Trial Title: Randomised controlled trial evaluating effectiveness of neoadjuvant endocrine treatment in post-menopausal women (EndoNET)

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Conflict of interest: The chief investigator has not declared a conflict of interest.

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Ramsey Cutress and Michael Douek jointly led the funding application to NIHR HTA and are considered equal contributors to the trial.

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Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	Signature	Site name or ID number	Date

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1. KEY TRIAL CONTACTS

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Committees	A Trial Steering Committee (TSC) and an independent Data and Safety Monitoring Committee (DSMC) will be set up. The details will be written in the relevant charters.

2. LAY SUMMARY

There are 50,000 people who develop breast cancer each year in the United Kingdom, mostly women after their menopause and of a type known as oestrogen-receptor positive, HER-2 negative (human epidermal receptor-2). 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) for 5-10 years. Most post-menopausal patients 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), will ensure that a limited amount of breast tissue is removed at surgery.

Endocrine therapy 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 endocrine therapy before surgery, known as neo-adjuvant endocrine therapy (NET). This study is to determine whether giving some of the endocrine therapy before surgery will shrink the tumour prior to 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 patients 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 better quality of life. This study therefore compares the traditional order of surgery within a month, to a period of treatment with endocrine therapy followed by surgery.

Participants in this randomised controlled trial are allocated by chance to one of two arms, which determines their treatment schedule. Endocrine therapy is usually started after surgery. However, all participants in both trial arms will start endocrine therapy (letrozole, anastrozole or exemestane) on joining the trial and prior to surgery. Therefore, they may have the opportunity to start treatment with endocrine therapy before they normally would. If patients start aromatase inhibitor endocrine therapy following their current diagnosis of breast cancer as part of routine care before the trial, this is allowed provided the endocrine therapy was not started more than 14 days prior to trial entry.

Participants in both arms have endocrine therapy for the same total length of time within the trial, but it is the timing of the surgery that differs. The type of surgery all participants will have will be determined by them and their clinical team as part of standard clinical care. Arm 1 will have surgery within 2-4 weeks (up to 8 weeks permitted for trial purposes) of starting their pre-surgical endocrine therapy; arm 2 will receive surgery after 6 months (+/-1 month) of pre-surgical endocrine therapy (neoadjuvant endocrine therapy;

NET). Participants in Arm 2 will receive an ultrasound (USS) scan at 3 months and 5 months to closely monitor their response to this endocrine therapy prior to their surgery.

Patients with breast cancer, included as part of the study leadership team, and others have been extensively consulted in the trial design. They indicated preserving the breast and overall quality of life as the most important outcomes by which to measure study success.

The trial aims to recruit at least 792 women from at least 30 NHS hospitals across the UK. Participants in both arms will have their surgical treatments recorded and will complete quality of life questionnaires at intervals during their 15-month participation in the study. The results will be published in medical journals and presented at international conferences and updates of study progress will be available on the website and by study newsletter.

As part of this research, we are also running sub-studies to which patient participation is optional:

- The 'Information study', called the QuinteT Recruitment Intervention study, will investigate the different factors that can affect patient participation in EndoNET. This is being led by researchers at the University of Bristol.
- The 'Nested Qualitative Study' will investigate the experiences of participants in the main trial. Specifically, it will focus on how well they have tolerated their endocrine therapy and how this and their other breast cancer treatments have affected their quality of life.

3. SYNOPSIS

Trial Title	Randomised controlled trial evaluating effectiveness of neoadjuvant endocrine treatment in post-menopausal women (EndoNET)
Internal ref. no. (or short title)	EndoNET
Trial registration	EudraCT number: 2022-000582-40 ISRCTN number: ISRCTN11896599
Sponsor	**University of Oxford** Research Governance, Ethics and Assurance (RGEA) Joint Research Office 1st Floor, Boundary Brook House Churchill Drive Headington Oxford OX3 7GB Tel: +44 (0)1865 289884 Email: rgea.sponsor@admin.ox.ac.uk
Funder	**National Institute for Health Research** Health Technology Assessment Programme
Clinical Phase	Phase III
Trial Design	EndoNET is a prospective, phase III, multicentre randomised controlled trial (RCT). Patients will be randomised 1:1 to either the intervention (NET) arm (6 +/- 1 months of NET followed by surgery and adjuvant ET) or the control arm

	(2-4 weeks of presurgical ET and surgery within 2-4 weeks [up to 8 weeks permitted for trial purposes] followed by adjuvant ET). Both arms will receive the same treatments (surgery, ET, and radiotherapy where indicated), but the sequencing of surgery will differ; both arms starting ET at randomisation*, with 6 months +/- 1 month of the course of ET delivered prior to surgery in the NET arm. *Some patients may have already started aromatase inhibitor endocrine therapy as part of their standard of care.
Trial Participants	Post-menopausal women with strongly ER+, invasive breast cancer where chemotherapy or anti-HER-2 therapy is not planned or has not started
Sample Size	Main Trial: We will recruit a maximum of 1060 (for 90% power), with a minimum of 792 (for 80% power) post-menopausal women with strongly ER+, invasive breast cancer who are not planned or have not started chemotherapy or anti-HER-2 therapy QRI 'Information study' (optional sub-study): Approximately 50 audio-recordings of patient recruitment discussions (all eligible patients to be approached for the duration of recruitment period). Approximately 30 interviews with clinicians or researchers involved in trial recruitment. Nested qualitative study (optional sub-study): Approximately 60 qualitative interviews with participants.
Planned Trial Period	The overall period of the trial is 69 months with an end date of 28/02/2027 including: 6 months set-up, 42 months recruitment, 15 months follow-up and 6 months data analysis and final reporting of results. A formal stop/go review took place on 31st December 2023. A second review is planned in December 2024. Participants will also be asked to give consent for the collection of routine NHS data for long-term follow up. This may be for a period of, for example, 20 years or more, subject to receipt of suitable funding and/or resources and submission via a substantial amendment.
Planned Recruitment period	42 months

	Objectives	Outcome Measures	Timepoints
Primary	The overall aim is to evaluate whether 6 (+/- 1) months of NET reduces surgical burden resulting in a higher proportion of breast conservation in post-menopausal women with ≥15mm, strongly ER+ invasive breast cancer who are not planned or have not started chemotherapy or anti-HER-2 therapy [1]	Proportion of patients who have breast conservation (surgery)	15 months post-randomisation
Secondary	1. To evaluate whether 6 months of NET results in better HRQoL over 15 months [1]	1. Difference in global HRQoL (as measured by FACT-B)	1. Baseline, 6 weeks or post-operative, 5 and 15 months post-randomisation
	2. To evaluate tumour response rates following NET [2]	2. Response rates according to RECIST (USS, clinical, relative to baseline); MRI where used as part of local unit centre policy	2. 2-4 weeks, 3 and 5 months post-randomisation (NET arm)
	3. To compare invasive tumour size, histological grade and lymph node status (including number of involved nodes) in both arms [1]	3. Tumour size, histological grade and lymph node status pre-surgery and final histology post-surgery	3. Pre and post-operative
	4. To compare, in both arms, the HRQoL related to body image and surgery (FACT-B with ES and +4, Breast Q, EQ-5D-5L, Hopwood Body Image Scale [BIS]) [1]	4. Patient reported outcomes as measured by FACT-B (with ES and +4), Breast-Q, Hopwood Body Image Scale and EQ-5D-5L	4. Baseline, 6 weeks or post-operative, 5, 7, and 15 months post-randomisation[3]

	5. To provide an estimate of the risk of relapse and measure of endocrine sensitivity in NET arm [2]	5. Pre-operative Endocrine Prognostic Index (PEPI) score	5. Baseline sample, 2-4 week sample and post-operative sample
	6. To compare post-surgical complications and AI side effects in both arms [1]	6. Post-surgical Complications, side effects; delays to commencement of subsequent treatment	6. 2-4 and 6 weeks, 3 months, 5, 7, 12 and 15 months post-randomisation
	7. To assess treatment compliance (MARS-5) [1]	7. Treatment Compliance and rates of cross-over	7. 2-4 weeks, 5 months and 15 months post-randomisation.
	8. To evaluate the prognostic significance of Ki67 [1]	8. Ki67 % in tumour cells, % reduction in Ki67 from baseline to biopsy or surgery	8. Baseline (both arms) and after 2-4 weeks of AI (in both arms) and at surgery (in comparator arm)
	9. To assess the surgical and locoregional management of the breast [1]	9. Rates of re-excision and further surgery after BCS; specimen weight after BCS; requirement for advanced BCS (therapeutic mammoplasty and local perforator flaps), rate of reconstruction postmastectomy, breast radiotherapy	9. Baseline, post-operative, 15 months post-randomisation
	10. To assess the surgical and locoregional management of the axilla [1]	10. Rates of sentinel node biopsy, axillary clearance, axillary radiotherapy	10. Baseline, post-operative, 15 months post-randomisation
	11. To compare rates of local and distant recurrence [1]	11. Rates of local and distant recurrence	11. 15 months post-randomisation, and periodically for long term follow up [4]
	12. To compare breast cancer specific survival in both arms [1]	12. Breast cancer specific and overall survival	12. 15 months post-randomisation and periodically

			for long term follow up [4]
	13. To assess the cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice of surgery followed by adjuvant ET for reduction in mastectomy (Health Care Use Questionnaire) [1]	13. Resource utilisation, cost and cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice.	13. Baseline, 6 weeks, 7 months and 15 months post randomisation
	14. To compare accuracy of Ultrasound (USS) and MRI (where available) for assessment of initial extent of disease and for detection of tumour response, using these two different imaging modalities [1]	14. Accuracy of USS (and MRI where available) to determine conversion to BCS	14. Up to 15 months post-randomisation
	15. To compare the requirement for adjuvant chemotherapy in both arms [1]	15. Number of patients receiving adjuvant chemotherapy in both arms	15. At 15 months
Intervention • IMP(s)		IMP: Pre-surgical (Neoadjuvant) Endocrine Therapy (aromatase Inhibitors, AI): letrozole, anastrozole or exemestane) following trial entry to surgery, in both arms: In intervention arm 6 (+/-1) months and control arm 2-4 weeks (up to 8 weeks permitted for trial purposes). Choice of AI is according to centre policy and may be either letrozole (2.5mg/day), anastrozole (1mg/day), or exemestane (25 mg/day).	

Comparator	Surgery within 2-4 weeks of trial entry ; up to 8 weeks permitted for trial purposes – either BCS or mastectomy +/- reconstruction followed by adjuvant therapy, including adjuvant ET. This is consistent with current best standard of care in the majority of patients where surgery takes place within the NHS 31-day time to treatment target.

[1] Outcomes within objective are measured in both the intervention (NET) and control arm.

[2] Outcomes within objective measured in intervention (NET) arm only.

[3] Breast-Q administered at baseline and 15 months only. EQ-5D-5L administered at baseline, 6 weeks, 7 months and 15 months only. Hopwood BIS administered at baseline, 5 months and 15 months only. FACT-B with ES and +4 administered at baseline, 6 weeks, 5 months and 15 months. Refer to schedule of trial procedures in Section 9.2.

[4] These are secondary objectives that will be assessed subject to additional funding and/or resources at 5, 10 and 20 years of EndoNET trial long-term follow up. Patients will be consented for long term follow-up on EndoNET trial entry.

4. ABBREVIATIONS

AE	Adverse Event
AI	Aromatase Inhibitors
AR	Adverse reaction
ATAC	Arimidex, Tamoxifen Alone or in Combination
BCS	Breast Conservation Surgery
BIS	Hopwood Body Image Scale
BNF	British National Formulary
CE	Conformité Européenne
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ER+	(O)estrogen Receptor Positive
ET	Endocrine Therapy
FACT-B	Functional Assessment of Cancer Therapy-Breast
FNAC	Fine-Needle Aspiration Cytology
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HER2	Human Epidermal Growth Factor Receptor 2
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPACT	Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen

IRB	Independent Review Board
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
NAC	Neoadjuvant Chemotherapy
NCRI	National Cancer Research Institute
NET	Neoadjuvant Endocrine Therapy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NQS	Nested Qualitative Study
OCTRU	Oxford Clinical Trials and Research Unit
OPA	Outpatient Appointment
PEPI	Preoperative Endocrine Prognostic Index
PI	Principal Investigator
PIL	Participant/Patient Information Leaflet
PPI	Patient and Public Involvement
POETIC	Pre-operative Endocrine Therapy for Individualised Care
PROMS	Patient-Reported Outcomes Measures
QoL	Quality of Life
QRI	QuinteT Recruitment Intervention
R&D	NHS Trust R&D Department
RCT	Randomised Control Trial
REC	Research Ethics Committee
RES	Research Ethics Service
RGEA	Research Governance, Ethics and Assurance
RP	Research Personnel
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SITU	Surgical Intervention Trials Unit
SMPC	Summary of Medicinal Product Characteristics

SoC	Standard of Care
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR	Suspected Unexpected Serious Adverse Reactions
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File
TMG	Trial Management Group
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group
USS	Ultrasound Scan

5. BACKGROUND AND RATIONALE

Earlier diagnosis and improved treatments for invasive breast cancer have resulted in improved survival rates (1). Breast cancer and its treatments, however, can have a negative impact on the quality of women's lives (2) and mastectomy is accepted to lead to greater psychological morbidity than breast conserving surgery (BCS). Despite earlier diagnosis and improved treatments, mastectomy rates remain high with 40% of breast cancer patients treated by mastectomy (3). Of the 45,000 women in England and Wales over 50 years old with ER+, HER2- invasive breast cancer, 45% with tumours >2 cm will undergo mastectomy and this increases with increasing age (4-6). Rates of immediate breast reconstruction following mastectomy in England have increased, but despite this over three quarters of patients do not have immediate post-mastectomy reconstruction (7). Of these, most do not proceed with delayed reconstruction and some will not be suitable for reconstruction due to risk factors such as smoking and high body mass index. Furthermore, following mastectomy, breast reconstruction does not fully compensate for the effects of mastectomy on quality of life (QoL) (8, 9). Complication rates are also high following implant-based and autologous post-mastectomy breast reconstruction (10, 11) and ongoing revisional surgery with attendant morbidity and cost, is commonly required (12). There is therefore an imperative to assess strategies that increase the rate of BCS and thereby improve HRQoL.

With BCS, cosmetic outcome and patient satisfaction are directly related to the percentage volume of breast tissue excised (13), and pronounced asymmetry is associated with poor psychosocial function (14). Following BCS the rate of re-excision is over 20% in the UK (15). The need for repeat surgery creates delays to further treatments (including radiotherapy) with adverse health-related quality of life (HRQoL) impact and cost. There is therefore additional benefit from reducing surgical burden beyond increasing the BCS rate alone.

Current standard of care (SoC) is surgical removal of the tumour followed by other (adjuvant) treatments including, in those with ER positive breast cancer, endocrine therapy (ET) for 5-10 years to reduce the risk of breast cancer recurrence (95). Altering the sequencing of these treatments such that surgery is performed after 6 months of the 5-10 year course (NET) has the potential to improve HRQoL by increasing BCS rates. In those having BCS, NET has the potential to improve HRQoL by shrinking the tumour prior to BCS resulting in reduced volume of surgical excision and thus improving cosmesis, potentially reducing re-excision rates and reducing the requirement for advanced breast conservation techniques.

Approximately 87% of patients with early invasive breast cancer have ER+ disease (4), and virtually all will receive ET after surgery to reduce risk of breast cancer recurrence. Currently, from 109,018 patients over the age of 50 with early invasive breast cancer in England and Wales, 35% of 50-69 year olds and 50% of those over the age of 70 had a tumour size greater than 2cm (4). Large numbers of patients could therefore potentially benefit from having this NET approach to down-size their disease and reduce the extent (convert mastectomy to BCS) or amount of surgery (reduce excision volumes and re-excision rates). Evidence suggests however that NET is infrequently used and practice varies greatly across NHS trusts with many reluctant to offer NET. NET is currently used in 1.5% of breast screening patients nationally (5). In the NeST study (16), including both symptomatic and screening patients, 14% of neoadjuvant therapy given was NET despite the lower toxicity and wider patient eligibility for NET compared to neoadjuvant chemotherapy (NAC) (17).

Although documented as an option by NICE Guidance 101 (95), many clinicians are reluctant to use NET as the potential benefits are not clearly defined or evaluated. In comparison, there is randomised trial evidence for NAC (18), and in pre-menopausal but not post-menopausal patients, response rates are better with NAC compared to NET (19). Consistent with this, NICE guidance recommends NET should be considered as an option in post-menopausal women to reduce tumour size but does not make this recommendation for pre-menopausal women. National data (17) shows good acceptance of NAC, but more mixed clinician views in respect of NET. In contrast, a survey indicates that patients over 70 years old wish to consider BCS, and many would be willing to take NET to downstage their breast cancer if it facilitated BCS (20). Furthermore, during the COVID-19 pandemic emergency guidance from specialist associations recommended commencement of NET (in this setting also called bridging endocrine treatment) where surgery was not immediately available or whilst patients were shielding (21, 22). In response to this guidance and in just under 2 months from 16 March to 8 May 2020 preliminary data from the B-MaP-C study suggests 951 patients in 64 centres were started on NET, equating to approximately 8 patients per centre per month potentially eligible for this approach (96). Increasing BCS rates are likely to benefit post-menopausal women since it is known that the detrimental effects of mastectomy to HRQoL and body image persist regardless of age (20, 23, 24). This study is therefore designed to determine whether NET will reduce surgical burden, increase BCS rate, reduce re-excision rate and lead to improvements in HRQoL.

5.1. NET as a strategy to downstage breast cancer

Adjuvant ET is standard of care for post-menopausal patients with early ER+ breast cancer (25). **Despite sporadic clinical use of NET, there is no randomised trial evidence supporting its effectiveness compared to primary surgery and adjuvant ET**. Although the NICE evidence synthesis (26) quoted a study comparing adjuvant ET with NET, the comparison was of primary ET alone (i.e. ET without planned surgery) with ET and surgery (27), confirming the importance of surgery in the treatment of breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient data meta-analysis of these studies in older women also concluded that both surgery and ET are required to optimise breast cancer survival and minimise distant recurrence (unpublished).

A meta-analysis identified 20 published randomised trials of NET (28) but none of these compare NET to the current standard of care of surgery first. Three compared NET with NAC, and in these NET was found to be at least as good as NAC in producing clinical radiological and pathological responses and downstaging surgery to BCS, but with less toxicity. Seven studies compared aromatase inhibitor (AI) NET with Tamoxifen NET, demonstrating AI superiority for clinical and pathological responses and downstaging surgery, consistent with earlier analysis (29).

Four studies reported on BCS rates in a comparison of AI against Tamoxifen. Whilst individually no study was significant, when combined, the results favoured AI (OR for BCS 1.62) (28). **We are therefore specifying use of an AI for this trial**. In a national US database study (30) 3% of 77,272 patients received NET. NET use increased with increasing tumour size and within each size category, those treated with NET underwent higher BCS rates. Rates of BCS were highest in those with T2 (>2cm, ≤5cm) disease (48% no NET v 59% NET). This rate of downstaging is consistent with the proposed effect size we have powered this study on.

Two single arm studies of NET suggest responses to NET are more apparent with longer treatment duration. Carpenter (31) in a multicentre single arm study of AI NET in patients initially unsuitable for BCS found that 69% were eligible for BCS with a median time to response of 7.7 months, consistent with our longer treatment duration arm. Dixon (32) in a single centre experience demonstrated that of those requiring a mastectomy at baseline, 60% were converted to BCS at 3 months with 72% eventually receiving BCS over longer periods, suggesting benefit continues with time. In support of this a third study also demonstrated increasing pathological complete response rates with increased duration of NET treatment (33).

Whilst effective for metastatic disease, CDK4/6 inhibitors have no confirmed utility for neo-adjuvant treatment in early breast cancer with potential for toxicity, the requirement for initial close medical monitoring and increased cost. Furthermore, a randomised trial has shown no benefit in surgical outcomes with addition of a CDK inhibitor to AI NET (34), and an adjuvant trial of a CDK inhibitor has been negative to date (35). CDK inhibitors will be also evaluated as adjuvant treatment directed by Ki67 testing in POETIC-A. It was therefore felt that in this pragmatic trial to evaluate the effectiveness of NET, CDK inhibitors should not be included as part of the neo-adjuvant treatment. We will however allow adjuvant CDK inhibitors after surgery if considered indicated or if administered as part of a trial such as POETIC-A.

For our trial, EndoNET centres should declare their first and second line AI to be used in both the neoadjuvant and 2-4 week pre-surgical window, and to continue through into the adjuvant setting. Participants must not be taking oestrogen containing medication including menopausal hormone replacement therapy at the time of randomisation and information related to this will be recorded. In both arms treatment with the centre's choice of first line AI should be started at trial entry and continue into the adjuvant setting.

Adjuvant treatment by AI will be according to usual clinical practice and national clinical guidelines. It is anticipated that participants will receive adjuvant AI for a minimum of 5 years.

5.2. Quality of Life in Breast Cancer Survivors

Very little is published about the impact of NET on HRQoL and we were unable to identify any studies that evaluated HRQoL in those receiving surgery followed by endocrine therapy in comparison with NET and surgery. One study of primary hormone therapy (endocrine therapy without subsequent surgery) (36) demonstrated a small benefit at 3 months from the omission of surgery, but scores were similar at 2 years. A single arm sub-study of neoadjuvant AI suggested that neoadjuvant letrozole did not impact on global QoL but letrozole did increase endocrine side effects (37). Extrapolation from studies including randomised trials in the adjuvant setting, demonstrate a negative impact of ET on HRQoL (38, 39) which is worst at 3 months and stabilises thereafter (38), but improves post completion of treatment (40). Since both arms of our proposed study are designed to start ET at randomisation and therefore receive ET for the same total duration during the study (from study entry to month 15), we would anticipate that although the ET impacts on HRQoL, this would be similar in the two arms.

The evidence that BCS leads to improved body image and psycho-sexual functioning is consistent across studies for surgical type (mastectomy vs BCS) (41, 42), and are independent of age (43). The effects on physical functioning and global HRQoL improve with time and predominantly in the first 2 years, whilst in

contrast the effects of mastectomy on body image and sexual functioning, less readily improve with time (44).

The NET strategy is more complex than simply a comparison of one procedure to another. Timing of surgery is different and this potentially leads to a different surgical procedures or extent of surgery. We would therefore anticipate more wide-ranging effects of the strategy than that relating to the surgery alone, since both the surgery and the timing of surgery may change. This was strongly supported by our patient advocates (including the Independent Cancer Patients' Voice) who felt that a global measure was the most appropriate HRQoL endpoint. We would, for example, expect the change in sequencing of surgery in the NET arm from standard treatment to benefit HRQoL, both in terms of the specific effects resulting from the potential increases in BCS rates, reduced extent of BCS (reduced volumes of excision and reduced re-excision rates) and also possibly more generally in terms of increased time to plan for surgery and surgical recovery from a personal family and employment perspective, and possibly for breast reconstruction. Table 1 below highlights these possible wider impacts of a NET strategy compared to current standard of care, both positive and negative which are wide ranging and extend beyond that of adjuvant or neoadjuvant ET alone. As a result, we have opted for a global measure and have selected FACT-B as our main HRQoL measure since the results from the subscales can be combined to produce a global score of HRQoL.

HRQoL encompasses a person's physical and psychological, spiritual and social relationships (2). Given the need to consider the impact of NET, surgery and adjuvant or neoadjuvant ET on women's HRQoL during this trial, the Functional Assessment of Cancer Therapy – Breast (45) FACT-B, will be used to assessHRQoL. FACT-B is a comprehensive measure of HRQoL with 44 items comprising 4 subscales: physical (7 items), social (7 items), emotional (6 items) and functional wellbeing (7 items) and concerns specific to patients with breast cancer (13 items). The subscales can be added to provide a measure of "overall" or global HRQoL (higher scores = better HRQoL). FACT-B has been used in a number of trials with demonstrated reliability, validity and sensitivity to change (Mansel et al., 2006). Given the complexity of the effect of the intervention and differing timing and extent of surgery and differing periods of recovery we have opted to evaluate HRQoL over the 15-month study period rather than at one specific time alone as it was felt this would provide a better overall evaluation of the effect of the intervention on HRQoL. Fifteen months are required since it is possible that a small number of participants in both arms might possibly require up to 3 operations (re-excision surgery followed by mastectomy) and this time point enables us to be confident that all such surgery will have been completed with at least a three-month recovery period before the end of the study.

Fallowfield *et al*. have also developed an Endocrine Sub-scale (FACT-ES) for use with FACT-B to gather information about endocrine side effects (46). As a secondary outcome measure, the FACT-ES will be used to assess side effects of endocrine therapy in both arms as per the timepoints in Section 6.2 Primary and secondary outcome measures (46). Our patient advocates also raised the possibility that the NET strategy might lead to reduction in axillary disease and surgery and so to evaluate any potential impact of this on arm morbidity, we will also as a secondary endpoint use the 4 additional questions in the arm morbidity sub-scale (47). The Breast Q (48) will be used to assess impact of surgery and the Hopwood Body Image Scale will assess impact on body image (49).

Current standard of care (surgery within 2-4 weeks)	**Neoadjuvant Endocrine Therapy (NET) (surgery at 6 months)**
Endocrine therapy is given in accordance with NICE guidance	Endocrine therapy is given in accordance with NICE guidance
Cancer removed within 31-day treatment target	6 months of NET and then cancer removed
• Surgery performed based on baseline characteristics • Surgery performed with target of 2-4 weeks (up to 8 weeks permitted)	• Opportunities to reduce burden of surgery due to tumour shrinkage - reduce mastectomy rate. Reduce requirement for postmastectomy reconstruction. • If mastectomy required, more time to plan and organise breast reconstruction. • If BCS required, may lead to reduced re-excision rate and/or excision volumes leading to improved cosmesis. Potential for reducing complexity of BCS, i.e. reducing requirement for advanced BCS techniques such as perforator flaps and therapeutic mammoplasty • Potential for reducing surgery to the axilla (reducing axillary clearance and axillary radiotherapy).
Minimal time to plan for surgery	Time to plan for surgery – employment, home circumstances, holidays, family commitments, carers/caring
If ET poorly tolerated tumour is already removed	If ET not tolerated will need to cross to surgery.
Once tumour is removed and on adjuvant ET patients can go to less intense follow-up	• Close monitoring whilst on NET for 6 months to ensure continued response • Possibility of participant feeling nervous e.g. whilst waiting for monitoring ultrasound scans.
Clip may be required	Clip will be required
Acquired resistance may occur to ET in adjuvant setting	• Acquired resistance may occur in the NET setting. In the small number with inherent resistance, response to NET will be reduced but mitigated with careful study entry criteria and close monitoring. • In these small numbers this may require switch to early surgery but may provide an early indicator of the requirement for further treatment that may be beneficial.
No additional prognostic information on sensitivity of tumour to ET	Additional prognostic information provided by response to NET (PEPI[1] score)

Table 1: Potential wide-ranging benefits and risks of NET compared to standard of care approaches.
[1] The Preoperative prognostic index (PEPI) score provides an estimate of the risk of relapse and measure of endocrine sensitivity in those treated with NET (50).

5.3. Ki67 as a biomarker for NET response

Ki67 is a marker of cell proliferation determined by immunohistochemistry. Two weeks of AI are associated with downregulation of genes involved in cell proliferation (51) and reduction of Ki67 expression. Greater Ki67 reduction, as a percentage of baseline expression, was seen with AI compared to tamoxifen in the IMPACT study (52). Several other clinical trials similarly provide evidence to support change in the expression of Ki67, after short-term treatment, to be a predictor of the benefit from adjuvant endocrine therapy. In addition, in the pre-surgical setting, the absolute level of Ki67 after 2 weeks of treatment was associated with recurrence free survival in the IMPACT and POETIC studies (53, 54).

Although Ki67 determination after 2-4 weeks of AI (in the NET setting) has been used to attempt to identify patients benefitting from a switch to NAC (55), in those patients with tumour with Ki67 >10%, the efficacy of chemotherapy was lower than expected. There is, however, little data on the role of Ki67 as a predictor of response or conversion to BCS in the longer-term NET setting. We will assess Ki67 as a secondary endpoint to determine its ability as an early 2-week marker to predict longer term 6-month response to NET. Of note, this will also allow inclusion of patients participating in our study into the POETIC-A study, without conflict.

Ki67 assessment remains poorly reproducible between laboratories, despite ongoing research by the International Ki67 in Breast Cancer Working Group; the assay is not therefore routinely applied for clinical care and further validation is still required (56). The same expert group maintains that "Automated average scoring methods show promise for assessment of Ki67 scoring" (57); we support this view and this is the approach we plan to apply centrally for analysis in the trial, with Consultant Pathologists' oversight.

The Ki67 level will be used in conjunction with the variables of pathological tumour size, node status and ER status/Allred score to obtain the preoperative endocrine prognostic index (PEPI) in accordance with the work by *Ellis et al.* (103).

5.4. Radiological response to NET

Ultrasound (USS) is available at all UK breast cancer centres and has therefore been selected as the primary modality to monitor response during the study. In the NET arm, in case of complete clinical response, a marker clip will be inserted under USS control between 2-4 weeks. The clip used to mark the biopsy/tumour location should be Conformité Européenne (CE) marked for this purpose. The opportunity will be taken at this timepoint to also provide a core biopsy sample for Ki67 to evaluate if this can be utilised as an early marker of NET response. USS will also be performed after 3 months and 5 months of NET treatment, to assess for continuing response to treatment. Our Patient and Public Involvement (PPI) consultation suggested that this would be important and requested close monitoring in NET arm to give participants confidence of continued response. Visibility of the tumour on USS is therefore one of the study inclusion criteria.

Not all centres will routinely utilise breast MRI in a NET setting. MRI is the most accurate imaging modality for delineating extent of disease and accurately determining response to treatment following NAC (58) and is useful in surgical planning. However, there is evidence for the value of MRI to assess response to NET (98), therefore a pragmatic sub-study analysis will be performed comparing accuracy for detection of initial extent of disease and for detection of response, using these two different imaging modalities where available.

For the study endpoints radiology reports will be used as the study source material, however linked-anonymised radiological images may be collected and used for future research purposes subject to further funding and governance approvals. The exact process and location of storage will be specified in a subsequent substantial amendment prior to this occurring.

5.5. Selection of patients where chemotherapy and/or anti-HER-2 therapy is not indicated at the time of trial entry

The study is designed to recruit patients who would not normally receive neoadjuvant or adjuvant chemotherapy since this is the context in which NET is recommended as an option within NICE guidance. Patient consultation confirmed that patients who knew they required chemotherapy would prefer to have NAC or immediate primary surgery and adjuvant chemotherapy, as chemotherapy following NET would significantly extend the duration of active treatment.

The recommendation for chemotherapy in early breast cancer is based on evaluation of risk and benefit. In clinically node negative patients with intermediate risk ER+/HER2-tumours baseline molecular profiling is currently available (59) and can be performed on the diagnostic core biopsy if this will inform decision making. If the oncological decision is that chemotherapy is not recommended, the patient can be approached for participation in the EndoNET trial. In patients in whom it was felt chemotherapy would not be given due to co-morbidity, patient preference or marginal benefit, then the patient can also be offered study participation.

Despite best efforts however, it is anticipated that there will be small numbers of cases where it is felt at baseline that chemotherapy or anti-HER2 therapy was not indicated, but at a later stage or following surgery the disease was found to be more extensive than anticipated; for example, patient with negative lymph nodes at diagnosis based on ultrasound assessment (+/- core biopsy or fine needle aspiration cytology) but with histologically positive lymph nodes at surgery. In these cases, adjuvant chemotherapy or anti-HER2 therapy should be given as per usual centre protocol. The control arm will follow usual clinical pathways after surgery. In the NET arm this will be after 6 months of NET and subsequent surgery. This possibility will be mentioned in the study literature for those who would opt for and be fit for chemotherapy should there be unexpectedly felt to be a benefit following surgery. If during the course of the study molecular profiling guidelines change, for example extending the indication for molecular profiling to node positive patients this will be permitted as part of a pragmatic “real-world” study design.

Patients with ER+ tumours where the HER-2 result is unknown or outstanding may be entered into the trial where this is felt by the treating clinical care team that chemotherapy/anti-HER-2 therapy would not be given, regardless of the result. If following trial entry and prior to surgery it becomes apparent that the tumour is HER-2 positive, participants will remain on the trial and within trial follow up and receive appropriate treatment.

5.6. The need for the EndoNET trial

During the COVID-19 pandemic, and its multiple waves, large numbers of patients within the UK and worldwide were placed on “bridging” NET until theatre capacity became available, despite lack of level 1

evidence. It is therefore important going forward to understand the significance, impact and effectiveness of a NET strategy, which continues to be used post-pandemic in secondary care UK hospitals.

If NET is shown to increase BCS rates (reducing mastectomy rates) and reduce burden of surgery (smaller volume resections, reduced re-excision rates and reduced axillary treatment) there would be significant benefit to both patients and to the NHS, including reduced quantity and extent of surgery, quicker recovery and progression to further adjuvant treatments, improved cosmesis, satisfaction, body image, self-esteem, sexuality and reduced anxiety and depression (8). These patient and health economic benefits are commensurate with the objectives of the national "getting it right first time" (GiRFT) initiative (60). The detrimental effects of mastectomy to HRQoL and body image persist regardless of age (20, 23, 24). Benefits to women of BCS include better HRQoL and a reduction in requirement for post-mastectomy reconstruction and its complications. For those treated by BCS, the benefits of NET potentially include reduction in excision volumes, fewer patients requiring for more complex BCS techniques and reduction in re-excision rates. Since ET is widely given and of low toxicity, benefit would be seen across the age spectrum. Improving cancer outcomes in the elderly is important (61) and as comorbidity and age increases, mastectomy is more likely, whilst reconstruction and chemotherapy (including as a neoadjuvant/downstaging option) is less frequently utilised (4).

Our trial design addresses the question defined in the NIHR brief which was also highlighted as important by NICE (26). The NICE systematic review compared NET to no NET (i.e. primary surgery followed by adjuvant treatment), or to NAC. The consensus amongst clinicians and patients was that the comparison of greatest clinical need was of NET compared to no NET since the majority (>70%) of post-menopausal women with ER+ breast cancer will not receive chemotherapy (4). Furthermore, despite advantages of NAC, a meta-analysis has failed to show benefit in terms of improvements in surgical outcomes (62), and a previous UK trial comparing NAC to NET closed due to failure to recruit (63). Our comparison of NET to no NET allows inclusion of patients less often included in clinical trials (e.g. older patients with co-morbidities) and provides a downstaging option for those who would not be treated with chemotherapy. Since all ER+ patients will usually receive adjuvant ET, it will allow us to apply the findings to a very wide group who would not benefit from NAC, and therefore would otherwise not have an option to have their tumour size reduced to facilitate less extensive surgery. A non-NET control arm also enables absolute quantification of the magnitude of effect on endpoints such as tumour shrinkage and breast conservation rates, as opposed to a relative quantification and would establish NET AI monotherapy as a safe comparator in future clinical trials of current and novel ET combinations, several of which are already established in the treatment of advanced disease.

5.7. The need for the Nested Qualitative Study (NQS)

The nested qualitative study (NQS) is a sub-study embedded within the main trial. The NQS, through the use of qualitative methods, will explore the experiences of participants in the trial and their subsequent treatments of breast cancer. This will provide context to the HRQoL data of women taking part in the trial and will guide and assist the analysis and interpretation of the HRQoL findings and outcomes.

It is important to implement the sub-study to ensure that questions that cannot be answered by the trial data alone, such as a lack of treatment effect, can be understood. Further information can be found in Section 9.15.

5.8. The need for Trans-EndoNET

Trans-EndoNET aims to characterise the relationship between patient insulin metabolism and tumour response to endocrine therapy in early breast cancer. Increased insulin levels are associated with higher breast cancer incidence and mortality. This will involve the collection of a fasted blood sample at baseline and use of the existing tissue samples collected for the main study. Trans-EndoNET will be conducted in a sub-set of participants at a later stage of the trial.

6. OBJECTIVES AND OUTCOME MEASURES

6.1 HYPOTHESIS:
Neoadjuvant endocrine therapy (NET) reduces breast cancer size prior to surgery, reducing surgical burden resulting in a higher proportion of patients treated with breast conservation surgery (BCS).

RESEARCH QUESTION: In post-menopausal women with ≥15mm, strongly ER+, invasive breast cancer, where chemotherapy or anti-HER-2 therapy is not planned, does NET increase the proportion of patients who have BCS by 15 months post-randomisation?

6.2 Primary and secondary outcome measures

	Objectives	Outcome Measures	Timepoints
Primary	The overall aim is to evaluate whether 6 (+/- 1) months of NET reduces surgical burden resulting in a higher proportion of breast conservation in post-menopausal women with ≥15mm, strongly ER+ breast cancer who are not planned or have not started chemotherapy or anti-HER-2 therapy [1]	Proportion of patients who have breast conservation (surgery)	15 months post-randomisation
Secondary	1. To evaluate whether 6 months of NET results in better HRQoL over 15 months[1]	1. Difference in global HRQoL (as measured by FACT-B)	1. Baseline, 6 weeks or post-operative, 5 and 15 months post-randomisation

	2. To evaluate tumour response rates following NET [2]	2. Response rates according to RECIST (USS, clinical, relative to baseline); MRI where used as part of local unit centre policy	2. 2-4 weeks, 3 and 5 months post-randomisation (NET arm)
	3. To compare invasive tumour size, histological grade and lymph node status (including number of involved nodes) in both arms [1]	3. Tumour size, histological grade and lymph node status pre-surgery and final histology post-surgery	3. Pre and post-operative
	4. To compare, in both arms, the HRQoL related to body image and surgery (FACT-B with ES and +4, Breast Q, EQ-5D-5L, Hopwood Body Image Scale [BIS]) [1]	4. Patient reported outcomes as measured by FACT-B (with ES and +4), Breast-Q, Hopwood Body Image Scale and EQ-5D-5L	4. Baseline, 6 weeks or post-operative, 5, 7, and 15 months post-randomisation [3]
	5. To provide an estimate of the risk of relapse and measure of endocrine sensitivity in NET arm [2]	5. Pre-operative Endocrine Prognostic Index (PEPI) score	5. Baseline sample, 2-4 week sample and post-operative sample
	6. To compare post-surgical complications and AI side effects in both arms [1]	6. Post-surgical complications, side effects; delays to commencement of subsequent treatment	6. 2-4 and 6 weeks, 3 months, 5, 7, 12 and 15 months post-randomisation
	7. To assess treatment compliance (MARS-5) [1]	7. Treatment Compliance and rates of cross-over	7. 2-4 weeks, 5 months and 15 months post-randomisation.
	8. To evaluate the prognostic significance of Ki67 [1]	8. Ki67 % in tumour cells, % reduction in Ki67 from baseline to biopsy or surgery	8. Baseline (both arms) and after 2-4 weeks of AI (in both arms) and at surgery (in comparator arm);

	9. To assess the surgical and locoregional management of the breast [1]	9. Rates of re-excision and further surgery after BCS; specimen weight after BCS; requirement for advanced BCS (therapeutic mammoplasty and local perforator flaps), rate of reconstruction postmastectomy, breast radiotherapy	9. Baseline, post-operative, 15 months post-randomisation
	10. To assess the surgical and locoregional management of the axilla [1]	10. Rates of sentinel node biopsy, axillary clearance, axillary radiotherapy	10. Baseline, post-operative, 15 months post-randomisation
	11. To compare rates of local and distant recurrence [1]	11. Rates of local and distant recurrence	11. 15 months post-randomisation, and periodically for long term follow up [3]
	12. To compare breast cancer specific survival in both arms [1]	12. Breast cancer specific and overall survival	12. 15 months post-randomisation and periodically for long term follow up [3]
	13. To assess the cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice of surgery followed by adjuvant ET for reduction in mastectomy (Health Care Use Questionnaire) [1]	13. Resource utilisation, cost and cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice.	13. Baseline, 6 weeks, 7 months and 15 months post randomisation
	14. To compare accuracy of Ultrasound	14. Accuracy of USS (and MRI where available) to	14. Up to 15 months post-randomisation

	(USS) and (MRI where available) for assessment of initial extent of disease and for detection of tumour response, using these two different imaging modalities [1]	determine conversion to BCS	
	15. To compare the requirement for adjuvant chemotherapy in both arms [1]	15. Number of patients receiving adjuvant chemotherapy in both arms	15. At 15 months.
Exploratory Objectives (optional sub-studies)			
Integrated research study (QuinteT Recruitment Intervention) to understand and address recruitment issues	1) To support recruitment processes from the outset of the trial, through: input with developing patient-facing information about the study and dedicated recruitment training for site-staff. 2) To understand recruitment issues arising in EndoNET in 'real-time', through: interviews with the trial team and site staff involved in recruitment processes; audio recording of recruitment discussions between site staff and patients; content analysis of study documentation, and quantitative analyses of screening logs. 3) To develop and implement 'actions' to support recruitment in collaboration with the TMG and PPI partners, based on findings from the above	In real time, from when the first site opens to recruitment until 12 months after the last site opens - 36 months of the recruitment period

Nested qualitative study (NQS). **The sub-study aims** to explore the experiences of patients during the trial recruitment period, generating an understanding of the acceptability and experiences of NET and subsequent treatments on women's HRQoL from the perspective of patients. This will guide and assist interpretation of HRQoL findings and outcomes.	1) To explore the experiences of participants in both the intervention and control arms of the trial to: • Understand participant experiences, beliefs and expections of NET • Generate an understanding of the acceptability of NET • Understand participant experiences of subsequent treatment after NET. 2) To understand how these experiences may affect their health-related quality of life, to help understand the FACT-B scores 3) To understand whether these experiences vary with participant characteristics (e.g. age, treatment type) and if so, how?	• Post-randomisation prior to NET starting, or as soon as possible after starting pre-surgical endocrine therapy • 6 months after surgery. • Participants in active follow up on the trial may also be interviewed at varying timepoints, for example if they have crossed over to early surgery.

Table 2: Primary and secondary outcomes measures

[1] Outcomes within objective measured in both the intervention (NET) and control arm.

[2] Outcomes within objective measured in intervention (NET) arm only.

[3] Breast-Q administered at baseline and 15 months only. EQ-5D-5L administered at baseline, 6 weeks, 7 months and 15 months only. Hopwood BIS administered at baseline, 5 months and 15 months only. FACT-B with ES and +4 administered at baseline, 6 weeks, 5 months and 15 months. Refer to schedule of trial procedures in Section 9.2.

[4] These are secondary objectives that will be assessed subject to additional funding and/or resource and via submission of an amendment, for example, at 5, 10 and 20 years or more within the EndoNET trial long follow up. Patients will be consented for long term follow-up on EndoNET trial entry.

7. TRIAL DESIGN

7.1 Type of trial

This is a prospective, phase III, parallel group, multicentre, superiority randomised controlled trial (RCT).

We will recruit a maximum of 1,060 (for 90% power) with a minimum of 792 (for 80% power) post-menopausal women with strongly ER+ invasive breast cancer who are not planned or have not started chemotherapy or anti-HER-2 therapy from secondary care UK hospital breast units. They will be randomised 1:1 to undergo 6 (+/- 1) months of NET followed by surgery and adjuvant ET or to surgery within 2-4 weeks (up to 8 weeks permitted for trial purposes) followed by adjuvant ET. Flexibility in the scheduling of a month either side of the target of 6 months in the NET arm and up to 8 weeks in the comparator arm is designed to accommodate the practicalities of the logistics of surgical planning. It was also highlighted an important factor by patients at the PPI meeting and is consistent with levels of pragmatic flexibility. Both arms receive the same treatment modalities (surgery, ET, and radiotherapy where indicated), but the sequencing of surgery will differ, with both arms starting ET at randomisation, with 6 months of the course of ET delivered prior to surgery in the NET arm. The primary outcome measure is the proportion of women who have BCS at 15 months. If aromatase inhibitor endocrine therapy has already been started following the current breast cancer diagnosis as part of routine care prior to joining the trial, then this is permitted, as long as trial entry is within 14 days of starting treatment.

The study duration is 69 months including, 6 months setup, 42 months recruitment, 15 months follow-up and 6 months data analysis and final reporting of results.

A formal stop/go review took place on 31st December 2023 to ensure 12 sites opened and 150 participants were randomised. The Funder granted a continuation of recruitment with a second review point in December 2024. Data from the internal pilot will be included in the final analysis.

7.2 Trial Schema (Main Trial)

Patient Related Outcome Measures (PROMs) will assess the participant's health status or HRQoL at individual time points and will be collected through questionnaires. PROMs include FACT-B (+4/ES), Breast-Q, BIS, EQ-5D-5L, Health Care Use Questionnaire and Compliance to ET/NET (MARS-5).

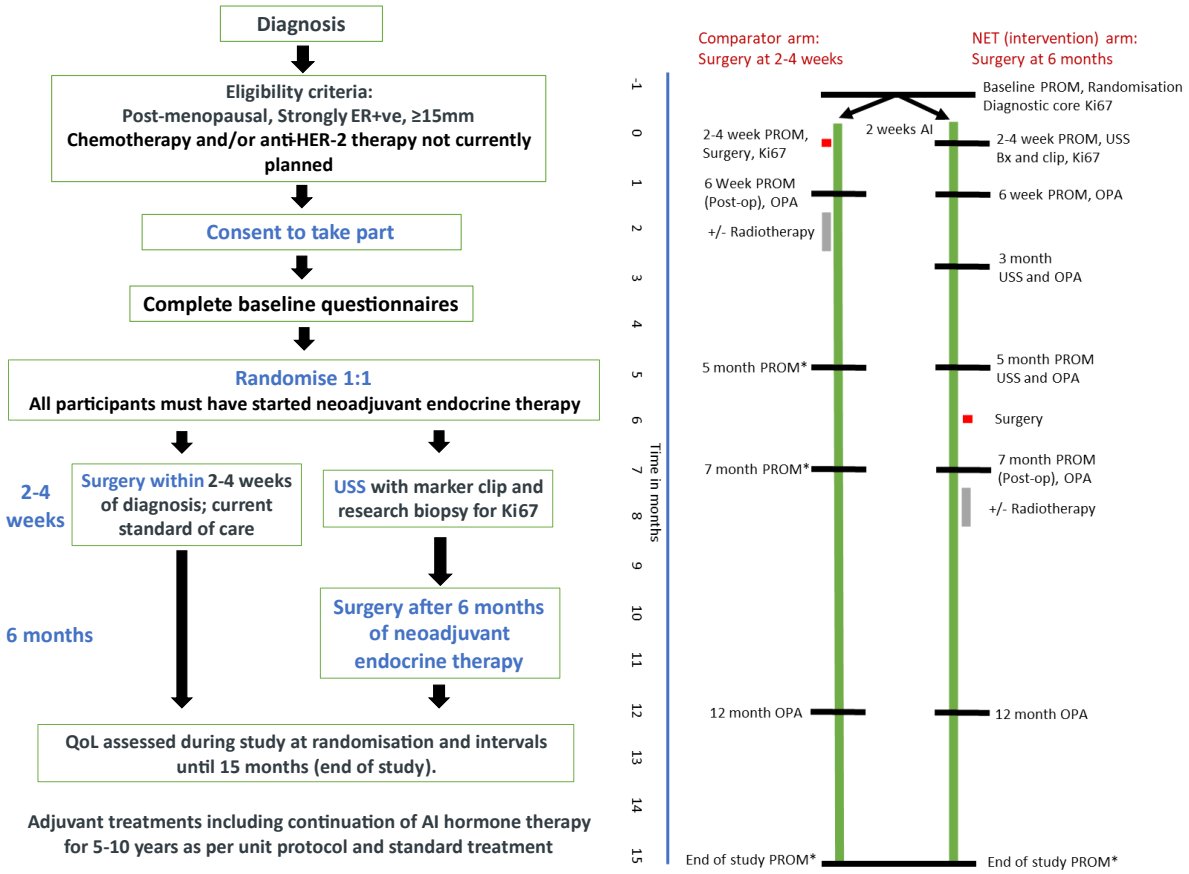

Figure 1. Left panel: Study schema. All participants should commence pre-surgical aromatase inhibitor endocrine therapy at randomisation if not already started as part of routine care; in comparator arm surgery at 2-4 weeks (within NHS 31-day target, although up to 8 weeks permitted for trial purposes) and in NET arm surgery at 6 months +/- 1 month. Additional core biopsy (Bx) and marker clip insertion at 2-4 weeks in NET arm. Right panel: All study measurement timepoints with corresponding clinical care visits for the two arms demonstrating study design to ensure comparability between arms and correspondence between timepoints and clinical pathway. Items marked * will be conducted remotely: PROMs either electronically or by posted letter (including by telephone in some circumstances) and outpatient appointment (OPA) by telephone.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Post-menopausal women with strongly ER+, invasive breast cancer who are not planned or have not started chemotherapy or anti-HER-2 therapy.

The optional QuinteT Recruitment Intervention (QRI) sub-study will also include Trial Management Group (TMG) members and researchers involved in recruitment as explained in section 9.2.1.

8.2. Main trial eligibility criteria

8.2.1. Inclusion Criteria

- Female;
- Clinically post-menopausal, according to established local criteria, and suitable for an aromatase inhibitor;
- Strongly ER+; defined as Allred scores of 7 or 8 or equivalent*
- Tumour size ≥15mm;
- Suitable for surgery and radiotherapy;
- 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*;
- Participant is able and willing to give informed consent for participation in the trial;
- In the Investigator's opinion, is able to comply with all trial requirements.

Notes:
*Or equivalent. May include a histochemical score (H-score) ≥ 200.

8.2.2. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Bilateral breast cancer;
- cN3 disease;
- cT4 disease *Note: T4 is defined as (i) chest wall (rib/intercostal) involvement (adherence/invasion to pectoralis is NOT 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;*
- Metastatic breast cancer (Stage IV disease);
- Chemotherapy or anti-HER-2 therapy for current breast cancer started or planned at time of randomisation;
- 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;
- Concurrent use (at the time of randomisation) of HRT or any other oestrogen-containing medication (including vaginal oestrogens) *Note: Presence of Mirena coil at time of randomisation is not an exclusion*;
- If clinically pre-menopausal, ovarian suppression/ablation for the purposes of trial entry not permitted;
- Aromatase inhibitor endocrine treatment following current breast cancer diagnosis taken for longer than 14 days at time of randomisation.

8.2.3. Protocol Waivers

Protocol waivers are **not** allowed; if a patient does not meet the eligibility criteria, they will not be randomised in the trial and will not form part of the trial.

8.3. QRI eligibility criteria

8.3.1. QRI Inclusion criteria

Patients:

- Patients approached for participation in the main trial;
- Patient inclusions are the same as for the main trial.

Health Care Professionals (HCPs) & Research Personnel (RP):

- HCPs or research personnel involved in management, operation or recruitment for the main trial;
- TMG members with a role in planning/coordinating recruitment.

8.3.2. QRI Exclusion criteria

Patients:

- Patient does not wish to have consultations recorded and/or participate in interview
- Patient exclusions are the same as for the main trial

Health Care Professionals & Research Personnel:

- HCPs or research personnel who do not wish to have consultations recorded and/or participate in interview

8.4. Nested Qualitative Study (NQS) criteria

8.4.1. NQS Inclusion criteria

- Patients who are taking part in the main trial.
- Patients who wish to take part in qualitative interview(s).
- Patient inclusions are the same for the main trial.

8.4.2. NQS Exclusion criteria

- Patient does not wish to participate in qualitative interview(s).
- Patient exclusions are the same as for the main trial.

9. TRIAL PROCEDURES

9.1. Schedule of trial procedures – sub-studies

9.1.1. Qualitative Recruitment Intervention (QRI)

A 'Information Study' (the QRI) will be integrated throughout the recruitment period of EndoNET, with the intention of investigating and addressing recruitment issues while the RCT is underway.

9.1.2. Nested Qualitative Study

A Nested Qualitative Study (NQS) is integrated in EndoNET, to investigate the experiences of participants in the main trial. It will focus on how well participants have tolerated their endocrine treatment and how this and their other breast cancer treatments have affected their quality of life. Qualitative interviews will take place after randomisation and whilst participants are taking part in the study. The study aims to recruit approximately 60 participants in total.

9.2. Schedule of trial procedures (Main Trial)

All follow-up visits in the standard of care comparator arm are designed to be in line with routine clinical practice with surgery by 31 days, as per NHS treatment targets (if this target is not met due to any local logistical or practical reason, the protocol will allow a window of up to 8 weeks, and therefore first surgery within 8 weeks does not constitute a protocol deviation). In the NET arm there are additional (excess treatment visits) for USS with core biopsy and marker clip at 2-4 weeks and for USS and clinical assessment at 3 months and 5 months. Assessment timings are designed to correspond to routine care visits and ensure that, wherever possible, participants are assessed at comparable timepoints in the care-pathway in both arms.

Participants will complete questionnaires electronically and be emailed links to complete HRQoL and Health Care-use questionnaires via the trial database of REDCap at baseline (pre-randomisation), 2-4 weeks, 6 weeks, 5 months, 7 and 15 months, with an option to be contacted by the Surgical Intervention Trials Unit (SITU) by posted letter with a paper version of the questionnaires, if the participant expresses this as their preference. In some circumstances, participants may complete questionnaires by telephone. The trial team may also contact participants by telephone if questionnaires are overdue or to query missing data, and this will be limited to two contacts before no further reminders or queries are made.

Visits / Procedures	Baseline – Day 0		2-4 Weeks (up to 8 weeks permitted)	6 Weeks (+/- 2 weeks)	3 Months (+/- 1 month) [N]	5 Months (+/- 1 month)	6 Months (+/- 1 month) [N]	7 Months (+/- 1 month)	12 Months (+/- 1 month)	15 Months (+/- 1 month)
	Pre-randomisation	Randomisation								
Screening and eligibility assessment	X									
Consent (QRI & main trial) [1]	X									
Audio recording (QRI only)	X									
Participant questionnaires: FACT-B+4/ES	X			X		X				X
Hopwood BIS	X					X				X
Breast-Q	X									X
EQ-5D-5L	X			X				X		X
Health care use	X			X				X		X
Compliance to NET/ET (MARS-5)			X			X				X
Randomisation		X								
Initiation of aromatase inhibitor (AI) treatment	X									
Baseline data collection	X									
Consent (NQS only)			X							
Qualitative interview (NQS only)			X					X^C	X^N	
Clinical assessment of tumour	X				X^N	X^N				
Surgery			X^C				X^N			
Ultrasound scan of tumour			X^N		X^N	X^N				
Research core biopsy (for Ki67 analysis) and clip marker insertion[2]			X^N							
Serious adverse events (SAEs)	X (SAEs related to the AI treatment are reportable until surgery as defined in Section 11.8)									
Outcome data collection	X	X	X	X	X^N	X^3	X^N	X^3	X	X^4

Notes: [N] NET arm only. [C] Control arm only. [1] Recommended more than 1 day before randomisation. [2] If marker clip is not already inserted at baseline. [3] Non-clinic visit in control arm. Requires research nurse to call participant. [4] Non-clinic visit in both arms. Requires research nurse to call participant.

9.3. Recruitment

Women will be recruited for this study from any breast cancer, screening, diagnostic, surgical and/or oncology clinics and screened for eligibility through multidisciplinary meetings and will be introduced to the study following diagnosis. The study will be introduced to potential participants by their clinical team during their routine care. Women who express an interest will then be given a patient information sheet and permission asked for a research nurse to contact them to discuss the study. After consenting, participant will be randomised 1:1 to undergo 6 (+/- 1) months of NET followed by surgery and adjuvant ET or surgery within 2-4 weeks (up to 8 weeks permitted for trial purposes) followed by adjuvant ET.

We may set up trial specific social media accounts to publicise the study and news relating to it, however no recruitment will be conducted through these accounts. There will be a dedicated website which will act as a hub of information for patients and the public seeking more information on the trial. The trial team may produce videos related to the trial, including animation videos which explain the trial in more detail. Additional videos which provide the latest news, our work with PPI, and developments in breast cancer research may be created. Specific videos involving discussions between clinicians and patients with breast cancer may also be used to discuss some of the key themes on the trial such as the importance of the research and frequently asked questions. Newsletters for patients and their family/friends may also be produced which shares the latest news relating to the trial and important information about the trial. We intend to use a trial poster for recruitment purposes in hospitals and clinics.

We aim to recruit patients from approximately 30 NHS Trusts across the UK. We estimate that each NHS centre treats approximately 30-100 eligible patients per year, depending on the size of the centre. Assuming conservative recruitment rates of 30-40% of eligible women, it is anticipated that each site will recruit 1-3 patients per month. Assuming staggered opening of 30 sites over a 20-month period, to allow for approvals to be obtained at each site (an average of 1.5 sites open per month), we consider a recruitment target of at least 792 women feasible.

To facilitate recruitment and mitigate against potential issues, we have integrated a QuinteT Recruitment Intervention (QRI) into the study.

9.3.1. QuinteT Recruitment Intervention (QRI) Study

The QRI will be implemented in EndoNET with the aim of optimising recruitment. Rather than simply increasing the numbers of patients recruited, the QRI will aim to reduce ‘missed opportunities’ for enrolling eligible patients, while safeguarding informed consent. We will draw on insights from application of QRI methods to previous RCTs and the latest recruitment related evidence to develop material and training to support participant accrual from the outset of EndoNET (see 9.2.1.1 below) (99). Once centres open to recruitment, the QRI will proceed by investigating and addressing recruitment issues that transpire ‘in real time’ throughout the remainder of the scheduled recruitment period (see sections 9.2.1.2 and 9.2.1.3 below).

9.3.1.1. *Pre-emptive training and materials to support recruitment to EndoNET*

The QRI team (the QRI lead and appointed QRI researcher, based at University of Bristol) will work closely with the EndoNET Trial Management Group (TMG) to support recruitment to EndoNET from the study

outset. This will include contributions to writing patient-facing documentation (e.g. patient information sheets) and the design of screening logs to monitor recruitment to EndoNET. The QRI team will also design and deliver pre-emptive recruitment training that will be tailored to EndoNET. Drawing on evidence from previous QRIs, this training will provide strategies for conveying equipoise, explaining trial concepts (e.g. randomisation) and engaging with patients' views and preferences about treatment. The training will be integrated into Site Initiation Visits (SIVs) and delivered at multi-site investigator meetings (e.g. the trial launch). We will also produce and disseminate pre-emptive 'tip and guidance' sheets for recruiters to reinforce this training and provide early support for explaining the trial to eligible patients. Once centres open to recruitment, the QRI will proceed by investigating and addressing recruitment issues in 'real-time' through two iterative phases, as described below.

9.3.1.2. *Understanding recruitment issues that transpire in EndoNET (phase 1)*

Mixed-methods will be used to investigate actual (rather than anticipated) issues hindering recruitment to EndoNET as the trial proceeds. A flexible approach will be taken to investigate these issues in real-time, using one or more of the following:

a. Semi-structured interviews with i) members of the Trial Management Group (TMG), ii) individuals involved in recruitment ('recruiters'); iii) patients invited to consider participating in the trial

Interviews with members of the TMG (n≈5-10) and recruiters (i.e. research and/or clinical personnel involved in trial recruitment) (n≈10-25) will be conducted to investigate perceptions of equipoise, interpretations of the RCT rationale and underpinning evidence, recruitment challenges encountered (where relevant), and how recruitment is organised within and across centres. Interviews with patients may also take place if further information is needed to better-understand the reasons underpinning recruitment issues. Patients will be purposefully selected, to build a sample of maximum variation based on the centre/clinic they attend, their decision about trial participation (i.e. accept or decline), and any other clinical characteristics that are deemed meaningful (informed by emerging insights form the QRI). Numbers of interviews for each arm will be guided by intentions to achieve saturation and pragmatic factors (i.e. finite numbers of recruiters/TMG members).

Interviews are anticipated to take around 45 minutes, and will be conducted remotely, via telephone or secure web-conferencing platforms that have been approved by the study sponsor at the time of data collection. As guidance around recommended platforms can vary, we will ensure that the QRI researchers are attuned to the latest guidance and policies to ensure secure data collection throughout the project.

b. Audio-recording recruitment discussions

Recruiters' explanations of the trial will be audio-recorded with encrypted audio-recording devices supplied by the QRI team. We will ask recruiters to audio-record appointments where they discuss the trial with eligible patients. This will provide direct insight into how the trial is presented by recruiters and interpreted by patients. We will pay particular attention to: i) whether the trial interventions are described in a clear, accurate and balanced way; ii) ways in which recruiters manage patients' treatment preferences; and iii) explanations of trial processes (e.g., randomisation, follow-up).

c. Mapping of recruitment pathways and screening log analyses

The screening log for EndoNET will capture information about each patient screened, including whether they were eligible, approached and randomised. The interviews with recruiters (above) will be used to map out the recruitment pathway for each centre, noting processes for screening and identifying eligible patients, how patients are approached, and the personnel involved in these activities. Recruitment pathways will be compared with screening log data to identify points where patients are lost, and practices that are conductive or counter-productive to efficient and effective recruitment.

Findings from the above sources will be triangulated (see 'QRI analysis' below) to generate an in-depth understanding of the 'root-causes' of recruitment issues in EndoNET. This will provide a foundation for designing and implementing 'actions' to optimise recruitment, as discussed below.

9.3.1.3. *Development and implementation of 'actions' to address recruitment challenges (Phase 2)*

The QRI team will work closely with the TMG and PPI partners to design and implement 'actions' to optimise recruitment. These actions will be tailored to address the root-causes of recruitment issues, based on Phase 1 findings. Actions may be applicable to all centres, specific centres, or individual recruiters, and will aim to increase the number of eligible patients approached, and/or improve conversion rates whilst safeguarding informed consent.

***Cross-centre actions*:** may include disseminating 'tips' documents with suggestions on how to explain the trial design and convey equipoise – a skill that is often trial-specific, as it requires an appreciation for the distinct advantage/disadvantages of the trial arms and patients' perceptions of these arms. Cross-centre actions may also entail changes to patient-facing materials (e.g. to address commonly held patient misconceptions). Group 'feedback sessions' will also be organised, to address recruitment issues that are rooted in clinicians' variable interpretations of eligibility criteria and different perceptions of equipoise. Bringing recruiters together to air these issues can be a powerful means of challenging ingrained views and practices.

***Centre-specific interventions*:** may entail changes to how recruitment is organised and delivered in a particular centre, facilitated by sharing examples of 'good practice' from other centres that have more efficient and effective recruitment models. These interventions will be delivered through site visits conducted in person or remotely (e.g. using web conferencing software).

A core component of Phase 2 will focus on delivering feedback on recruiters' communication with patients. Interactive 'feedback sessions' will be delivered to groups of recruiters (e.g., during centre visits, or multi-centre events). These sessions will use anonymised extracts from audio-recorded consultations to illustrate how recruiters' communication can influence patients' responses to invitations of trial participation. Training videos showing simulated recruiter-patient interactions may also be developed. Individual confidential feedback will be offered to recruiters who provide recordings of their consultations.

9.3.2. Iterative nature of QRI phases

The QRI phases described above will run iteratively. New avenues of enquiry will emerge throughout the conduct of the QRI, through discussion in feedback meetings and continued monitoring of screening logs.

We will pay close attention to screening log data before/after QRI-actions to formatively evaluate the impact of actions, and the need for further investigation (Phase 1) or actions (Phase 2). As mentioned above, part of the QRI will entail up-front training for centres as they open to recruitment. This training will evolve to become increasingly trial-specific as we develop our understanding of recruitment issues, with a view to ensuring centres that open in the latter stages of the trial benefit from the QRI insights that have emerged to date.

9.3.3. Analysis of QRI data

Screening log data will be analysed and summarised descriptively. All qualitative interviews will be audio-recorded using digital encrypted recorders, transcribed verbatim, and edited to ensure anonymity. Audio-recordings will be transcribed by internal University of Bristol staff or an external transcription company which has signed the necessarily University of Bristol confidentiality agreements. Transcripts will be linked-anonymised. Interview data will be managed using NVivo software (QRS International) and analysed thematically using constant comparative approaches adopted from Grounded Theory (76). Audio-recorded recruitment consultations will be subjected to content, thematic, and novel analytical approaches, including targeted conversation analysis and appointment timing (the 'Q-Qat method') (94). There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Standard approaches to enhancing rigour, such as double-coding, triangulating, and seeking out 'negative cases', will be employed throughout the conduct of the QRI. A detailed description of how the QRI methodology achieves rapid analysis whilst maintaining rigour is detailed elsewhere (77).

9.4. Screening and Eligibility Assessment (Main Study)

Patients will be screened for eligibility at breast, surgical and diagnostic clinics and breast multidisciplinary team (MDT) meetings, by members of the direct clinical care team including but not limited to surgeons, oncologists and research nurses and/or practitioners. Eligibility will be confirmed by a doctor and if eligible patients will be provided with the study patient information sheet prior to informed consent being obtained. Participation in other clinical trials is permitted provided the endpoints do not confound/conflict with EndoNET. The TMG will be informed by the trial management team of any requests for study co-enrolment, including the nature of the study and its endpoints. The Chief Investigator(s) of each study will determine whether co-enrolment is acceptable.

9.4.1. Screening logs

Screening logs are essential to monitor EndoNET recruitment. *A dedicated, EndoNET specific screening log will be designed with input from the QRI team*. The electronic screening log per site will be updated in real-time. All post-menopausal women with strongly ER+, HER2- invasive Breast Cancer who are unlikely to require chemotherapy should be screened for trial participation and entered onto the screening log in advance of discussion at the breast MDT meeting.

The MDT meetings should ideally identify and record those patients who are eligible for EndoNET, but the route for identifying eligible patients may vary in different centres. For each potentially eligible EndoNET patient, the outcome of the screening process will be captured: eligibility (Y/N) and reason ineligible;

approached for trial (Y/N) date approached or reason not approached; and decision about trial participation – randomised (Y/N) and randomisation outcome and (if relevant) treatment selected; or reason not randomised and treatment selected.

9.5. Informed Consent

The Participant Information Sheet (PIS) and the Informed Consent Form (ICF) will be presented to the patients. The patient must personally sign and date the latest approved version of the ICF before any trial specific procedures are performed. The PIS introduces the nature of the trial; what it involves for the patient; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It also explains that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. The QRI is explained in a separate QRI 'Information Study' PIS and will detail the QRI processes, the voluntary nature of participation, and rights to withdraw.

The patient will be allowed sufficient time and to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial.

Informed written consent may be obtained in person (e.g. in clinic) or remotely. An electronic version of the ICF will be offered to patients in clinic as a form on a tablet device if available (with the consent form being filled in directly on REDCap), or on paper if specifically requested. Where it is not possible for a consent form to be completed in clinic (for example; during the Covid-19 pandemic where patients have only had telephone appointments), remote electronic informed consent will be obtained by means of an e-consent form emailed securely to patients as a link via the trial's instance of REDCap. This emailed link will direct the patient to an electronic consent form on REDCap, which is identical to the electronic consent form used in clinic on a tablet device. After the patient has had sufficient time to consider the information and ask any questions that may arise from the written information, the remote electronic consent form will be signed with a participant dated signature. The consent form will be counter-signed by the individual who has been delegated the responsibility of confirming consent and who has been involved in the process.

As EndoNET is a Type A trial, under HRA/MHRA guidance (https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf), patients using e-consent in person or clinic will be required to provide a simple electronic signature in the form of a handwritten signature using a finger or a stylus on their tablet, mobile phone or other electronic device. It is also possible to sign the consent form using a computer and web-browser, provided the patient has access to the internet. If patients are unable to use the internet or do not have access to an email address, paper-based methods will be sought. The electronic consent form will include a participant dated signature and will be counter-signed by the individual who has been delegated the responsibility of confirming the consent.

The paper consent form (if requested by the patient) will include a participant dated signature and dated name of the person who presented and obtained the Consent. The person who obtains the consent must be suitably qualified and experienced and have been authorised to take consent by the site's Principal Investigator. If electronic consent or electronic remote consent is obtained, a copy of the signed Consent

Form will be emailed securely via the trial's own instance of REDCap as a PDF to the participant (or a printed version provided if requested), a copy placed in the medical notes, and the original will be retained securely on REDCap.

9.5.1. QRI consent process

a. QRI consent processes for TMG members and recruiters

TMG members and recruiters (defined above) will be invited to take part in a QRI interview and/or audio-recording of recruitment appointments, as is appropriate to their role. Individuals will be informed about the QRI study processes via a single QRI information sheet, which will be disseminated at Site Initiation Visits (if conducted in person) or via email. The information sheet will explain the QRI processes described above (specifically, interviews and audio-recording of recruitment consultations). Research nurses or the QRI researcher will obtain written consent from TMG members/recruiters using a 'QRI consent form for health care professionals and research personnel', which will seek permission for each of the individual QRI elements described above. Potential participants may opt to participate in just one, both, or neither of the QRI activities.

If infection transmission mitigation strategies are in place (e.g. during the Covid-19 pandemic) at the time of data collection, we will employ a remote consent process. Potential participants will be sent a copy of the study information sheet and consent form via email. The QRI researcher will call the HCP or research personnel and read each statement on the 'QRI consent form for health care professionals and research personnel', initial these as the HCP or RP responds in the affirmative, and sign to confirm consent has been obtained. All QRI consent forms will be sent to and/or retained at sites.

b. *QRI consent processes for patients*

The dedicated QRI PIS explains the QRI study processes: specifically, the audio-recording of recruitment discussions and the possibility of patients being approached for an interview. We will employ a two-step consent process for audio-recording recruitment discussions. In brief:

- Audio-recording of consultations will only proceed if the TMG member/recruiter has also provided consent. A health care professional or research personnel will obtain verbal consent to record the initial discussion about EndoNET. If the patient agrees, the professional will record the outcome on the QRI consent form and sign to document that verbal consent has been obtained, and the discussion will be audio-recorded. This is necessary, given the intention to capture how the RCT is introduced to and received by patients.
- Patients will receive the PIS in the above clinic visit and will be provided sufficient time to ask any questions and consider their participation in the QRI.
- A healthcare professional or research personnel will obtain informed consent for the QRI study during a subsequent visit or remote discussion, using the dedicated QRI consent form. The consent form will include individual clauses relating to use of audio-recorded consultations, and the possibility of being contacted for a future interview to discuss how patients reached their decision about RCT participation. If informed consent for the audio-recording of consultations is obtained, the recordings will be sent to the QRI team. If consent is not obtained, any recordings already collected will be deleted.

Patients may accept or decline participation in the audio-recordings, interviews, or both elements of the QRI study. They will be informed that their decision about QRI participation will have no bearing on their decision about RCT participation, and that patients may participate in the QRI if they have declined the RCT participation. Informed consent for the different elements of the QRI (i.e. audio recording consultations and interviews) will be recorded on the dedicated QRI ('Information Study') consent form.

9.5.2. Nested Qualitive Study (NQS) Consent

Participants in the main trial are asked if they are willing to be contacted about taking part in future research. Of those participants indicating a willingness to be contacted, the University of Oxford's instance of REDCap will automatically send an email to the NQS researcher to notify them when a participant has been randomised into the trial.

The NQS researcher at the University of Southampton will login to REDCap or the Study Information Management System (SIMS) to view pseudonymised data including: screening ID number, age category (for example <60 years old), randomisation outcome and recruiting hospital, baseline surgical plan (BCS vs. mastectomy) and nodal status. Potential participants will then be purposefully selected based on selective sampling criteria and the NQS researcher at the University of Southampton will ask the central trial team at the University of Oxford to provide that potential participant with a copy of the NQS invitation letter or email, NQS information sheet, copy of the ICF and reply slip/envelope.

If potential participants are interested in learning more about the NQS and are considering taking part, they can return the reply slip to the University of Southampton using the freepost envelope provided. If they do not want to take part, the reply slip contains an option to indicate they are not interested in participating. The reply slip also indicates that they can contact the researcher by phone/email instead to provide their response. If potential participants do not return the reply slip, they will be contacted by the University of Oxford by phone/email to check if they are interested in the study. If they are interested, they will be given the contact details of the University of Southampton team and be asked to contact them directly. If they do not want to take part, no further communication will be made.

The potential participant will be given sufficient time to consider the information and the NQS researcher at the University of Southampton will call the potential participant usually within 7 days. This will provide sufficient time for the patient to review the NQS information further, whilst also enabling the first interviews to take place as soon as possible after they have started their endocrine therapy. Potential participants will be given the opportunity to ask any questions that may have arisen from the written materials and will be asked if they would like to take part. The NQS researcher will then arrange a date to consent the patient and conduct the first interview, ensuring that they have received a copy of the invitation pack in advance.

Only a small number of main trial participants will be contacted and only those who have indicated a willingness to be contacted about future research will be asked about the NQS. In order to minimise fatigue for those women who do not use a reply slip, the follow up phone call to potential participants by the University of Oxford will be kept short and it will be established quickly whether they are happy to hear more information on the NQS and if they have already responded to the University of Southampton. It is necessary to follow up with participants promptly after the invitation letter, rather than solely relying on

participants contacting the central trial team using a reply slip, to ensure discussion of the NQS occurs in a timely manner after the receipt of the information. It is important for interviews to take place promptly after randomisation as the integrity of the qualitative interviews and their findings depends on talking to women who have recently started their hormone treatment and before any side effects have developed.

The NQS researcher will call the potential participant on the agreed date using their preferred method, either by telephone or videoconferencing (Microsoft Teams). Verbal consent (audio-recorded on an Olympus DS-9000 audio recorder with encryption) will be obtained by the NQS researcher reading out each statement on the consent form to the patient. The participant will say "yes" to each statement if in agreement, with the researcher recording the outcome on the consent form before the interview starting. The researcher will sign and date the consent form to conclude the consent process. The audio-recorded consent and original version of the ICF will be stored securely at the University of Southampton and a copy of the ICF will be sent securely to the participant by post or email.

9.6. Randomisation (Main Trial)

We will randomise eligible patients using the centralised validated computer randomisation program through a secure (encrypted) web-based service, RRAMP (https://rramp.octru.ox.ac.uk), provided by the Oxford Clinical Trials Research Unit (OCTRU), accessed via the study's REDCap instance, with a minimisation algorithm to ensure balanced allocation across treatment arms, stratified in a 1:1 ratio to either NET followed by standard of care or standard of care using:

- Age group (<60, 60-70, 70+ years);
- Nodal status (N0 vs N1 or N2);
- Recruiting centre, and
- Surgical indication at baseline (BCS vs mastectomy)

To ensure the unpredictability of treatment allocation the minimisation algorithm will include a probabilistic element and a small number of participants randomised by simple randomisation. Stratification by centre will help to ensure that any centre-effect will be equally distributed in the trial arms and enable practical issues associated with the active intervention to be overcome. In the unlikely event that the randomisation system is down for any reason, if delays in randomisation occur to such an extent that they impact treatment planning felt to affect the prognosis of the participant, then they will be withdrawn and returned to the usual standard of care pathway if deemed necessary by the treating clinician. For participants who do not wish to or who are unable to comply with their randomisation outcome (according to the investigator and/or clinical team), they will continue to participate in the study but will be analysed on an intention to treat basis.

9.7. Blinding and code-breaking

Due to the nature of the intervention, it is not possible to blind individuals for the purpose of the trial. However, a pre-specified statistical analysis plan will be written in advance of un-blinding the data and any comparative analyses.

9.8. Baseline Assessments (Main Trial)

Case Report Forms (CRF) will include collection of routine clinical data including patient and tumour characteristics, co-morbidity (using the Charlson Comorbidity Index) and cancer treatments and progress through treatment pathway. This information will be collected as required to describe the cohort and assess the representativeness of those recruited within the study to the general breast cancer population. It will also be used to explore for association and relationships between variables and to control for potential confounders.

The information will be recorded on the web-based form (which goes straight into the password protected study database) by the attending clinician or delegate including a member of the research team and in addition to routine clinical data, patient and tumour characteristics will also include:

- Ethnicity
- BMI (height/weight)
- Family history of breast cancer (first degree relatives only)
- Major comorbidity and medical history
- Questionnaire preference (email/post).

9.9. Trial imaging (Main Trial)

9.9.1. Imaging for trial purposes

USS +/- breast MRI, are used in most centres to monitor response to preoperative neo-adjuvant treatment. In the NET arm USS is required 2-4 weeks after start of treatment in order to place the marker clip and take core biopsies for Ki67 measurements. USS is then required at 3 and 5 months to evaluate any possible tumour response to the AI. If a patient has dense breasts or a discrepancy between mammography and USS size estimates a baseline MRI is undertaken to assess disease extent. If local policy, the participant may have MRI at the follow up timepoints (e.g. at 3 and/or 5 months) to correspond to the USS evaluation. If breast MRI is standard practice for neo-adjuvant treatment at a centre then this may be used in this trial, in addition to USS.

Baseline USS examination should include examination of the whole breast to assess disease extent. The tumour is measured in at least two dimensions (usually perpendicular to each other) and documented in millimetres with the accurate position of the probe recorded and images archived to improve inter-observer accuracy. In line with standard practice, the maximum tumour diameter will be recorded and used to assess tumour response using RECIST 1.1 criteria (102). It is advised that for the 3 and 5 month USS in the NET arm, that the radiologist should review any previous image(s) in order to try and replicate the same measurement planes to minimise the subjective bias in USS. It is also recommended that USS images are captured in both planes. This will also allow for use in future research.

The axilla should be assessed carefully prior to entry to the trial by USS (as per national guidelines for all patients with invasive breast cancer) with any abnormal nodes biopsied by core biopsy or fine needle aspiration cytology (FNAC). The number of abnormal nodes should be recorded and documented. USS guided core biopsy and marker clip insertion is undertaken at 2-4 weeks. Prior to biopsy the tumour size is measured taking care to use the same positioning as the baseline examination.

MRI examinations if undertaken should follow local protocol.

9.9.2. Imaging for standard of care

Baseline USS examination should include examination of the whole breast to assess disease extent. The tumour is measured in at least two dimensions (usually perpendicular to each other) and documented in millimetres with the accurate position of the probe recorded and images archived to improve inter-observer accuracy. In line with standard practice, the maximum tumour diameter will be recorded and used to assess tumour response using RECIST 1.1 criteria (102).

The axilla should be assessed carefully prior to entry to the trial by USS (as per national guidelines for all patients with invasive breast cancer) with any abnormal nodes biopsied by core biopsy or fine needle aspiration cytology (FNAC). The number of abnormal nodes should be recorded and documented.

If a patient has dense breasts or a discrepancy between mammography and USS size estimates a preoperative MRI is undertaken to assess disease extent. Any additional disease which would alter planned surgical procedure should be biopsied to confirm the abnormality is indeed malignant.

MRI examinations can be undertaken at 1.5T or 3T machines. T2W, Pre and post contrast sequences are undertaken at minute intervals up to 6 minutes with a pixel size of less than 2 mm x 2mm and slice thickness of 2 mm. Diffusion weighted imaging is undertaken with b values of 60 and 800 so that ADC can be calculated. The entire examination should be less than 30 minutes in length while aiming to achieve highest resolution imaging with good temporal dynamic post contrast imaging.

9.10. Surgical treatment (Main Trial)

Since surgical treatments constitute the primary endpoint, and several of the secondary endpoints, these will be recorded in detail within the CRFs. Surgery to the breast will be mastectomy or breast conservation according to local protocols, national guidance and surgeon and patient agreement. Immediate breast reconstruction and oncoplastic procedures will also be performed as appropriate. Following breast conservation clear margins should be obtained. Margin involvement will be according to local and national protocols and if margins are considered involved re-excision should be performed.

Surgery to the axilla will also be according to local protocols, national guidance and surgeon and patient agreement. Sentinel node biopsy (SNB) should be performed where pre-operative staging indicate no axillary node involvement. Where axillary node involvement is confirmed pre-operatively SNB or axillary dissection is acceptable according to the clinical situation and local and national guidance. In the NET arm clip placement or others forms of localisation of axillary nodes confirmed to be involved pre-NET is acceptable according to local protocols and where required for targeted axillary dissection. Where the sentinel node shows evidence of involvement (micro or macrometastases) further treatment should be according to local and national protocols and can include monitoring, completion axillary clearance or radiotherapy.

9.11. Histopathology

Diagnostic, post-surgical and further surgery histopathology data will be collected on dedicated CRFs. We have used the fields recommended in the RCPath dataset for histopathological reporting of breast cancer

surgical resections as score cancer minimum dataset fields (https://www.rcpath.org/uploads/assets/7763be1c-d330-40e8-95d08f955752792a/G148_BreastDataset-hires-Jun16.pdf).

9.12. Radiotherapy

9.12.1. Breast Radiotherapy

Radiotherapy, where required, should be given according to local protocols and national guidance. Consistent with NICE NG101 guidance for neo-adjuvant chemotherapy, both pre-treatment imaging findings as well as post-surgical histology should be considered in radiotherapy decision making in patients allocated to NET. Partial breast radiotherapy can be considered following breast conservation where tumour size is 3 cm or less on imaging at presentation and final histology. We note the recent adoption of a 5 fraction regimens nationally. The same radiotherapy fractionation protocol should be used for patients in both arms of the trial in individual centres.

Radiotherapy data will be collected on a dedicated CRF and will include information on whether the participant received radiotherapy, the type of radiotherapy and dosage. Further information related to the details of the radiotherapy given will also be recorded.

9.13. Subsequent Follow Up Visits

All follow-up visits in the standard of care comparator arm are in line with routine clinical practice with surgery by 2-4 weeks (up to 8 weeks permitted for trial purposes), as per NHS treatment targets.

In the NET arm, there are additional visits for USS with core biopsy and marker clip at 2-4 weeks and for USS and clinical assessment at 3 months and 5 months. Assessment timings are designed to correspond to routine care visits and ensure that, wherever possible, patients are assessed at comparable timepoints in the care-pathway in both arms.

Participants will complete questionnaires electronically and be emailed HRQoL and Health Care use questionnaires via REDCap at baseline, 2-4 weeks, 6 weeks, 5 months, 7 and 15 months, with an option to be contacted by the Surgical Intervention Trials Unit (SITU) by posted letter with a paper version of the questionnaires, if the participant expresses this as their preference. Participants may be contacted by telephone for any outstanding PROMs/questionnaires. In some circumstances, where it is not feasible to complete questionnaires using our preferred method(s), participants may complete questionnaires over the telephone. This may be due to a patient being located in a remote geographical location. Participants may be contacted by the central trial team to query any overdue data.

9.14. Sample Handling (Main Trial)

9.14.1. Sample handling for standard of care

The breast core biopsy samples (and any other relevant diagnostic samples, such as lymph node core biopsies or FNACs) should be fixed, processed and reported as per the latest UK guidelines. ER and HER2

should be assessed and reported on the diagnostic core biopsy, again as per UK RCPath guidelines, in a centre which (as mandatory) participates in UK NEQAS, or equivalent (https://www.rcpath.org/uploads/assets/4b16f19c-f7bd-456c-b212f557f8040f66/G150-Non-op-reporting-breast-cancer-screening-Feb17.pdf).

All breast and lymph node surgical specimens should be handled and reported as per the latest UK guidelines(https://www.rcpath.org/uploads/assets/7763be1c-d330-40e8-95d08f955752792a/G148_BreastDataset-hires-Jun16.pdf).

9.14.2. Sample handling for trial purposes

Participants in both arms will receive, as standard of care, a breast core (or percutaneous image guided) biopsy for diagnosis. A further sample should be available from the surplus tissue at surgery. The trial will request tissue surplus to diagnostic requirements from biopsy blocks at baseline and the resected surgical specimen. In the NET arm, a further research core biopsy of the tumour will be taken for the trial, at the same time as the marker/clip is inserted after 2-4 weeks. All samples collected for the trial will be labelled with a unique trial ID number. Sample cores collected will vary in size, but usually those taken from diagnostic samples and from the 2-4 week clip insertion (NET arm only) will be the equivalent to a few grains of rice.

The research core biopsy samples should be formalin fixed and processed as per the latest UK guidelines (https://www.rcpath.org/uploads/assets/4b16f19c-f7bd-456c-b212f557f8040f66/G150-Non-op-reporting-breast-cancer-screening.pdf). H&E examination should be undertaken to confirm the presence of breast carcinoma; full histological review and report for this sample is not required.

The core biopsy specimen blocks (both from diagnostic and research cores) and representative block(s) from the surgical specimen will be collated by the Faculty of Medicine Tissue Bank at the University of Southampton (HTA Licence No: 12009) as part of this study. Sites are responsible for ensuring that samples are sent securely to the Tissue Bank with the appropriate tracking documentation in place. Samples should be packaged safely and appropriately under the right environmental conditions accompanied with a signed and dated consent form. The Tissue Bank is responsible for storing the samples under the appropriate environmental conditions and for tracking the samples with the relevant documentation.

The tissue blocks will be transferred to the Comprehensive Cancer Centre at Guy's Hospital (London, UK) from the Faculty of Medicine Tissue Bank at the University of Southampton in batches for biomarker analysis (such as Ki67), where there will be stored as part of this study at the King's HealthCare Cancer Biobank (HTA Licence No: 12121) and where study assays will be undertaken and until results are finalised Following completion of trial analysis all specimens will be returned from the Comprehensive Cancer Centre at Guy's Hospital to the University of Southampton Faculty of Medicine Tissue Bank.

Biomarkers such as Ki67 will be assessed at baseline (both arms), 2-4 weeks (NET arm only) and from the resected surgical specimen (both arms). Depending on developments, the exact detail of how Ki67 and other biomarkers will be determined may be modified to ensure it is consistent with current methodology and recommendations at the time of testing, however samples will all be analysed in the same way to ensure consistency. The assessment is not required in real time for decision-making and will be examined centrally in batches. As the vast majority of centres will not assess Ki67 locally (as this is not routinely

reported and because of recognised laboratory variation), repeat assessment of Ki67 on all cores will be undertaken, with Consultant Pathologist oversight, even if previously assessed locally.

At any point the referring laboratory may request the diagnostic core biopsy be returned if needed for additional tests locally. At the end of the trial, blocks originally taken for clinical purposes will be returned to recruiting centres. Blocks taken for research purposes will be retained for further translational studies and in accordance with the trial consent for the use of these anonymised samples in future research. Hence, research core biopsy samples may be transferred to a licensed tissue bank where they will be managed in accordance with applicable host institution policies and Human Tissue Act (HTA) requirements after the end of the study.

If during the course of the trial further biopsies or surgery are performed, from which there is tissue surplus to diagnostic requirements which would be of relevance or benefit to the biomarker or translational research studies undertaken, then these blocks may also be collected for study purposes.

9.15. Nested Qualitative Study (NQS) - Impact of NET on HRQoL of patients

Clinical trials often raise important questions that cannot be answered by trial data alone, such as reasons for lack of treatment effect and facilitators/barriers to implementation of the trial (85). Failure to identify the context, characteristics, experiences and practicalities of implementing clinical trials significantly reduces the replicability and usability of trial findings (85, 86). Important considerations include contextual barriers to implementation, causal mechanisms and pathways of delivery and the experience, attitudes and behaviours of trial participants (85, 87). Process evaluations enable these issues to be addressed and are frequently undertaken alongside trials to explain outcomes (87, 88). Qualitative methods are increasingly recommended as a means to understand the outcomes of complex interventions (89).

9.15.1. Nested qualitative study objectives

To explore the experiences of patients in both arms of the trial during the trial recruitment period, generating an understanding of the acceptability and experiences of NET and subsequent treatments on women's HRQoL. This will guide and assist interpretation of HRQoL findings and outcomes. The following will be explored:

1) To explore the experiences of participants in both the intervention and control arms of the trial to:
    - Understand participant experiences, beliefs and expections of NET
    - Generate an understanding of the acceptability of NET
    - Understand participant experiences of subsequent treatment after NET
2) To understand how these experiences may affect their health-related quality of life, to help make sense of the FACT-B scores
3) To understand whether these experiences vary with participant characteristics (e.g. age, treatment type) and if so, how?

9.15.2. Methods

Semi-structured interviews will be conducted with participants at two time points:

- Post-randomisation and prior to endocrine therapy starting or as soon as possible after starting endocrine therapy
- 6 months after surgery
- Participants in active follow up on the trial may also be interviewed, for example if they have crossed over to early surgery.

NB. Wherever possible, first and second time point interviews will be conducted with the same participants. However, participants may be interviewed at any point during active trial follow up. To ensure recruitment to time and target, interviews conducted prior to endocrine therapy starting and post-surgery may be undertaken with different participants.

9.15.3. Interview topic guides:

Patient interviews will be informed by PPI and clinical input and a review of the literature. Patient interviews will explore:

- Personal preferences for treatment
- Expectations of the treatments received
- Experiences of receiving treatment and impact on HRQoL
- Thoughts and feelings concerning NET and its staging with subsequent treatment
- Experiences of surgery and subsequent treatment and its impact

9.15.4. Participants

Up to 60 participants will be selected from a range of participating sites, selected on the basis of site characteristics and including one pilot site, enabling qualitative data to understand the impact of the trial on HRQoL. A purposive sample will be used to identify women from both trial arms, based on age and randomisation outcome, surgical plan at baseline (BCS vs mastectomy) and nodal status will be taken into account.

On entry to the main EndoNET trial, patients will be asked to consent to being contacted about taking part in future research. From those willing to be contacted, potential participants will be purposefully selected based on the sampling criteria above and will be provided with information relating to the NQS (as detailed above). Participants in active follow up on the trial may also be interviewed, for example if they have crossed over to early surgery.

9.15.5. Analysis

All interviews will be audio-recorded on an encrypted device and fully transcribed. Once transcribed and checked audio-recordings will be deleted. Transcripts will be pseudonymised, with all names removed and replaced by codes. Identifiable data will be stored separately from transcripts. All data will be stored in encrypted files on a University of Southampton computer within the School of Health Sciences and will be under appropriate password protection. Only authorised personnel will have access. Personal data will be pseudonymised, and the key will be stored separately to the data. Data will be recorded and retained in accordance with the Data Protection Act 1998. In addition, data will also be collected, recorded, and retained in accordance with University of Southampton Data Protection Policy . Transcripts will be analysed using directed content analysis within a Framework Approach and interrater reliability will be assessed by independent coding of a sample of transcripts by a member of the research team.

9.16. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw their consent to continue with the study intervention and/or follow-up at any time without prejudice, without this affecting their clinical care. Withdrawn participants will not be replaced. Participants may be withdrawn from the trial intervention only; this may be at the discretion of the Investigator due to safety concerns. If a participant is withdrawn from the intervention only, they will continue to be followed-up in accordance with the protocol.

At trial entry, participants will have been informed that continued data collection is important to ensure the research produces reliable results. In the event of a participant's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the participant wishes to withdraw and record the details on the CRF. For participants withdrawing from all aspects of the trial, the Investigator should ascertain from the participant if they agree to continue to consent to collecting routine information from hospital records, and/or linkage with existing databases e.g. NHS England and eDRIS, cancer registries and national public health bodies. As such, data collection will continue and will only cease if participants explicitly withdraw their consent for continued data collection at follow-up time points.

If a participant withdraws from the study follow-up, we will use the data collected up to the point of withdrawal and continue to capture data on hospital admissions and death, unless they request otherwise. All participants will continue to receive their treatment as per routine NHS standard of care.

If the participant withdraws from follow-up before the resolution of an adverse event (AE), the Investigator will arrange for follow-up visits or telephone calls until the SAE has resolved or stabilised.

Participants can withdraw from the QRI study at any time, without needing to provide an explanation for this. Their data will still be used unless they specify to a member of the QRI team that they would like it to be destroyed, although this will only be possible within 3 weeks of the recordings having been made. After this point, data is likely to have been anonymised, subjected to analysis, and reporting (e.g. through de-identified quotes) in QRI outputs. Withdrawal from the QRI will not affect participation in the EndoNET trial, and vice versa.

Participants can withdraw from the NQS at any time, without needing to provide an explanation. Withdrawal from the NQS will not affect participation in the EndoNET trial. Participants who wish to

withdraw will be asked whether any data already collected as part of the NQS can be retained in the study. If they wish their data to be removed from the study all data from the NQS for this participant will be deleted. In addition, the Investigator may discontinue a participant from the study treatment (but not the follow-up) at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Significant protocol deviation
- Clinical decision including a decision that it is unsafe to proceed
- An adverse event which results in inability to continue to comply with trial procedures.

9.17. Switching to second line AI or early surgery

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE. If either of these occurs, the participant will switch to second line AI.

A participant may also proceed to early surgery if, in the opinion of their treating team, there is evidence of disease progression whilst on NET.

9.18. Definition of crossover

Crossover in this trial is defined as:

- When a participant who is randomised to the comparator arm's first surgery is late (e.g. anaesthetic review being unfit for surgery may be a reason for this)
- When a participant who is randomised to the NET arm has early surgery.

9.19. Definition of End of Trial

The end of the trial is the point at which all the data has been entered and queries resolved for the final patient's 15-month visit of all recruited patients. The CI will notify the Sponsor, participating sites and the REC within 90 days of the end of the study, or within 15 days if the study is ended prematurely.

9.20. Long-term Follow-up

The period of funded follow up for each participant is 15 months. The collection of long-term follow-up information is important to understand if there are long-term oncological benefits or risks to the neo-adjuvant endocrine approach and funding and or resources will be sought to undertake this. Nationally held data will be used to monitor long-term outcomes for example for up to 20 years, and as such we will seek patient consent for this as part of the EndoNET trial. This nationally held medical data includes those held by the NHS, at the General Register Office, NHS England/NHS Central Register, eDRIS, NHS Spine/ISD Scotland, the Health and Social Care Information Centre and the national cancer registries and a number

of other related datasets and databases. To obtain the information required from these national data sources some patient identifiable information will need to be provided (which might include the NHS/CHI number and date of birth and trial ID) to the managing organisations, so that they link to the records of individual cases. The patient identifiable information will be sent to the University of Oxford and kept separately to the main trial database. It will be subject to strict confidentiality policies and only used for the purpose of analysis of the long-term outcomes of the trial. Patients will specifically consent to confirm permission to access their national medical records.

10. TRIAL INTERVENTIONS

10.1 Investigational Medicinal Product(s) (IMP) Description (Main Trial) including labelling

The IMP is defined as pre-surgical (Neoadjuvant) Endocrine Therapy (Aromatase Inhibitors (AI): letrozole, anastrozole or exemestane) following trial entry and up to surgery in both arms: In intervention arm 6 (+/- 1) months and in control arm 2-4 weeks (up to 8 weeks permitted for trial purposes).

The choice of AI is according to centre policy and may be either letrozole (2.5mg/day), anastrozole (1mg/day), or exemestane (25 mg/day).

Each centre will be requested to use the same first line and second line AI for all patients in both arms of the trial. Centres are required to have a medically qualified doctor on the delegation log to prescribe the AIs in the pre-surgical period, however these can be dispensed according to local centre policy (e.g. in the hospital pharmacy) or in the community.

Some patients may have started their pre-surgical aromatase inhibitor endocrine therapy as part of their routine care prior to trial entry following their current breast cancer diagnosis. In this instance, local centres may choose to create a trial prescription for the IMP or nominate a medically qualified doctor on the delegation log to take responsibility for the pre-surgical AI prescription. Sites are encouraged to ensure a handover discussion takes place between the original prescriber and the researcher who takes responsibility for prescribing on the trial delegation log, to ensure the requirements regarding safety reporting and prescribing are clear.

Letrozole will be used within its licensed indication as neo-adjuvant treatment. Anastrozole and exemestane are licensed for adjuvant treatment of hormone receptor positive breast cancer, but will be used in this trial as neo-adjuvant treatment; routine off-label use for neoadjuvant endocrine therapy is established practice and supported by enough published evidence and guidelines (including NICE Guidance 101). This is also consistent with NICE guidance NG101 point 1.11.6 which is to “Consider neoadjuvant endocrine therapy for postmenopausal women with ER positive invasive breast cancer as an option to reduce tumour size if there is no definite indication for chemotherapy [2018]”. All are oral preparations formulated as tablets.

No trial specific labelling is required for this Type A trial (as determined by the trial risk assessment and in accordance with the MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Version 10th October 2011).

Adjuvant treatment by AI will be according to usual clinical practice and national clinical guidelines. It is anticipated that patients will receive adjuvant AI for a minimum of 5 years. The AI prescription should be done by the GP in the post-surgical period in accordance to usual clinical care.

10.1.1. Blinding of IMPs

Not applicable.

10.1.2. Storage of IMP

Any licensed brand of the IMP can be used. The storage of the IMP will be handled as pharmacies per local policies.

10.1.3. Compliance with Hormonal Treatment within the Trial

We define compliance with hormone treatment in this study as when the participant takes the AI medication as assessed with the Compliance CRF.

This is a pragmatic trial, compliance will be assessed based on the participant making their own notes and from the Compliance CRF based on the MARS-5 questionnaire. Participants will be asked about their compliance at 2-4 weeks, 5 months and 15 months post-randomisation and about taking their pills in the previous 7 days.

10.1.4. Accountability of the Hormonal Treatment within the Trial

As EndoNET a Type A trial, no trial specific drug accountability is required above usual local practice.

10.1.5. Concomitant Medication

No specific medications are listed in the BNF as being contra-indicated with the aromatase inhibitors letrozole, anastrozole or exemestane. Patients must be postmenopausal for trial entry and must not take any oral oestrogen preparations. Clinicians are advised to refer to the BNF when prescribing AIs, which at the time this protocol was written, manufacturers advise caution with the following drugs which have warnings about decreased exposure to exemestane: Apalutamide, Carbamazepine, Enzalutamide, Fosphenytoin, Mitotane, Phenobarbital, Phenytoin, Primidone, Rifampicin and St John's wort.

It is important to ensure that use of adjuvant non-trial therapy, including consideration of participation in an adjuvant treatment trial, is not influenced by the patients' treatment allocation within EndoNET. If such a practice occurred, with differential use of adjuvant therapy between the arms, this would undermine the scientific integrity of the trial and affect its ability to reach its stated objectives. In order to avoid this, all non-trial therapy should be given according to standard local practice guidelines. All Non-Trial Treatment, as Adjuvant Chemotherapy and systemic therapy, adjuvant radiotherapy and Bisphosphonates, must be recorded in the Case Report Forms (CRF).

10.1.6. Post-trial Treatment

Not applicable.

10.2 Other Treatments (non-IMPS) (Main Trial)

Pre-surgery, some patients may have started an AI for their current breast cancer as part of their routine care. These patients can be considered eligible for the study, provided, on trial entry, that they have not exceeded 14 days of AI treatment and it remains possible to schedule their surgery within 8 weeks of starting their aromatase inhibitor endocrine treatment

Post-surgery, adjuvant treatment with AI will be according to usual clinical practice and national clinical guidelines, and hence from this point onwards the AIs will no longer be considered as IMPs. It is anticipated that patients will receive adjuvant AI for a minimum of 5 years and up to 10 years and according to guidance.

10.3 Other Interventions (Main Trial)

There are no additional interventions in the trial.

11. SAFETY REPORTING (Main Trial)

The trial will be run in accordance with OCTRU's Standard Operating Procedures (SOPs) and operational policies, which all adhere to applicable UK regulatory requirements.

An independent Data and Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC) will be appointed. The DSMC will monitor data arising from the trial, review confidential interim reports of accumulating data, and recommend whether there are any ethical or safety reasons why the trial should not continue. The TSC will monitor the trial's progress and will provide independent advice. Both committees will comprise independent clinicians, statisticians, health service researchers and patient representatives.

11.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

11.2. Assessment results outside of normal parameters as AEs and SAEs

Only events considered related to the AI treatment in the pre-surgical window and considered serious are recorded as SAEs. This includes any assessment results outside of normal parameters.

11.3. Events exempt from reporting as AE/SAEs

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a reportable serious adverse event; e.g., hospitalisation for procedures and treatments specified within the protocol, and standard supportive care for the disease under study are not reportable SAEs, and do not require SAE reporting.

11.4. Reporting complications in relation to surgery

Any complications related directly to breast surgery and not considered related to AI treatment (example: prolonged hospitalisation, infection etc.) will not be part of the safety reporting but will be collected in the relevant trial CRF. These will be assessed using the Clavien-Dindo Classification of surgical complications.

11.5. Reporting side effects in relation to IMP treatment

Side effects frequently experienced by patients undergoing AI therapy for breast cancer are collected as outcomes in the trial's CRF for the duration of patient participation in the trial (15-months for both arms) and include the following:

- Vasomotor including hot flashes/flushes and night sweats/hyperhidrosis
- Musculoskeletal including myalgia and arthralgia/joint pain;
- Central nervous system including nausea, vomiting, and fatigue;
- Urogenital including vaginal haemorrhage/bleeding, vaginal dryness and urinary tract infection;
- Gastrointestinal including anorexia;
- Other including alopecia.

Generally, these are mainly mild or moderate in nature, and most are associated with oestrogen deprivation.

The above events must also be reported as SAEs if they meet the definition of serious and occur during the trial's defined safety reporting window.

11.6. Assessment of Causality

The relationship of each serious adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

	Attribution (Causality)	**Description**
Non-related	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possibly	The AE may be related to the intervention
	Probably	The AE is likely related to the intervention
	Definitely	The AE is clearly related to the intervention

11.7. Severity grading

Severity of events in this trial will be assessed based on the most recently published Common Terminology Criteria for Adverse Events (CTCAE) scale (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Referenc

e_5x7.pdf). AEs will be rated according to these grades: 1 = mild, 2 = moderate, 3 = severe or medically significant, 4 = life-threatening and 5 = death related to AE.

11.8. Safety reporting window

The safety reporting window is defined as the time the AI is given in the pre-surgical (neoadjuvant) period for the trial in both arms (between patient consent and the surgery: target of 2-4 weeks (up to 8 weeks permitted for trial purposes) in the control arm, and 6 months (+/- 1 month) in the NET arm). The justification of the chosen safety window is based on the use of adjuvant AI post-surgery as the current SoC where the AI is no longer classified as an IMP.

11.9. Reporting Adverse Events and SAEs including reporting period

All side effects collected as outcomes in the CRF that also meet the definition of serious will need to be reported as an SAE during the trial's safety reporting window. All other SAEs considered related to the AI treatment should also be reported on an SAE form. Reporting must be within 24 hours of the site being aware of the SAE. Once a SAE is entered in the database, this automatically triggers a notification to the CTU.

The following information will be reported on the SAE form: relevant brief medical history, description of event (i.e. diagnosis term), date of onset and end date, severity, assessment of relatedness to trial medication, or drug–to drug interaction if participant is taking concomitant drugs; reason for seriousness, and action/s taken to deal with the event. SAEs will be closed following resolution. Follow-up information should be provided as necessary.

In the event that the clinical database is not available for reporting of SAEs within 24 hours, sites must complete a paper SAE Form and email it to the trial inbox email account: endonet@nds.ox.ac.uk.

11.10. CTU Review of reported SAEs

On notification/receipt of a SAE, the Trial Management Team at the CTU will perform an initial check of the report and request any additional information from the site team. The SAE will also be reviewed by a Nominated Person for the trial.

11.11. Assessment of Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the section 4.8 of the Summary of Product Characteristics of the relevant IMP Letrozole, anastrozole and or exemestane. The nominated SmPCs for each of the trial AIs is Femara (letrozole), Arimidex (anastrozole) and Aromasin (exemestane). The RSI used (within the SmPC) will be the current Sponsor and MHRA approved version at the time of the event occurrence, even for any follow-up information of the same event. If an event is deemed to be either more severe or specific in nature than what is listed in the RSI used then it may be considered as unexpected.

This assessment will be performed by the Nominated Person for the trial in the CTU.

11.12. SUSAR Reporting

11.12.1. Reporting to the MHRA/REC

All SUSARs will be reported by the CTU (sponsor delegate) to the MHRA and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

11.12.2. Reporting SUSARs to the PIs

PIs will be informed of all SUSARs that occur in the trial reporting period at the same time that the MHRA/REC are being informed.

11.13. Development Safety Update Reports (DSUR)

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the MHRA, Ethics Committee, HRA (where required) and Sponsor. The DSUR will only be sent to sites, on request.

As the trial is a Type A trial under the MHRA notification scheme, the HRA Annual Progress Report (APR) form will be used as a template for the DSUR. The cover letter will state that this is an APR in lieu of a full DSUR, and include the EudraCT number and CTA reference number.

For assessment of SARs in the DSUR, the RSI that was approved at the **start of the DSUR safety reporting period** will be used for assessment of expectedness, as per OCTRU's SOP on DSUR. The date of the CTA authorisation will be the start of the safety reporting period of the trial.

12. STATISTICS (Main Trial)

12.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a pre-specified statistical analysis plan (SAP) that will be finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Trial Statistician in accordance with the current OCTRU SOPs and will be finalised and agreed by the Trial Statistician, the CI and the TMG.

12.2 Description of Statistical Methods

Results will be reported in line with the CONSORT statement and relevant extensions (101, 104, 105).

All outcomes will be summarised using descriptive statistics overall and, when collected for both arms, split by treatment groups. Binary and categorical data will be summarised by frequencies and percentages. Continuous data will be summarised by means and standard deviations (SDs), or median and inter-quartile range if data are skewed. Corresponding 95% confidence intervals will be presented where possible. Visual representation of outcomes will be considered and, where it will support interpretation, presented.

The primary analyses will be performed according to the intention-to-treat principle. Additionally, a per protocol analysis will be considered to examine the robustness of the primary analysis under the intention-to-treat principle.

The primary endpoint, rates of breast conserving surgery, will be compared between the two arms using a mixed effects logistic regression model, adjusting for treatment and clinical stratification factors as fixed effects and centre as a random effect. Additionally, a sensitivity analysis will be conducted that adjusts for other important prognostic factors.

Secondary endpoints, measured in both treatment groups, will be analysed comparatively as far as practically possible. Statistical methods used for comparison will depend on the outcome type and full details will be included in the SAP. QoL will be compared using a mixed effects linear regression model. The model will include treatment, baseline score and clinical stratification factors as fixed effects, centre will be included as a random effect. When QoL is assessed at additional time points between baseline and 15 months, time-by-treatment interactions will be incorporated as fixed effects and patient as a random effect. Mean scores and standard deviations will be plotted over time for visual representation. The predictive ability of Ki67 will be explored using logistic regression models. Time-to-event endpoints will be analysed using Kaplan-Meier curves, log rank tests, and Cox proportional hazards models or, in the presence of competing risks, by using cumulative incidence plots and Fine and Gray survival regression models. Continuous clinical endpoints will be compared using a two-group t-test and the difference in means will be presented with a 95% confidence interval. Binary clinical endpoints will be compared using a chi-squared test and the effect estimate reported in terms of the relative risk and 95% confidence interval. Ordinal clinical endpoints will be compared using a chi-squared test for trend. Multilevel regression models, with adjustment for stratification factors in line with the primary endpoint analyses, will be applied to secondary endpoints where it is both practical to do so and there are sufficient events to support this approach.

The primary analysis is planned in the final six months of the study period, at which point all participants will have completed at least 15 months of follow-up.

It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other well validated statistical package.

* **Note:** From Protocol 4.0, FACT-B +4/ES will no longer be collected at 7 and 12 months (see Appendix 1). Data collected on patients up until this timepoint will be reported descriptively and will not be included in formal comparisons due to low numbers in comparison with the overall sample size. The SAP will provide further detail.

12.3 Sample Size Determination

We aim to recruit a maximum of 1060 patients (for 90% power, 530 per arm), with a minimum of 792 (for 80% power, 396 per arm) women from at least 30 NHS centres. UK-based registry data indicates that ~45% of women with tumours >2cm undergo mastectomy; based on discussions with patient representatives and confirmed at the NCRI Dragons Den, we consider a reduction of 10% (i.e. mastectomy rate reduced from 45% to 35% resulting in BCS rate increase from 55% to 65%) to be clinically meaningful to patients and lead to a change in clinical practice.

The sample size of 1060, and 792, would allow us to detect this difference with 90% and 80% power respectively at a two-sided 5% significance level allowing for a cross-over and attrition at 15 months up to 5%.5% is based on loss to follow up experienced for the clinical endpoints in the iBra study.

80% power is considered to be sufficiently robust and in line with other similar and recent trials (104, 105). However, if recruitment to 1060 (for 90% power) seems achievable, given the observed recruitment trajectory, then the DSMC and TSC will be contacted to consider continuation of recruitment to 1060 patients.

12.4 Analysis of Trial Populations by Intention to Treat

The principal analysis will be performed on the intention-to-treat population, analysing with participants with available outcome data in their randomised groups, regardless of adherence.

12.5 Stopping Rules

No formal interim comparative analyses are anticipated prior to completion of follow-up for the designated time points. The DSMC may request interim analyses at any point in the trial, which will be performed by the trial statistician. A DSMC charter will be in place for the EndoNET trial.

Internal Trial Pilot

Formal stop/go review will be at the end of the trial pilot, which took place on 31st December 2023 to ensure 12 sites opened and 150 patients were randomised.

Target	**Actual recruitment at end of trial pilot**		
	>150 participants	100-150	<100 participants
Stop-Go Criteria	• Recruitment feasible • Proceed with study	• Review recruitment strategies • Report to TSC • Continue but modify and monitor closely	• Recruitment not feasible • Decision not to proceed

Table 3: Study stop-go criteria

Should a decision be made not to proceed, recruitment to the trial will stop but we will continue trial participation within the follow-up period for those already recruited.

Interim Review Point

As a result of the internal trial pilot, the Funder has requested a second review point on 1st December 2024.

12.6 The Level of Statistical Significance

Outcomes, collected in both treatment arms, will be considered statistically significant for p-values <0.05. There will be no adjustment for multiplicity, relevant results from other studies already reported in the literature will be taken into account to support the interpretation.

12.7 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical analysis plan will be described and justified in a revised version of the SAP.

12.8 Health Economics Analysis

A within-trial analysis will be conducted to assess the cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice of surgery followed by adjuvant ET for reduction in mastectomy at 15 months. Resource utilisation, cost and cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice will be assessed, adhering to good economic evaluation practice with an NHS and Personal Social Services perspective (78, 79).

A detailed health economics analysis plan will be prepared in the first 4 months of the programme, setting out the proposed analyses in detail. The health economists will work with the project team and PPI group to identify and design the collection of health care resource use information and HRQoL. A self-complete health care use questionnaire will be used to collect all resource events associated with treatment and administering NET, side effects or complications and follow-up consultations in primary and secondary care settings. The self-completed health care use questionnaire will be administered at baseline (T0), 6 weeks (F1), 7 months (F2) and 15 months (F3) post randomisation to indicate health care resource use from 6 weeks prior to randomisation to baseline, baseline to 6 weeks, from 6 weeks to 7 months and from 7 to 15 months. Where possible, resource utilisation items will be valued using national unit cost schedules (e.g. NHS Reference costs) and medication costs calculated using British National Formulary pricing. Where unit costs are unavailable (e.g. intervention costs) bottom-up micro-costing will be undertaken. Number of work/usual activity days lost due to the treatment process and any related complications and any over-the counter medications purchased by participants will also be captured by the participant questionnaires. We will test for baseline difference in health care resource use between the trial arms and if required, adjust for these differences using the most appropriate recommended method. The impact of the inclusion of societal costs on the base-case cost effectiveness results will be explored in the sensitivity analysis. All costs and effects will be discounted at 3.5% following the guidelines from the National Institute for Health and Care Excellence (78).

To determine quality-adjusted life-years (QALYs), the EQ-5D-5L (80) will be used to measure HRQoL at baseline (T0), 6 weeks (F1), 7 months (F2) and 15 months (F3). Each time interval will be weighted by the utility scores apportioned to that time with linear interpolation between data collection time points. At present EQ-5D-5L responses would use a mapping algorithm/function to the EQ-5D-3L and the existing UK valuation set applied, in line with NICE recommendations, but an approved UK value set for the EQ-5D-5L may be available by the later stage of this trial. We will test for baseline difference in utilities between the trial arms and if required adjust for these differences using the most appropriate recommended method (81).

The health care use questionnaire and the EQ-5D-5L will be sent for self-completion via email but, if requested, they could be undertaken by mail. In some circumstances, where it is not feasible to complete questionnaires using our preferred method(s), participants may complete questionnaires over the telephone with their local NHS team. The central trial team may also contact participants by telephone to complete questionnaires and to remind participants to complete them if they are overdue.Incremental cost effectiveness ratios (ICERs; cost per QALY) will be estimated. Sampling uncertainty concerning

estimated costs and quality adjusted survival observed in the trial, will be fully reported. Any remaining methodological uncertainty (e.g. discount rates, sources of unit cost information or future therapy costs) will be explored using sensitivity analysis. The ICERs will be compared against the threshold used to establish value for money in the NHS (currently in the region of £20,000 to £30,000 per QALY) (78).

13. DATA MANAGEMENT

A data management and sharing plan will be produced for the trial in accordance with OCTRU Standard Operating Procedures (SOPs), this will include reference to confidentiality, access and security arrangements.

All data will be processed following relevant SOPs, which have been written in line with all applicable regulatory requirements. All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. All patient data will be stored and transported securely in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford, and authorised personnel.

Data will be collected from participants via questionnaires and case report forms. Paper questionnaires (where used) will be returned to the central trial office in Oxford via post using a pre-addressed freepost envelope. Electronic questionnaires will feed directly into an online secure database – the study's dedicated instance of REDCap.

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.

Consent will be obtained to allow long term follow-up (subject to additional funding and/or governance approvals) through utilisation of nationally held data as outlined in section 9.20, including the relevant checks and confirmation of data held on national registries as required by the relevant recruiting centres for the purposes of data cleaning and checking.

13.1. Source Data (Main Trial)

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, radiographs.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

13.2. Access to Data (Main Trial)

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13.3. Data Recording and Record Keeping

13.3.1. Main Trial data

The following information will be recorded on a secure web-based form in the REDcap database and in the study randomisation system (RRAMP) by the attending clinician or delegate including a member of research team to enable follow-up:

- Patient details e.g. name, address, NHS/CHI number, date of birth, telephone number, email address, GP name and GP address

Note: *These data fields will allow sites to check their local hospital records to for any admissions. The GP details are required to allow the central trial team to send a letter to the patient's GP informing them of their EndoNET participation. The email address will enable a copy of the completed consent form to be sent to the patient or, at their request, a different individual for safekeeping. Depending upon patient preference the email /postal address may be utilised for follow up questionnaires. The telephone number will enable the central trial team to call participants to ask about the status of questionnaires (e.g. in case they are overdue) and to query missing data.*

The trial data (including screening logs, CRF data and participant questionnaires) will be entered onto a validated REDCap study database developed and maintained by OCTRU and which can only be accessed by authorised users via the application. The application resides on a webserver hosted and managed by the University of Oxford's Medical Services Division IT Services department (http://www.imsu.ox.ac.uk/). The server is on the university's backbone network and is backed up nightly to a secure off-site location. Any indirect identifiers that may lead to deductive disclosures will be removed to reduce the risk of identification. The processing of participant personal data will be minimised by making use of a unique trial specific number and/or code in any database and on study documents.

After closure of the trial and data analyses, the data will be made publicly available at the time of publication. The Trial Master File will be archived for a maximum of twenty years from the end of the study.

Where data is submitted directly to the trial office, contemporaneous access by local research teams to the online database will enable the local research teams at sites to download copies of their participants' data.

13.3.2. QRI data

Upon initial consent, participants will be given a unique identifying number (EndoNET QRI ID). All data will be labelled by the reference number (with no personal information). Where relevant (e.g. for interviews), the QRI ID will be linked to personal information in a key breaker document which will be encrypted, password protected and stored securely on the University of Bristol servers.

Audio recordings of clinical consultations taken as part of the QRI will be captured on encrypted audio-recording devices, which the QRI research team will provide to the site (with instructions). Recordings will be periodically transferred securely to the University of Bristol research team using a Trust-approved

secure data transfer system (e.g. BOLT), or an encrypted device (e.g. password-protected flash drives or memory cards).

The recordings from interviews and audio-recorded consultations will be transcribed and anonymised by a University of Bristol employee or a University of Bristol approved contracted transcribing service that has signed the University of Bristol's Confidentiality Agreements. Transcripts and voice-modified recordings will be held up to 20 years on a secure database at the University of Bristol which will only be accessed by authorised members of staff in the QuinteT team. Any paper copies of the transcripts will be stored securely in a locked filing cabinet at the University of Bristol and destroyed at the end of the EndoNET study.

At the end of the study identifiable information will be securely returned to University of Oxford and deleted from University of Bristol servers. Non-identifiable data held by the University of Bristol (including voice-modified audio files and transcripts) will be stored on secure servers for a maximum of twenty years.

13.3.3. Nested Qualitative Study (NQS) data

Upon initial consent, participants will be given a unique EndoNET NQS study ID (e.g., NQS1, NQS2). A password protected log will link these to their original EndoNET screening number (stored separately from interview transcripts and main study log). All data will be anonymised and labelled only by the study ID. The study ID will be linked to personal information in a main study log which will be encrypted, password protected and stored securely on University of Southampton servers.

The NQS study will comply with current data protection regulations, and follow University of Oxford and University of Southampton guidance. The data will be handled in compliance with Good Clinical Practice (GCP) guidelines and all interviewers will be trained in GCP. Appropriate monitoring will be undertaken by the central trial team in accordance with the trial monitoring plan.
All data will remain confidential at all times.

- Audio recorders will be password protected. Audio files will be downloaded to the University of Southampton network as soon as possible after completion of the interview, and the file deleted from the recorder.
- Audio files will be transcribed by University approved transcribers who have signed a confidentiality agreement. Audio files and the resultant transcriptions will be sent to transcribers and returned via the secure University drop off system.
- Interview transcripts will contain a study ID number rather than the respondent's name. Should the respondent mention a person or organisation by name, these will be removed and a descriptor (e.g. 'participant's husband'; 'name of hospital') added instead.
- Interview and consent audio files will be destroyed once transcripts have been verified.
- Any paper copies of transcripts will be stored in a locked cabinet in secure entry offices at the University of Southampton. Electronic copies will be stored on the University of Southampton server with password protection. Interview audio files and transcripts will be stored separately from the participant's contact information.

- Study data will be kept for 10 years from the end of the study, in accordance with University of Oxford policy.

14. QUALITY ASSURANCE PROCEDURES

14.1 Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. The trial risk assessment and monitoring plan will be will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2 Monitoring

Regular central monitoring will be performed by SITU, according to the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.3 Trial committees

14.1.1. Trial Management Group

The Trial Management Group (TMG) consists of those individuals responsible for the operational management of the trial such as the CI, key members of the scientific and clinical team (scientists, pathologists and research nurses) and the Trial Manager. The TMG will meet every month throughout the recruitment phase of the trial and every two/six months throughout the follow up phase of the trial, and will:

- Supervise the conduct and progress of the study, and adherence to the study protocol.
- Assess the safety and efficacy of the interventions during the study.
- Monitor the safety of the participants, and review safety data to look for any emerging trends including increases in severity or frequency of SAEs or SARs (which may require expedited reporting to the MHRA and relevant REC).
- Evaluate the quality of the study data.
- Review relevant information from other sources (e.g. related studies).
- Escalate any issues for concern to the Sponsor (or delegate), specifically where the issue could compromise patient safety or the integrity of the study or quality of the study data.

14.1.2. Trial Steering Committee

The TSC is an independent body responsible for overall supervision of this study on behalf of the Sponsor (the University of Oxford) and the Funder (NIHR HTA Programme) in order to ensure that:

- Progress is satisfactory and the study is adhering to its overall objectives as set out in the protocol.
- Patient safety is not being compromised.
- The study is being conducted according to the Principles of Good Clinical Practice (GCP) and the UK Clinical Trial Regulations.

Decisions about continuation or termination of the study or substantial amendments to the protocol are usually the responsibility of the TSC, and the TSC will provide information and advice to the Sponsor (or delegate), Funder and TMG in this regard.

Meetings of the TSC will take place annually, or at shorter intervals if required. Representatives of the Sponsor (or delegate) and the Funder will be invited to all TSC meetings. The TSC will adopt a Charter as per OCTRU SOPs.

14.1.3. Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee (DSMC) will be established to safeguard the interests of trial participants, potential participants and future patients, to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DSMC will adopt a DAMOCLES-based charter, which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that data by treatment arm. They will also consider emerging evidence from other trials or research on the intervention. They may advise the chair of the TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least once a year during the recruitment phase of the study and the reports will be forwarded to the TSC. The TSC will ultimately have the final say in stopping the trial early. Full details will be found in the DSMC and TSC Charters.

15. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

16. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

17.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4 Other Ethical Considerations (Main Trial)

The timing of surgery for those participants in the NET Arm by 6 months (+/- 1 month), in comparison to the NHS SoC which specifies a treatment target of 31 days, does not pose a risk to an NHS site's targets. Hormone therapy constitutes starting treatment and therefore no targets should be missed. Taking part in EndoNET may mean that patients will not have to wait 31 days before starting some form of treatment, and a participant will get their first line of AI much sooner than they would have compared to SoC.

17.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

17.7 Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

17.8 Expenses and Benefits

Participants will not receive any payments for taking part in this study.

18. FINANCE AND INSURANCE

18.1 Funding

The study is funded by National Institute for Health Research - Health Technology Assessment Programme (HTA) (NIHR HTA Reference Number: HTA NIHR131046).

18.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

18.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

19. PUBLICATION POLICY

The trial has been prospectively registered, prior to ethics approval, on the International Standard Randomised Controlled Trial Number register. The trial protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The trial results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org), in particular the extensions for non-pharmacological interventions, patient-reported outcomes and pilot and

feasibility studies. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention, ensuring that replication is possible.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by National Institute for Health Research – Health Technology Assessment Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

21. ARCHIVING

The Trial Master File and QRI data will be archived for a maximum of twenty years from the end of the study. The main trial data will stored securely on University of Oxford servers. The de-identified transcripts/recordings of the QRI study will be held at the University of Bristol for 20 years. The de-identified transcripts of the NQS study will be held at the University of Southampton servers for 10 years following the end of the study.

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APPENDIX 1: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
001	2.0	10Jun2022	Charles Malyon on behalf of Prof. Michael Douek and Prof. Ramsey Cutress	1. Secondary endpoint 1 clarified to state response rates are relative to baseline in outcome table in 3.0 Synopsis and Section 6.2. 2. Secondary endpoint 5 timepoints corrected in line with trial CRFs in outcome table in 3.0 Synopsis and Section 6.2. 3. Secondary endpoint 12 timepoint changed from 12 months to 6 weeks in outcome table in 3.0 Synopsis and Section 6.2. Timepoints updated in Sections 9.1 and 12.8. 4. Footnotes added to outcomes table in 3.0 Synopsis and Section 6.2. 5. Updated trial schema in Section 7.2. 6. Update schedule of trial procedures in Section 9.1. 7. Added social media accounts to publicise news relating to the study in Section 9.2. 8. Removed emergency randomisation procedure in Section 9.5. 9. Wording clarified in withdrawal Section 9.14. 10. Wording clarified in reporting side effects Section 11.5. 11. Removed option to complete PROMs by telephone in Section 13.3. 12. Updated various typographic errors in document.
004	3.0	25Jan2023	Charles Malyon on behalf of Prof. Michael Douek and Prof. Ramsey Cutress	1. Added Association of Breast Surgery Logo and updated NIHR Logo. 2. Added missing abbreviations. 3. Updated primary objective to align with the change in inclusion criteria relating to tumour size to include T1-3 Tumours ≥ 15 mm.

				4. Clarified wording in Section 5.1 relating to EBCTCG reference. 5. Updated benefits and risks table in Section 5.2 to specify that participants may feel nervous whilst being monitored on NET. 6. Updated trial schema to align with updated inclusion criterion. 7. Updated Inclusion Criterion 'T-stage 2 or 3 (< 2cm)' to include T-Stage 1 and tumours ≥15mm. 8. Clarified Inclusion Criterion 'Strongly ER+; defined as Allred scores of 7 or 8 or equivalent' to define equivalent as a histochemical score (H-Score) ≥ 200. 9. Updated reference in Section 12.8 to reflect the latest NICE guidance. 10. Various references updated in Section 22.0. 11. Typographical errors have been corrected throughout document where appropriate.
008	4.0	21Aug2024	Charles Malyon on behalf of Prof. Michael Douek and Prof. Ramsey Cutress	1. Change of co-investigator from Prof. Richard Gray to Prof. Jonathan Cook. 2. Removal of Ms. Lucy Davies as co-investigator. 3. Update to Lay Summary and Section 3 Synopsis and Outcomes Table to align with changes in protocol. 4. Update to Section 5.2 for change in primary outcome and benefits/risk table. 5. Update to Section 5.5 for inclusion of patients when chemotherapy and/or anti-HER-2 therapy is not indicated at trial entry. 6. Addition of Section 5.7 to identify the need for the NQS. 7. Addition of Section 5.8 to identify need for Trans-EndoNET. 8. Update to Section 6.1 hypothesis and research question to reflect to reflect change from co-primary outcomes

				(FACT-B and BCS rates) to single primary outcome (proportion of BCS rates) and changes to trial inclusion/exclusion criteria. 9. Updates to primary and secondary outcome measures in Section 6.2: a. Co-primary outcomes (FACT-B and BCS rates) changed to single primary outcome (BCS rates). b. FACT-B co-primary outcome moved to secondary outcome. c. Removal of collection of FACT-B +4/ES at 7 and 12 months. d. Addition of NQS outcomes and timepoints. e. Correct timepoints of secondary outcomes 9, 10, 11, 12 and 14. f. Update to outcome table to include outcomes and timepoints. 10. Update to Section 7.1 after the outcome of internal trial pilot and changes to the eligibility criteria. 11. Updated trial schema in Section 7.2 to reflect changes in trial eligibility, patients who have already started endocrine therapy and the removal of 12-month completion of PROMs. 12. Simplification and modifications to inclusion criteria: a. Added 'according to established local criteria and suitable for an aromatase inhibitor' to clinically post-menopausal. b. Added a clarification note for unifocal, newly diagnosed breast cancer to ensure satellite lesions can be included.

				c. Removed 'HER2- by immunohistochemistry, or 2+ and not amplified by in situ hybridisation.' Replaced with exclusion criteria. d. Changed 'T-stage 1, 2 or 3' to 'Tumour size'. e. Removed 'chemotherapy unlikely to be indicated'. Replaced with exclusion criteria. 13. Simplification and changes to exclusion criteria: a. Removed 'ER- or HER2+'. ER- is covered by inclusion criterion 'Strongly ER+'. b. Added 'cN3' disease to replace inclusion criteria 'Axillary N0-1 on diagnostic USS'. c. Added 'cT4 diseased'. d. Clarified 'Stage IV disease' refers to metastatic breast cancer. e. Added 'Chemotherapy or anti-HER-2 therapy for current breast cancer started or planned' to replace 'unlikely to require chemotherapy' and 'HER2 by immunohistochemistry' inclusion criteria. f. Added that previous invasive malignancies within 5 years are excluded if they are likely to affect safety or efficacy assessment of compliance with protocol or interpretation of results'. g. Added a note that the presence of a 'mirena coil' does not exclude patients. h. Added 'Aromatase inhibitor endocrine treatment

				following current breast cancer diagnosis taken for longer than 14 days' as an exclusion criterion. 14. Added inclusion and exclusion criteria for NQS sub-study in Section 8.0. 15. Added schedule of trial procedures NQS in Section 9.1 and updated visit table to remove FACT-B +4/ES completion at 7 and 12 months. 16. Provided information about how information will be shared with patients and the public e.g. trial animation video in Section 9.3. 17. Update to Section 9.4 to mention process for co-enrolment with other studies. 18. Removal of requirement for 'the recommended minimum of 24 hours' for considering trial information in Section 9.5. 19. Added information on NQS sub-study consent in Section 9.5. 20. Added a note in Section 9.13 that patients may complete PROMs by telephone in some circumstances. 21. Added a clarification in Section 9.14 that if further biopsies or surgery are performed, then these blocks may also be collected for study purposes. 22. Added information relating to objectives, methods, analysis and withdrawal for NQS in Section 9.15 and 9.16. 23. Added Section 9.18 for the definition of crossover, which was previously in the compliance sub-section. 24. Added that patients who have already started pre-surgical endocrine therapy as part of standard of care may be considered for the trial in Section 10 if they have not exceeded 14 days of AI treatment

				25. Specified in Section 10.1 that a medically qualified doctor on the delegation log must prescribe the endocrine therapy in the neo-adjuvant period. 26. Added in Section 10.1 further information on requirements for the IMP for patients who enrol on the study who have started pre-surgical endocrine therapy as part of their standard of care. 27. Updated Section 12.1 to reflect the update to the statistical analysis plan. 28. Updated Section 12.2 to reflect change from co-primary outcomes to single primary outcome. 29. Updated Section 12.3 to reflect change in sample size and relevant power calculations. 30. Updated Section 12.4 with updated information on the primary analysis. 31. Updated Section 12.5 with the outcome of the internal trial pilot. 32. Updated Section 12.6 with the updated to the level of statistical significance. 33. Added information on NQS data collection in Section 13.3. 34. Added archiving arrangements in Section 21.0. 35. Updated NHS Digital to NHS England. 36. Added two references in Section 22.0.