon joining the trial through an online platform to either the comparator arm or the intervention arm.

The intervention in this trial is endocrine treatment tablets of a type known as aromatase inhibitors (AIs). All participants will start their endocrine treatment tablets for oral use: letrozole (2.5 mg/day), anastrozole (1 mg/day) or exemestane (25 mg/day) at randomisation. The endocrine treatment offered in both arms of the trial is the same but the timing of the surgery differs:

1. Comparator arm – surgery after 2-4 weeks of endocrine treatment; up to 8 weeks permitted for trial purposes
2. Intervention arm – surgery after 6 +/- 1 months of endocrine treatment

Participants will complete quality-of-life questionnaires periodically during their 15-month participation and rates of breast conservation surgery (lumpectomy) will be recorded. Participants will continue their adjuvant treatment including their endocrine treatment for 5-10 years as per their usual standard treatment.

Intervention Type

Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Letrozole, anastrozole, exemestane

Primary outcome measure
Current primary outcome measure as of 04/10/2024:
Rates of breast conservation surgery measured using surgical burden data stored in patient records at 6 months (+/- 1 month) of NET

Previous primary outcome measure:
The EndoNET Trial has co-primary outcome measures:
1. Global HRQoL is measured by FACT-B at baseline, 6 weeks or post-operative, 5, 7, 12, and 15 months
2. Rates of breast conservation surgery measured using surgical data stored in patient records at 15 months

Secondary outcome measures
1. Tumour response rates are measured by the RECIST scale (CR, PR, PD or SD) at 2-4 weeks, 3 and 5 months (intervention arm)
2. Tumour size, histological grade and lymph node status according to histology reports pre- and post-surgery
3. Health-related QoL is measured by FACT-B +4/ES, Breast-Q, EQ-5D-5L and Hopwood Body Image Scale at baseline, 6 weeks or post-operative, 5, 7, 12 and 15 months
4. Risk of relapse and ability to measure endocrine sensitivity according to PEPI score at baseline, 2-4 weeks and post-operative sample (intervention arm)
5. Post-surgical complications and endocrine treatment side effects reported at 2-4 weeks, 6 weeks (intervention arm), surgery, post-operative, 3, 5, 6, 12 and 15 months
6. Participant compliance to ET/NET is measured by the MARS-5 questionnaire at 2-4 weeks, 5 months and 15 months
7. Significance of Ki67 in the prognosis of breast cancer measured using Ki67 score in tumour sample(s) at baseline, after 2-4 weeks of endocrine treatment and at surgery (in comparator arm)
8. Surgical management of the breast using rates of re-excision and further surgery after lumpectomy, requirement for advanced lumpectomy and rates of reconstruction post-mastectomy, and radiotherapy post-operative and at 15 months
9. Surgical management of the axilla using rates of sentinel node biopsy, axillary clearance and radiotherapy post-operative and at 15 months
10. Rates of local and distance recurrence measured using data stored in patient records post-surgery, at 15 months and periodically for long-term follow up
11. Breast cancer specific and overall survival measured using data stored in patient records post-surgery, at 15 months and periodically for long-term follow up
12. Resource use, cost and cost-effectiveness of implementing intervention compared with current practice measured by the Health Care Use questionnaire at baseline, 7, 12 and 15 months
13. Accuracy of ultrasound (and MRI if available) for assessing initial disease extent and detection of tumour response at 2-4 weeks, 3 and 5 months

14. Requirement of adjuvant chemotherapy measured using chemotherapy data stored in patient records by 15 months

Added 12/10/2022:
*subject to additional funding and/or resource

Overall study start date
01/06/2021

Completion date
28/02/2027

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 04/10/2024:
Main study:
1. Female
2. Clinically post-menopausal, according to established local criteria, and suitable for an aromatase inhibitor
3. Strongly ER+; defined as Allred scores of 7 or 8 or equivalent*
4. Tumour size ≥15mm
5. Suitable for surgery and radiotherapy
6. Unifocal, newly diagnosed breast cancer visible on USS Note: Satellite lesions ≤5 mm and ≤10 mm in distance from the edge of the primary lesion are permitted as long as they can be removed en bloc;
7. Participant is able and willing to give informed consent for participation in the trial
8. In the Investigator's opinion, is able to comply with all trial requirements
* or equivalent may include a histochemical score (H-score) ≥ 200.

QRI (information study) Patients:
1. Patients approached for participation in the EndoNET study
2. Patient inclusions are the same as for the EndoNET study

Healthcare professionals (HCPs) and research personnel (RPs):
1. HCPs or RPs involved in management, operation or recruitment for the EndoNET study
2. Trial management group (TMG) members with a role in planning/coordinating recruitment

Current inclusion criteria as of 02/06/2023 to 04/10/2024:
Main study:
1. Female
2. Clinically post-menopausal; including one of:
2.1. Amenorrhoea >12 months and an intact uterus
2.2. Bilateral oophorectomy
2.3. For those with a history of hysterectomy, or hormone replacement therapy (HRT) within 12 months, venous FSH levels classified as post-menopausal by the testing laboratory if any doubt
3. Unifocal, newly diagnosed breast cancer visible on USS
4. Strongly ER+; defined as Allred scores of 7 or 8 or equivalent*
5. HER2- by immunohistochemistry, or 2+ and not amplified by in situ hybridisation
6. T-stage 1, 2 or 3 (≥15 mm)
7. Axillary N0-1 on diagnostic USS +/- negative fine-needle aspiration (FNA) or core biopsy

8. Suitable for surgery and radiotherapy
9. Chemotherapy unlikely to be indicated
10. Participant is able and willing to give informed consent for participation in the trial
11. In the Investigator's opinion, is able to comply with all trial requirements
* or equivalent may include a histochemical score (H-score) ≥ 200.

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3. Unifocal, newly diagnosed breast cancer visible on USS
4. Strongly ER+; defined as Allred scores of 7 or 8 or equivalent
5. HER2- by immunohistochemistry, or 2+ and not amplified by in situ hybridisation
6. T-stage 2 or 3 (>2 cm)
7. Axillary N0-1 on diagnostic USS +/- negative fine-needle aspiration (FNA) or core biopsy
8. Suitable for surgery and radiotherapy
9. Chemotherapy unlikely to be indicated
10. Participant is able and willing to give informed consent for participation in the trial
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2. Patient inclusions are the same as for the EndoNET study

Healthcare professionals (HCPs) and research personnel (RPs):
1. HCPs or RPs involved in management, operation or recruitment for the EndoNET study
2. Trial management group (TMG) members with a role in planning/coordinating recruitment

Participant type(s)
Mixed

Age group
Adult

Sex
Female

Target number of participants
1060

Key exclusion criteria
Current participant exclusion criteria as of 04/10/2024:
Main study:
The participant may not enter the trial if ANY of the following apply:
1. Bilateral breast cancer
2. cN3 disease
3. cT4 disease Note: T4 is defined as (i) chest wall (rib/intercostal) involvement (adherence /invasion to pectoralis is NOT an extension to the chest wall and is not defined as T4 here) or (ii) skin ulceration, skin nodules or oedema such as in inflammatory breast cancer. Dimpling of the skin, nipple retraction or other skin other changes without ulceration, nodules or oedema, do not make a tumour T4;
4. Metastatic breast cancer (Stage IV disease)
5. Chemotherapy or anti-HER-2 therapy for current breast cancer started or planned at the time of randomisation
6. Previous invasive malignancy within 5 years which is likely to affect the safety or efficacy assessment or compliance with the protocol or interpretation of results
7. Concurrent use (at the time of randomisation) of HRT or any other oestrogen-containing medication (including vaginal oestrogens) Note: Presence of Mirena coil at the time of randomisation is not an exclusion;
8. If clinically pre-menopausal, ovarian suppression/ablation for the purposes of trial entry is not permitted
9. Aromatase inhibitor endocrine treatment following current breast cancer diagnosis taken for longer than 14 days at time of randomization.

QRI (information study):
Patients:
1. Patient exclusions are the same as for the EndoNET study
2. Patient does not wish to have consultations recorded and/or participate in interview

HCPs and RPs:
1. HCPs or RPs who do not wish to have consultations recorded and/or participate in interview

Previous participant exclusion criteria:
Main study:
The participant may not enter the trial if ANY of the following apply:
1. Bilateral breast cancer
2. ER- or HER2+
3. Stage IV disease (distant metastasis)
4. Previous neoadjuvant treatment for breast cancer
5. Previous invasive malignancy within 5 years other than basal cell carcinoma
6. Concurrent use (at the time of randomisation) of HRT or any other oestrogen-containing medication (including vaginal oestrogens)
7. Ovarian suppression/ablation for the purposes of trial entry not permitted

QRI (information study):
Patients:
1. Patient exclusions are the same as for the EndoNET study
2. Patient does not wish to have consultations recorded and/or participate in interview

HCPs and RPs:
1. HCPs or RPs who do not wish to have consultations recorded and/or participate in interview

Date of first enrolment
23/08/2022

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

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

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

Study participating centre
Belfast City Hospital
51 Lisburn Rd
Belfast
United Kingdom
BT9 7AB

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

Study participating centre
University Hospital Llandough
Penlan Road
Llandough
Penarth
United Kingdom
CF64 2XX

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

Study participating centre
Royal Albert Edward Infirmary
Wigan Lane
Wigan
United Kingdom
WN1 2NN

Study participating centre
Basildon University Hospital
Nethermayne
Basildon
United Kingdom
SS16 5NL

Study participating centre
Southend University Hospital
Prittlewell Chase
Westcliff-on-Sea

United Kingdom
SS0 0RY

Study participating centre
Southmead Hospital
Southmead Road
Bristol
United Kingdom
BS10 5NB

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Royal Hampshire County Hospital
Romsey Road
Winchester
United Kingdom
SO22 5DG

Study participating centre
Whiston Hospital
Warrington Road
Rainhill
Prescot
United Kingdom
L35 5DR

Study participating centre
University Hospital Hairmyres
218 Eaglesham Road
East Kilbride
Glasgow
United Kingdom
G75 8RG

Study participating centre
St. Albans City Hospital
Waverley Rd
St Albans
United Kingdom
AL3 5PN

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

Study participating centre
Glenfield Hospital
Groby Rd
Leicester
United Kingdom
LE3 9QP

Study participating centre
Macclesfield District General Hospital
Victoria Rd
Macclesfield
United Kingdom
SK10 3BL

Study participating centre
Airedale General Hospital
Skipton Rd
Steeton
Keighley
United Kingdom
BD20 6TD

Study participating centre
Medway Maritime Hospital
Windmill Rd
Gillingham

United Kingdom
ME7 5NY

Study participating centre
Cumberland Infirmary
Newtown Rd
Carlisle
United Kingdom
CA2 7HY

Study participating centre
Basingstoke and North Hampshire Hospital
Aldermaston Road
Basingstoke
United Kingdom
RG24 9NA

Study participating centre
Royal Free Hospital
Pond St
London
United Kingdom
NW3 2QG

Study participating centre
Barnsley Hospitals
118 Gawber Road
Barnsley
United Kingdom
S75 2PS

Study participating centre
Royal Berkshire Hospital
Royal Berkshire Hospital
London Road
Reading
United Kingdom
RG1 5AN

Study participating centre
Rotherham General Hospital
Moorgate Road
Rotherham
United Kingdom
S60 2UD

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

Study participating centre
Ninewells Hospital
Ninewells Avenue
Dundee
United Kingdom
DD1 9SY

Study participating centre
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
United Kingdom
M8 5RB

Study participating centre
Torbay and South Devon NHS Foundation Trust
Torbay Hospital
Newton Road
Torquay
United Kingdom
TQ2 7AA

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way

Birmingham
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B15 2GW

Study participating centre
Altnagelvin Area Hospital
Glenshane Road
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BT47 6SB

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Broomfield
Chelmsford
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CM1 7ET

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Yeovil District Hospital
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Luton
United Kingdom
LU4 0DZ

Study participating centre
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Sketty Ln, Sketty,
Swansea
United Kingdom
SA2 8QA

Study participating centre
St Marys Hospital
Imperial College Healthcare NHS Trust
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United Kingdom
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Study participating centre
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County Hospital
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Lincoln
United Kingdom
LN2 5QY

Sponsor information

Organisation
University of Oxford

Sponsor details
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ctrg@admin.ox.ac.uk

Sponsor type
University/education

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ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Submission to regulatory authorities
6. Other

Intention to publish date
28/02/2028

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date. Upon completion of the trial, fully de-identified research data may be shared with other organisations subject to review and approval of a suitable application. Patients will be informed about this possibility within the patient information the reasons why this is important for future research and that this will be done anonymously.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

HRA research summary			28/06/2023	No	No
Participant information sheet	version 5.0	21/08/2024	04/10/2024	No	Yes
Participant information sheet	version 3.0	21/08/2024	04/10/2024	No	Yes
Protocol file	version 4.0	21/08/2024	04/10/2024	No	No