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

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Chief Investigator Signature: The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Statistician Signature:

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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Trial Statistician	**Trial Statistician** Elizabeth Conroy Oxford Clinical Trials Research Unit, Centre for Statistics in Medicine

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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 treatment) 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 treatment 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 treatment 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 hormonal therapy followed by surgery.

Participants in this controlled trial are allocated by chance to one of two arms, which determines their treatment schedule. Hormone therapy is usually started after surgery. However, all participants in both trial arms will start hormone treatment (letrozole, anastrozole or exemestane) on joining the trial and prior to surgery. Therefore, they may have the opportunity to start treatment with hormone therapy before they normally would.

Participants in both arms have hormonal treatment 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 joining the trial; arm 2 will receive surgery after 6 months (+/-1 month) of NET. Participants in arm 2 will receive an ultrasound (USS) scan at 3 months and 5 months to closely monitor their response to this hormone 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 that overall quality of life and preserving the breast were the most important outcomes by which to measure study success.

The trial aims to recruit 1,440 women from at least 30 NHS hospitals across the UK. Participants in both arms will complete quality of life questionnaires at intervals during their 15-month participation in the study and rates of breast conservation surgery will be documented. The results will be published in medical journals and presented at international conferences and updates of study news will be available on the website and by study newsletter.

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

- The 'Information study', called the QRI study, will look at the different factors that can affect patient participation in EndoNET. This is being led by researchers at the University of Bristol.

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: ISRCTNXXXXXXXX
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: ctrg@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 NET 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.

Trial Participants	Post-menopausal women with strongly ER+, HER2- invasive breast cancer who are unlikely to require chemotherapy
Sample Size	Main Trial: We will recruit 1,440 post-menopausal women with strongly ER+, HER2- invasive breast cancer who are unlikely to require chemotherapy. QRI 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.
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. Formal stop/go review will be at month 18 (after 12 months recruitment) to ensure 12 sites have opened and 150 participants are randomised. If met, the trial will recruit for a further 30 months. 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 better HRQoL over 15 months and higher rates of breast conservation surgery (BCS) for post-menopausal women with >T1, strongly ER+, HER2- invasive breast cancer who do not require chemotherapy [1]	Co-primary outcome measures of:	
		1. Difference in global HRQoL (as measured by FACT-B)	1. Baseline, 6 weeks or post-operative, 5, 7, 12, and 15 months post-randomisation
		2. Rates of breast conservation surgery	2. 15 months post-randomisation
Secondary	1. To evaluate tumour response rates following NET [2]	1. Response rates according to RECIST (USS, clinical); MRI where used as part of local unit centre policy	1. 2-4 weeks, 3 and 5 months post-randomisation (NET arm)

	2. To compare invasive tumour size, histological grade and lymph node status (including number of involved nodes) in both arms [1]	2. Tumour size, histological grade and lymph node status pre-surgery and final histology post-surgery	2. Pre and post-operative
	3. To compare, in both arms, the HRQoL related to body image and surgery (FACT-B with ES and +4, Breast Q, 5Q-5D-5L, Hopwood Body Image Scale [BIS]) [1]	3. Patient reported outcomes as measured by FACT-B (with ES and +4), Breast-Q, Hopwood Body Image Scale and EQ-5D-5L	3. Baseline, 6 weeks or post-operative, 5, 7, 12, and 15 months post-randomisation
	4. To provide an estimate of the risk of relapse and measure of endocrine sensitivity in NET arm [2]	4. Pre-operative Endocrine Prognostic Index (PEPI) score	4. Baseline sample, 2-4 week sample and post-operative sample (NET arm)
	5. To compare post-surgical complications and AI side effects in both arms [1]	5. Post-surgical Complications, side effects; delays to commencement of subsequent treatment	5. 2-4 and 6 weeks (in NET arm), surgery, post-operative, 3, 5, 6, 12 and 15 months post-randomisation
	6. To assess treatment compliance (MARS-5) [1]	6. Treatment Compliance [1] and rates of cross-over [2]	6. 2-4 weeks, 5 months and 15 months post-randomisation.
	7. To evaluate the prognostic significance of Ki67 [1]	7. Ki67 % in tumour cells, % reduction in Ki67 from baseline to biopsy or surgery	7. Baseline (both arms) and after 2-4 weeks of AI (in both arms) and at surgery (in comparator arm);
	8. To assess the surgical and locoregional management of the breast [1]	8. 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	8. Post-operative, 15 months post-randomisation
	9. To assess the surgical and locoregional	9. Rates of sentinel node biopsy, axillary clearance, axillary radiotherapy	9. Post-operative, 15 months post-randomisation

	management of the axilla [1]		
	10. To compare rates of local and distant recurrence [1]	10. Rates of local and distant recurrence	10. Post-surgery, 15 months post-randomisation, and periodically for long term follow up [3]
	11. To compare breast cancer specific survival in both arms [1]	11. Breast cancer specific and overall survival;	11. Post-surgery, 15 months post-randomisation and periodically for long term follow up [3]
	12. 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]	12. Resource utilisation, cost and cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice.	12. Baseline, 7, 12 and 15 months post randomisation
	13. 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]	13. Accuracy of USS (and MRI where available) to determine conversion to BCS	13. 2-4 weeks, 3 months and 5 months post-randomisation
	14. To compare the requirement for adjuvant chemotherapy in both arms [1]	14. Number of patients receiving adjuvant chemotherapy in both arms	14. By 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	Current standard of care is surgery within 2-4 weeks of a confirmed diagnosis of breast cancer (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] These are secondary objectives that will be assessed subject to additional funding and/or resources and via submission of a substantial amendment, for example, 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
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
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
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
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. 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 maximise oncological outcomes (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 start after randomisation 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 our primary HRQoL instrument to include a global measure and have selected FACT-B as our primary 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 as the primary outcome measure to assess HRQoL. 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)**
Cancer removed within 31-day treatment target	6 months of NET and then cancer removed
Surgery performed based on baseline characteristics	• 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 immediate 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 can go to less intense follow-up	Close monitoring whilst on NET for 6 months to ensure continued response
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* score)

Table 1: Potential wide-ranging impact of a NET compared to standard of care approaches.
*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 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 considered unlikely to require chemotherapy

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+/HER 2-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 lymph node positive patients at baseline, if it was felt chemotherapy would not normally 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 was not indicated, but 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 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.

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.

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, 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.

6. OBJECTIVES AND OUTCOME MEASURES

6.1 HYPOTHESIS:

Neoadjuvant endocrine therapy (NET) reduces breast cancer size prior to surgery, reducing surgical burden leading to better HRQoL and higher rates of breast conservation surgery (BCS).

RESEARCH QUESTION: In post-menopausal women who will not require chemotherapy for >T1, strongly ER+, HER2- invasive breast cancer, does NET improve global HRQoL over 15 months and increase breast BCS rates?

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 better HRQoL over 15 months and higher rates of breast conservation surgery (BCS) for post-menopausal women with >T1, strongly ER+, HER2- invasive breast	Co-primary outcome measures of:	
		1. Difference in global HRQoL (as measured by FACT-B)	1. Baseline, 6 weeks or post-operative, 5, 7, 12, and 15 months post-randomisation
		2. Rates of breast conservation surgery	2. 15 months post-randomisation

	cancer who do not require chemotherapy [1]		
Secondary	1. To evaluate tumour response rates following NET [2]	1. Response rates according to RECIST (USS, clinical); MRI where used as part of local unit centre policy	1. 2-4 weeks, 3 and 5 months post-randomisation (NET arm)
	2. To compare invasive tumour size, histological grade and lymph node status (including number of involved nodes) in both arms [1]	2. Tumour size, histological grade and lymph node status pre-surgery and final histology post-surgery	2. Pre and post-operative
	3. To compare, in both arms, the HRQoL related to body image and surgery (FACT-B with ES and +4, Breast Q, 5Q-5D-5L, Hopwood Body Image Scale [BIS]) [1]	3. Patient reported outcomes as measured by FACT-B (with ES and +4), Breast-Q, Hopwood Body Image Scale and EQ-5D-5L	3. Baseline, 6 weeks or post-operative, 5, 7, 12, and 15 months post-randomisation
	4. To provide an estimate of the risk of relapse and measure of endocrine sensitivity in NET arm [2]	4. Pre-operative Endocrine Prognostic Index (PEPI) score	4. Baseline sample, 2-4 week sample and post-operative sample (NET arm)
	5. To compare post-surgical complications and AI side effects in both arms [1]	5. Post-surgical complications, side effects; delays to commencement of subsequent treatment	5. 2-4 and 6 weeks (in NET arm), surgery, post-operative, 3, 5, 6, 12 and 15 months post-randomisation
	6. To assess treatment compliance (MARS-5) [1]	6. Treatment Compliance [1] and rates of cross-over [2]	6. 2-4 weeks, 5 months and 15 months post-randomisation.
	7. To evaluate the prognostic significance of Ki67 [1]	7. Ki67 % in tumour cells, % reduction in Ki67 from baseline to biopsy or surgery	7. Baseline (both arms) and after 2-4 weeks of AI (in both arms) and at surgery (in comparator arm);
	8. To assess the surgical and locoregional management of the breast [1]	8. 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	8. Post-operative, 15 months post-randomisation

		reconstruction postmastectomy, breast radiotherapy	
	9. To assess the surgical and locoregional management of the axilla [1]	9. Rates of sentinel node biopsy, axillary clearance, axillary radiotherapy	9. Post-operative, 15 months post-randomisation
	10. To compare rates of local and distant recurrence [1]	10. Rates of local and distant recurrence	10. Post-surgery, 15 months post-randomisation, and periodically for long term follow up [3]
	11. To compare breast cancer specific survival in both arms [1]	11. Breast cancer specific and overall survival;	11. Post-surgery, 15 months post-randomisation and periodically for long term follow up [3]
	12. 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]	12. Resource utilisation, cost and cost-effectiveness of implementing NET followed by surgery and adjuvant ET compared with the current practice.	12. Baseline, 7, 12 and 15 months post randomisation
	13. 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]	13. Accuracy of USS (and MRI where available) to determine conversion to BCS	13. 2-4 weeks, 3 months and 5 months post-randomisation
	14. To compare the requirement for adjuvant chemotherapy in both arms [1]	14. Number of patients receiving adjuvant chemotherapy in both arms	14. By 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. *This sub-study will be included in EndoNET via submission of a substantial amendment at a later date.* **The sub-study aims** to explore the experiences of patients during years 2 and 3 of 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	The following will be explored in both arms of the trial: • Experiences, beliefs, expectations and preferences of women in the trial and how this may affect HRQoL • Whether experiences vary with participant characteristics (e.g. age, treatment type), and if so, how?	Prior to NET starting and 6 months after surgery

interpretation of HRQoL findings and outcomes.		

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] These are secondary objectives that will be assessed subject to additional funding and/or resource and via submission of a substantial 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 1,440 post-menopausal women with strongly ER+, HER2- invasive breast cancer who are considered unlikely to require chemotherapy 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 and it was 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 co-primary outcome measures are global HRQoL over 15 months measured by FACT-B and the BCS rate.

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 will be at month 18 (after 12 months recruitment) to ensure 12 sites have opened and 150 participants are randomised. If met, the trial will recruit for a further 30 months. Data from the internal pilot will be included in the final analysis. Full-scale recruitment has not been factored into the trial until month 27 to allow staggered opening of centres.

7.2 Trial Schema

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

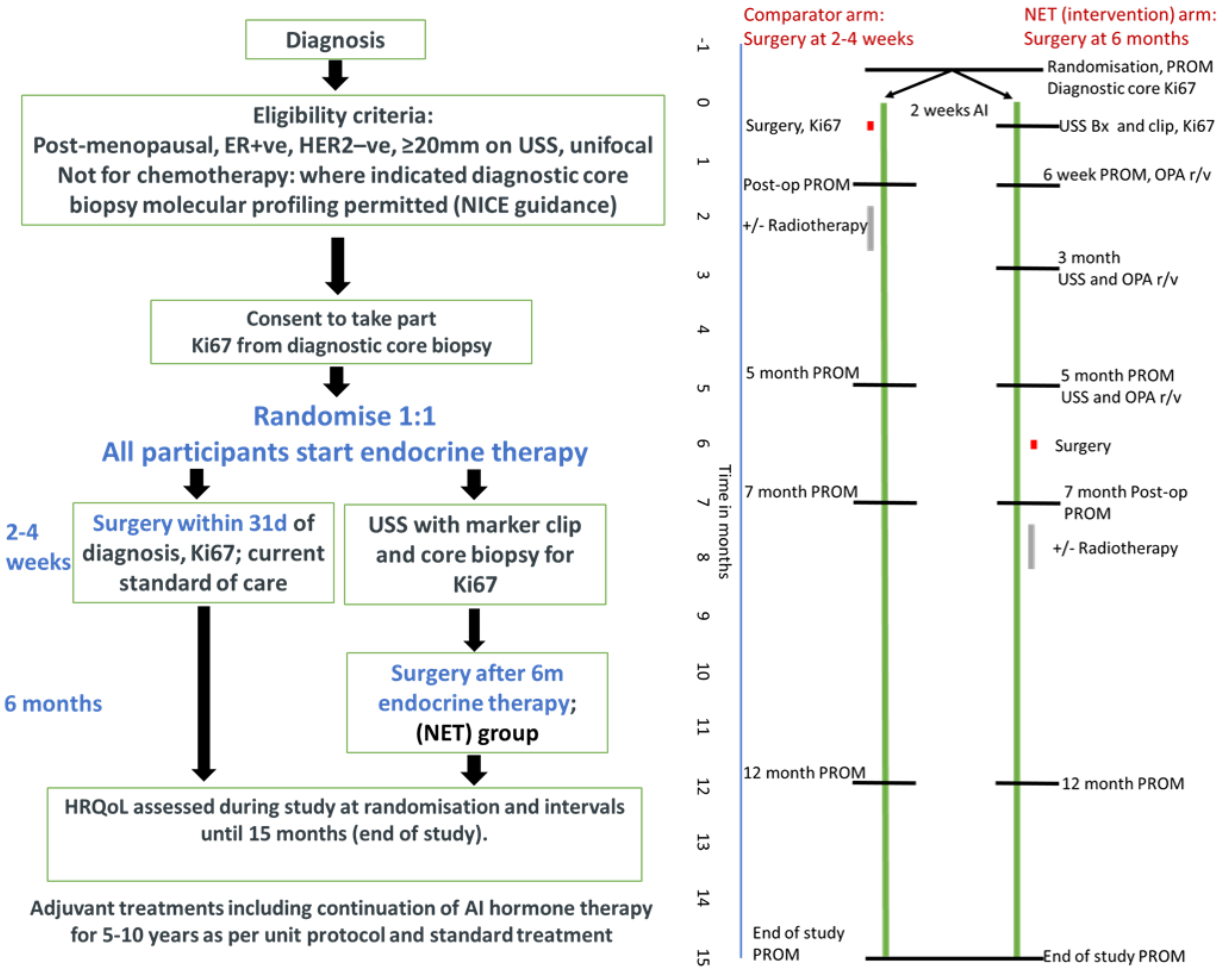

Figure 1. Left panel: Study schema. All participants commence endocrine therapy at randomisation; in comparator arm surgery at 2-4 weeks (within NHS 31-day target, although up to 8 weeks permitted for

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.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Post-menopausal women with strongly ER+, HER2- invasive breast cancer who are considered unlikely to require chemotherapy.

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; including one of:
    - amenorrhoea >12 months and an intact uterus.
    - bilateral oophorectomy
    - for those with a history of hysterectomy, or HRT within 12 months, venous FSH levels classified as post-menopausal by the testing laboratory if any doubt.
- Unifocal, newly diagnosed breast cancer visible on USS;
- Strongly ER+; defined as Allred scores of 7 or 8 or equivalent
- HER2- by immunohistochemistry, or 2+ and not amplified by in situ hybridisation
- T-stage 2 or 3 (>2cm);
- Axillary N0-1 on diagnostic USS +/- negative FNA or core biopsy;
- Suitable for surgery and radiotherapy;
- Chemotherapy unlikely to be indicated;
- 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.

8.2.2. Exclusion Criteria

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

- Bilateral breast cancer;
- ER- or HER2+;
- Stage IV disease (distant metastasis);
- Previous neoadjuvant treatment for breast cancer;
- Previous invasive malignancy within 5 years other than basal cell carcinoma;

- Concurrent use (at the time of randomisation) of HRT or any other oestrogen-containing medication (including vaginal oestrogens);
- Ovarian suppression/ablation for the purposes of trial entry not permitted.

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

9. TRIAL PROCEDURES

9.1. **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, 12 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. A nested '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.

Visits / Procedures	Baseline – Day 0		2-4 Weeks (up to 8 weeks permitted)	6 Weeks (+/- 2 weeks)	3 Months (+/- 1 month)	5 Months (+/- 1 month)	6 Months (+/- 1 month)	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									
Participant questionnaires: FACT-B+4/ES	X			X		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									
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*			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^3	X^3	X^3	X^3	X^3	X^2	X^2

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

9.2. **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 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 1,440 women over 3.5 years feasible.

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

9.2.1. **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).

9.2.1.1. *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.

9.2.1.2. *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.

9.2.1.3. *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.

9.2.2. **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.

9.2.3. **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).

9.3. 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.

9.3.1. 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.

9.4. 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 the recommended minimum of 24 hours 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.

9.4.1 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. **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);
- 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. If RRAMP is down for any reason, the research nurse/site will need to contact the central trial office in order to resort to the emergency randomisation schedule which will be created for the trial.

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 be continue to participate in the study but will be analysed on an intention to treat basis.

9.6. 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.

9.7. 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).

9.8. Trial imaging (Main Trial)

9.8.1. 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.

9.8.2. **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.

9.9. **Surgical treatment (Main Trial)**

Since surgical treatments constitute one of the co-primary endpoints 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.

9.10. 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).

9.11. Radiotherapy

9.11.1. 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.

9.12. Subsequent 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 (pre-randomisation), 2-4 weeks, 6 weeks, 5 months, 7, 12 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.

9.13. Sample Handling (Main Trial)

9.13.1. 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).

9.13.2. 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.

9.14. 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 an and/or follow-up at any time without prejudice, without this affecting their clinical care. Participants will be considered withdrawn if they have been withdrawn from ALL trial procedures including collection of follow-up information via all sources. 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 Digital 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.

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:

- Ineligibility
- Significant protocol deviation
- Significant non-compliance with the investigation or study requirements
- Clinical decision including a decision that it is unsafe to proceed to biopsy
- An adverse event which results in inability to continue to comply with trial procedures.

9.15. 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.

9.16. 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 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.

9.17. 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. If and when such funding or resources are obtained and subject to submission via substantial amendment, 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 Digital/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.

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**

Compliance in this trial is to be distinguished from crossover. Here we define compliance as when the participant takes the AI medication as assessed with the Compliance CRF. Crossover is defined as when a participant, who is randomised to the NET arm, has early surgery. Non-compliance or an inability to tolerate trial medication may be one reason for this.

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)

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.

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_Reference_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 . 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 with 24hrs, 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)

Full details of the statistical analysis will be detailed, in advance of un-blinding of the data, in a pre-specified statistical analysis plan (SAP). The SAP will be written in accordance with the current OCTRU SOPs and will be finalized and agreed by the study statistician, the CI and the TMG.

12.2 Description of Statistical Methods

Results will be reported in line with the CONSORT statement (101).

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 of the co-primary endpoints 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 first co-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.

The second co-primary endpoint, FACT-B scores will be compared between the two arms using a mixed effects linear regression model. The model will be include treatment, baseline score, time-by-treatment interaction and clinical stratification factors as fixed effects. Patient and centre will be included as a random effect. The mean FACT-B score and standard deviations will be plotted over time for visual representation. Additionally, a sensitivity analysis will be conducted that adjusts for other important prognostic factors.

Secondary outcomes, 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. HRQoL outcomes will be compared with methods that mirror that of the co-primary outcome, FACT-B. The predictive ability of Ki67 will be explored using logistic regression models. Time-to-event outcomes 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 outcomes will be compared using a two-group t-test and the difference in means will be presented with a 95% confidence interval. Binary outcomes will be compared using a chi-squared test and the effect estimate reported in terms of the relative risk and 95% confidence interval. Ordinal outcomes will be compared using a chi-squared test for trend. Multilevel regression models, with adjustment for stratification factors in line with the primary outcome analyses, will be applied to all secondary outcomes where it is both practical to do so and there are sufficient events to support these approaches.

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. To allow for having co-primary outcome measures, a p-value of <0.025 will be considered statistically significant. All secondary outcomes, collected in both treatment arms, will be considered statistically significant for p-values <0.05. Rather than adjust for multiplicity, relevant results from other studies already reported in the literature will be taken into account when interpreting results.

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

12.3 Sample Size Determination

We aim to recruit 1,440 (720 per arm) women over 3.5 years 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. This sample size would allow us to detect this difference with 90% power at a two-sided 2.5% significance level allowing for a cross-over and non-completion of FACT-B questionnaire at 15 months up to 18%; 18% is based non-completion rates in the ATAC trial quality of life study (38) and data from discontinuation rates within 7 RCTs of AI treatment in breast cancer (66). If the event rates in the control arm is lower than anticipated, say 35%, statistical power would be over 90% to detect a clinically meaningful 10% difference.

Additionally, assuming a 15-month improvement in the FACT B score in the NET arm of a 0.2 SD effect size difference, this sample size would provide 88% power at a two-sided 2.5% significance level and allow for 15% cross-over to detect this difference. The assumed difference of a 0.2 SD is the recommended minimally clinically important difference score in FACT-B scores and equates to a four-point difference in the overall score. A 5-point difference is also considered clinically meaningful (38, 45). The sample size provides 90% power at a two-sided 2.5% significance level to detect a standardised effect difference of at least 0.22.

12.4 Analysis Populations

The primary analysis population will be all randomised participants according to the intention-to-treat principle.

12.5 Stopping Rules

No formal interim 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.

Formal stop/go review will be at month 18 (after 12 months recruitment) to ensure 12 sites have opened and 150 patients are randomised.

Target	**Actual recruitment in 12 months**		
	>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.

12.6 The Level of Statistical Significance

The primary analysis will be performed at a 2-sided 2.5% significance level to account for co-primary outcome measures. All other outcomes will be analysed at a 2-sided 5% significance level.

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), 7 months (F1), 12 months (F2) and 15 months (F3) post randomisation to indicate health care resource use from 6 weeks prior to randomisation to baseline, baseline to 7 months, from 7 to 12 months and from 12

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 be cross-walked 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.

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 9.17, 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 and/or telephone may be utilised for follow up questionnaires.*

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.

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.

22. REFERENCES

1. Peto et al. UK and USA breast cancer deaths down 25% in year 2000. Lancet. 2000;355(9217):1822.
2. Chopra I, Kamal KM. A systematic review of quality of life instruments in long-term breast cancer survivors. Health Qual Life Outcomes. 2012;10:14.
3. The second all breast cancer report. National Cancer Intelligence Network; West Midlands Cancer Intelligence Unit. 2011. Available from http://www.ncin.org.uk/publications/. Accessed 28 November 2019.
4. The National Audit of Breast Cancer in Older Patients 2019 Annual Report. ABS and RCSEng, Available: https://www.nabcop.org.uk/reports/nabcop-2019-annual-report/. Accessed 28 November 2019.
5. NHS BSP & ABS. An audit of screen detected breast cancers April 2017 to March 2018. Available: https://associationofbreastsurgery.org.uk/media/65088/nhsbsp-abs-audit-2017-to-2018.pdf.
6. Pariser AC et al. Utilization, duration, and outcome of neoadjuvant endocrine therapy in the US BCRT. 2019.
7. Jeevan R et al. National trends and variation in immediate reconstruction. BJS. 2016;103(9):1147-56.
8. Al-Ghazal SK et al. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. EJC. 2000;36(15):1938-43.
9. Harcourt DM et al. The psychological effect of mastectomy with or without breast reconstruction: a prospective, multicenter study. Plast Reconstr Surg. 2003;111(3):1060-8.
10. Potter S et al. Short-term safety outcomes of mastectomy and immediate implant-based breast reconstruction with and without mesh (iBRA). The Lancet Oncology. 2019;20(2):254-66.
11. ABS and BAPRAS National Mastectomy and Breast Reconstruction Audit 2010. Third annual report. Available from: https://associationofbreastsurgery.org.uk/media/1084/nmbra-annual-report-2010.pdf
12. Rusby JE et al. Immediate reconstruction after mastectomy. AnnRCollSurgEngl. 2010;92(3):193-7.
13. Cochrane RA et al. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. The British journal of surgery. 2003;90(12):1505-9.
14. Waljee JF et al. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. Journal of clinical oncology. 2008;26(20):3331-7.
15. Jeevan R et al. Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics. BMJ : British Medical Journal. 2012;345:e4505.
16. Irwin GW et al. The NeST (neoadjuvant systemic therapy in breast cancer) study – Protocol for a prospective multi-centre cohort study. International Journal of Surgery Protocols. 2019;18:5-11.
17. McIntosh SA et al. National utilisation of neoadjuvant systemic therapy and impact on surgical treatment- A prospective multi-centre cohort. DOI: 101158/1538-7445SABCS19-P2-16-04 Published February 2020.
18. Early Breast Cancer Trialists Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast
cancer: meta-analysis of individual patient data. The Lancet Oncology. 2018;19(1):27-39.
19. Alba E et al. Chemotherapy and hormonotherapy as neoadjuvant treatment: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Annals of oncology. 2012;23(12):3069-74.
20. Smith LI et al. Attitudes towards breast conservation in patients over 70. Springerplus. 2016;5:478-
21. Van de Haar J et al. Caring for patients with cancer in COVID-19 era. Nat medicine. 2020;26(5):665-71.
22. Association of Breast Surgery. 15th March 2020. Confidential advice for health professionals. Available from: https://associationofbreastsurgery.org.uk/media/252009/abs-statement-150320-v2.pdf
23. Hind D et al. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). The Cochrane database of systematic reviews. 2006(1):Cd004272.

24. Walton L et al. Breast reconstruction in elderly women breast cancer. Cancer tr rev. 2011;37(5):353-7.
25. Early and locally advanced breast cancer: diagnosis and management. NICE NG101. Available from https://www.nice.org.uk/guidance/ng101/chapter/Recommendations. Accessed 28 November 2019.
26. Early and locally advanced breast cancer: diagnosis and management. NICE NG101 Evidence summary J. Available from https://www.nice.org.uk/guidance/ng101/history. Accessed 28 November 2019.
27. Mustacchi G et al. Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized GRETA trial. Annals of oncology : 2003;14(3):414-20.
28. Spring LM et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology. 2016;2(11):1477-86.
29. Seo JH et al. Meta-analysis of pre-operative aromatase inhibitor versus tamoxifen in hormone receptor positive breast cancer. Cancer chemotherapy and pharmacology. 2009;63(2):261-6.
30. Chiba A et al. Trends in Neoadjuvant Endocrine Therapy Use and Impact on Rates of Breast Conservation A National Cancer Data Base Study. Annals of surgical oncology. 2017;24(2):418-24.
31. Carpenter R et al. Optimum duration of neoadjuvant letrozole to permit breast conserving surgery. Breast cancer research and treatment. 2014;144(3):569-76.
32. Dixon JM et al. Increase in response rate by prolonged treatment with neoadjuvant letrozole. BCRT. 2009;113(1):145-51.
33. Allevi G et al. Increased pathological complete response rate after a long-term neoadjuvant letrozole treatment in postmenopausal breast cancer. Br J Cancer. 2013;108(8):1587-92.
34. Johnston S et al. Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy: PALLET Trial. Journal of Clinical Oncology. 2019;37(3):178-89.
35. Update on Phase 3 PALLAS Trial of palbociclib: https://investors.pfizer.com/investor-news/pressrelease-details/2020/Pfizer-Provides-Update-on-Phase-3-PALLAS-Trial-of-IBRANCE-palbociclib-PlusEndocrine-Therapy-in-HR-HER2--Early-Breast-Cancer/default.aspx. Accessed 16 July 2020.
36. Fallowfield L. Quality of Life in the Elderly Woman with Breast Cancer Treated with Tamoxifen and Surgery or Tamoxifen Alone. Journal of Women's Health. 1994;3(1):17-20.
37. Taira N et al. Health-related quality of life and psychological distress during neoadjuvant endocrine therapy with letrozole. Breast cancer research and treatment. 2014;145(1):155-64.
38. Fallowfield L et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. Journal of clinical oncology. 2004;22(21):4261-71.
39. Fallowfield LJ et al. Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen. Journal of clinical oncology: 2006;24(6):910-7.
40. Fallowfield LJ et al. Long-term assessment of quality of life in the Intergroup Exemestane Study: 5 years post-randomisation. Br J Cancer. 2012;106(6):1062-7.
41. Kiebert GM et al. The impact of breast-conserving treatment and mastectomy on the quality of life of early-stage breast cancer patients: a review. Journal of clinical oncology. 1991;9(6):1059-70.
42. Irwig L et al. Quality of life after breast conservation or mastectomy Aust N Z J Surg.1997;67(11):750-4.
43. de Haes JC, van Oostrom MA, Welvaart K. The effect of radical and conserving surgery on the quality of life of early breast cancer patients. European journal of surgical oncology. 1986;12(4):337-42.
44. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Hölzel D. Quality of life following breast-conserving therapy or mastectomy: results of a 5-year prospective study. The breast journal. 2004;10(3):223-31.
45. Brady MJ et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality of-life instrument. Journal of clinical oncology: 1997;15(3):974-86.

46. Fallowfield LJ et al. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. BCRT. 1999;55(2):189-99.
47. Coster S et al. The validation of a quality of life scale to assess the impact of arm morbidity in breast cancer patients post-operatively. Breast cancer research and treatment. 2001;68(3):273-82.
48. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient reported outcome measure for breast surgery: the BREAST-Q. Plast Reconstr Surg. 2009;124(2):345-53.
49. Hopwood P et al. A body image scale for use with cancer patients. EJC. 2001;37(2):189-97.
50. Fumagalli D et al. A common language in neoadjuvant breast cancer clinical trials: proposals for standard definitions and endpoints. The Lancet Oncology. 2012;13(6):e240-e8.
51. Gao Q et al. Impact of AI treatment on global gene expression and its association with antiproliferative response in ER+ breast cancer in postmenopausal patients. Breast Cancer Res. 2019;22(1):2.
52. Smith IE et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both: IMPACT multi center double-blind randomized trial. Journal of clinical oncology. 2005;23(22):5108-16.
53. Dowsett M et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. Journal of the National Cancer Institute. 2007;99(2):167-70.
54. Robertson J et al. Abstract GS1-03: Peri-operative AI treatment in determining or predicting long term outcome in early breast cancer. The POETIC Trial. Cancer Research. 2018;78(4 Supplement)
55. Ellis MJ et al. Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the Z1031 Trial (Alliance). Journal of clinical oncology : 2017;35(10):1061-9.
56. Leung SCY et al. Analytical validation of a standardized scoring protocol for Ki67: phase 3 of an international multicenter collaboration. NPJ Breast Cancer. 2016;2:16014.
57. Rimm DL et al. An international multicenter study to evaluate reproducibility of automated scoring for assessment of Ki67 in breast cancer. Mod Pathol. 2019;32(1):59-69.
58. Marinovich ML et al. Agreement between MRI and pathologic tumor size after neoadjuvant chemo, comparison with alternative tests: individual patient meta-analysis. BMC Cancer. 2015;15:662.
59. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Diagnostics guidance [DG34] December 2018: https://www.nice.org.uk/guidance/dg34/chapter/1-Recommendations.
60. Getting it right first time GIRFT: https://gettingitrightfirsttime.co.uk/. Accessed 2 December 2019.
61. All Party Parliamentary Group on Cancer: https://www.macmillan.org.uk/_images/APPGC%20-%20Measuring%20Progress_tcm9-291260.pdf. Accessed 3 December 2019.
62. Karakatsanis A et al. Meta-analysis of neoadjuvant therapy and its impact in facilitating breast conservation in operable breast cancer. British Journal of Surgery. 2018;105(5):469-81.
63. Palmieri C et al. NEOCENT: a randomised translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal breast cancer. BCRT 2014;148(3):581-90.
64. Davies C et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378(9793):771-84.
65. Ellis MJ et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer. JCO 2001;19(18):3808-16.
66. Verma S et al. Patient adherence to AI treatment. Curr Oncol. 2011;18 Suppl 1(Suppl 1):S3-S9.
67. Samsa G et al. Determining Clinically Important Differences. PharmacoEconomics. 1999;15(2):141-55.
68. Guerrero-Zotano AL, Arteaga CL. Neoadjuvant Trials in ER(+) Breast Cancer: A Tool for Acceleration of Drug Development and Discovery. Cancer Discov. 2017;7(6):561-74.

69. Skriver SK et al. Neoadjuvant letrozole for postmenopausal estrogen receptor-positive, HER2-negative breast cancer. Acta oncologica (Stockholm, Sweden). 2018;57(1):31-7.
70. Rooshenas L et al. The QuinteT Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation. Journal of clinical epidemiology. 2019;106:108-20.
71. Rooshenas L et al. Conveying Equipoise during Recruitment for Clinical Trials: Qualitative Synthesis of Clinicians' Practices across Six Randomised Controlled Trials. PLoS medicine. 2016;13(10):e1002147.
72. Donovan JL et al. The intellectual challenges and emotional consequences of equipoise contributed to the fragility of recruitment in six RCTs. Journal of clinical epidemiology. 2014;67(8):912-20.
73. Stein RC et al. OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer. Health technology assessment. 2016;20(10):xxiii-xxix, 1-201.
74. Conefrey C et al. Strategies to Improve Recruitment to a De-escalation Trial: A Mixed-Methods Study of the OPTIMA Prelim Trial in Early Breast Cancer. Clinical oncology. 2020;32(6):382-9.
75. Donovan JL et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). Trials. 2016;17(1):283.
76. Glaser B SA. The discovery of grounded theory. Chicago: Aldine Pub. Co.; 1967.
77. Rooshenas L et al. Intensive Triangulation of Qualitative Research and Quantitative Data to Improve Recruitment to Randomized Trials: The QuinteT Approach. Qualitative health research. 2019;29(5):672-9.
78. NICE. Guide to technology appraisal 2013. https://www.nice.org.uk/process/pmg9/resources/guide-tothe-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 28 November 2019.
79. Glick HA et al. Economic Evaluation in Clinical Trials. Volume 2. Oxford: Oxford University Press; 2015.
80. Herdman M et al. Development and preliminary testing of EQ-5D-5L. QOL research 2011;20:1727-36.
81. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health economics. 2005;14(5):487-96.
82. Breast-Q | Breast Cancer. Available from: https://qportfolio.org/breast-q/breast-cancer/. Accessed 20 January 2022.
83. Bojke L et al. How to Extrapolate Costs and Utilities. PharmacoEconomics. 2017;35(8):767-76.
84. Menon U et al. Cost-effectiveness of screening for ovarian cancer. Br J Cancer. 2017;117(5):619-27.
85. Moore GF et al. Process evaluation of complex interventions: MRC guidance. BMJ 2015;350:h1258.
86. Glasziou P et al. Reducing waste from biomedical research. Lancet. 2014;383(9913):267-76.
87. Cheng KKF, Metcalfe A. Qualitative Methods and Process Evaluation in Clinical Trials Context: Where to Head to? International Journal of Qualitative Methods. 2018;17(1):1609406918774212.
88. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. BMJ (Clinical research ed). 2009;339:b3496.
89. Drabble SJ et al. Describing qualitative research undertaken with randomised controlled trials in grant proposals: a documentary analysis. BMC Medical Research Methodology. 2014;14(1):24.
90. NICE BNF Treatment summary: Breast Cancer. Available from: https://bnf.nice.org.uk/treatmentsummary/breast-cancer.html. Accessed 19 July 2020.
91. RCP Diagnostic procedures in breast screening: https://wwwrcpathorg/uploads/assets/4b16f19c-f7bd456c-b212f557f8040f66/G150-Non-op-reporting-breast-cancer-screening-Feb17pdf.
92. RCP reporting breast disease in surgical specimens: https://wwwrcpathorg/uploads/assets/7763be1cd330-40e8-95d08f955752792a/G148_BreastDataset-hires-Jun16pdf.
93. Pinder SE et al. Discrepancies in central review re-testing of patients with ER-positive and HER2-negative breast cancer in the OPTIMA prelim randomised clinical trial. Br J Cancer. 2017;116(7):859-63.

94. Paramasivan, S. et al. (2015). A simple technique to identify key recruitment issues in randomised controlled trials: Q-QAT—Quanti-Qualitative Appointment Timing. Trials, 16, Article 88. doi:10.1186/s13063-015-0617-1.
95. NICE Guidance. Early and locally advanced breast cancer: diagnosis and management. Overview | Early and locally advanced breast cancer: diagnosis and management. Available from: https://www.nice.org.uk/guidance/ng101. Accessed 30 August 2021.
96. Dave R.V. et al. Breast cancer management pathways during the COVID-19 pandemic: outcomes from the UK 'Alert Level 4' phase of the B-MaP-C study. Br J Cancer. 2021 May;124(11):1785-1794. doi: 10.1038/s41416-020-01234-4.
97. Fleissig A et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat. 2006 Feb;95(3):279-93. doi: 10.1007/s10549-005-9025-7.
98. Reis et al. Accuracy of breast MRI in patients receiving neoadjuvant endocrine therapy: comprehensive imaging analysis and correlation with clinical and pathological assessments
Breast Cancer Research and Treatment volume 184, pages407–420 (2020).
99. Wilson C et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. Trials. 2018 Jan 19;19(1):50. doi: 10.1186/s13063-017-2413-6.
100. https://www.rcpath.org/uploads/assets/7763be1c-d330-40e8-95d08f955752792a/G148_BreastDataset-hires-Jun16.pdf
101. Schulz KF, Altman DG ,Moher D. CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–58.doi:10.7326/0003-4819-152-11-201006010-00232.
102. Eisenhauer E.A et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer (45). 2009: 228-247. oi:10.1016/j.ejca.2008.10.026.
103. Ellis MJ et al. Outcome Prediction for Estrogen Receptor–Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics. JNCI: Journal of the National Cancer Institute, Volume 100, Issue 19, 1 October 2008, Pages 1380–1388, https://doi.org/10.1093/jnci/djn309.

23. APPENDIX 1: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made