



Protocols

The NeST (neoadjuvant systemic therapy in breast cancer) study – Protocol for a prospective multi-centre cohort study to assess the current utilization and short-term outcomes of neoadjuvant systemic therapies in breast cancer

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ARTICLE INFO

Article history:

Received 20 September 2019

Received in revised form 17 October 2019

Accepted 19 October 2019

Available online 11 November 2019

Keywords:

Breast cancer

Neoadjuvant chemotherapy

Neoadjuvant endocrine therapy

Surgery

Pathology

Radiology

Patterns of care

Outcomes

ABSTRACT

Introduction: Neoadjuvant systemic therapy (NST) has several potential advantages in the treatment of breast cancer. However, there is currently considerable variation in NST use across the UK. The NeST study is a national, prospective, multicentre cohort study that will investigate current patterns of care with respect to NST in the UK.

Methods and analysis: Phase 1 – a national practice questionnaire (NPQ) to survey current practice.

Phase 2 – a multi-centre prospective cohort study of breast cancer patients, undergoing NST.

Women undergoing NST as their MDT recommended primary breast cancer treatment between December 2017 and May 2018 will be included. The breast surgery and oncological professional associations and the trainee research collaborative networks will encourage participation by all breast cancer centres.

Patient demographics, radiological, oncological, surgical and pathological data will be collected, including complications and the need for further intervention/treatment. Data will be collated to establish current practice in the UK, regarding NST usage and variability of access and provision of these therapies. Prospective data on 600 patients from ~50 centres are anticipated.

Trial registration: ISRCTN11160072.

Ethics and dissemination: Research ethics approval is not required for this study, as per the online Health Research Authority decision tool. The information obtained will provide valuable insights to help patients make informed decisions about their treatment. These data should establish current practice in the UK concerning NST, inform future service delivery as well as identifying further research questions.

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This protocol will be disseminated through the Mammary Fold Academic Research Collaborative (MFAC), the Reconstructive Surgery Trials Network and the Association of Breast Surgery. Participating units will have access to their own data and collective results will be presented at relevant conferences and published in appropriate peer-reviewed journals, as well as being made accessible to relevant patient groups.

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1. Background

Breast cancer affects 54,000 women per year in the United Kingdom (UK) [1], and treatment comprises a combination of loco-regional therapies (surgery and radiotherapy) as well as systemic treatments (chemotherapy, endocrine and biological therapies). Selection of systemic therapies is made at an individual patient level, based on tumour biology, clinicopathological variables and patient fitness and preference.

Randomised trials have shown that systemic chemotherapy is equally effective in both the neoadjuvant and adjuvant settings, in terms of overall and distant disease-free survival [2,3]. However, the prescription of systemic therapies in the neoadjuvant setting may have some specific advantages over their adjuvant use.

Neoadjuvant therapy facilitates *in vivo* assessment of tumours' sensitivity to specific treatments. Attaining a pathological complete response (pCR) following neoadjuvant treatment is an excellent prognostic indicator at an individual patient level [4]. Pathological complete response rates vary according to breast cancer subtype, and may be as high as 60% in the HER2 positive subgroup [5–7]. Where pCR is not achieved patients at high risk of relapse may be stratified to additional adjuvant treatments to improve their outcome. Neoadjuvant therapy (NST) may also downsize primary cancers in order to facilitate breast-conserving surgery, where a mastectomy would otherwise have been required. This is an attractive option for many patients who wish to preserve their breast. Notably however a recent meta-analysis demonstrated that the modest gains in breast conservation with the use of NST, are associated with higher local recurrence rates, although this reflects historical patient data who received suboptimal local therapy when compared to today's standards [8].

Neoadjuvant endocrine therapy has also been utilised in oestrogen receptor (ER) positive breast cancer [9]. Indeed, some studies have suggested that in strongly hormone receptor positive disease, it may be as effective as chemotherapy. In current practice neoadjuvant endocrine therapy tends to be reserved for older, less fit patients [10,11].

There are limited data about the utilization of NST throughout the UK. A recent study in the Netherlands found wide variance in NST use, with rates ranging from 0–97% in different centres [12]. The UK Mastectomy Decisions Audit (MasDA) highlighted inconsistencies in the utilisation of neoadjuvant treatment across the UK [13]. Many patients with large ER positive or HER2 positive tumours, who were potentially candidates for NST and were likely to benefit most from downstaging, proceeded directly to mastectomy without being offered NST.

Where NST takes place, increasing pCR rates have not been matched by increasing rates of breast conservation [14,15]. One issue is a lack of consensus in surgical approach to excising the tumour footprint in the breast and axilla, and indeed, whether or not surgery is required at all following apparent complete response. This is an area of ongoing research [16]. Furthermore, there is variation in surgical practice with respect to the timing of SLNB in relation to neoadjuvant therapy, with some centres performing pre-treatment SLNB, and others tailoring axillary treatment to the post-neoadjuvant clinical and radiological picture

[17]. There is also substantial variation in methods for reporting response to NST, both in terms of radiological monitoring of response during treatment and assessing clinical response [18]. Finally, the lack of consistency in reporting of pathological treatment response makes the interpretation of clinical trial outcomes and the planning of further treatment or future research difficult given much variability [19].

Therefore, there appears to be considerable variation in the utilization of NST across the UK. There is a need to explore current UK practice through a large-scale, multicentre prospective cohort study, and to use the data generated to define best practice.

Although there are challenges in undertaking such a large-scale, prospective, multicentre cohort study, the trainee research collaborative model has emerged as both a time- and cost-efficient method for delivering high-quality prospective audit and research [20,21]. These have a proven track record in prospective cohort studies [22–24], and more recently, this model has been applied successfully in the field of breast surgery through the iBRA and MasDA studies [13,25–27]. The NeST (Neoadjuvant Systemic Therapy in breast cancer) study aims to work with the Northern Ireland Surgical Research Collaborative, the Mammary Fold Academic and Research Collaborative and existing networks of enthusiastic breast surgery trainees and MDT consultants to deliver a robust assessment of current practice and a high-quality prospective audit of practice and outcomes of NST across the UK.

2. Methods and analysis

2.1. Primary aim

The aim of NeST is to work with the trainee collaborative network to elucidate current practice of NST in breast cancer in the UK. Specific objectives will be

1. To establish current stated practice regarding the use of NST across the UK
2. To determine the current practice of NST including
 - Indications for use
 - Treatment modalities in common use
 - Monitoring of response to treatment
 - Pathological reporting of response to NST
3. To document surgical decision-making in the context of NST with respect to both the breast and axilla
4. To determine the use of further adjuvant therapies (radiotherapy and systemic therapies) following NST
5. To determine pathological response rates to NST in routine clinical practice
6. To establish best practice with regards to the use of NST, with a view to generating national guidelines

The study aims and objectives are summarised in Table 1.

2.2. Study design

The NeST study consists of two parts:

Table 1
Study objectives and endpoints

	Endpoint	Outcome measure
Primary endpoints	To investigate variation in use of neoadjuvant systemic therapies in the UK	<ul style="list-style-type: none"> Percentage of patients being treated with neoadjuvant chemotherapy and endocrine therapy Percentage of patients in each tumour molecular subtype Percentage of patients having mastectomy/breast conserving surgery
	To assess surgical practice following neoadjuvant therapy	
Secondary endpoints	Determine pathological response rates after neoadjuvant therapy	<ul style="list-style-type: none"> Pathological complete response rate (as a percentage of all treated patients) to neoadjuvant therapy
	Explore the stated indications for the use of neoadjuvant systemic therapy in current UK practice	<ul style="list-style-type: none"> Indications given by multidisciplinary team for choice of treatment
	Examine treatment regimens in common use	<ul style="list-style-type: none"> Prescribed treatment regimens for neoadjuvant therapy
	Investigate how response to neoadjuvant therapy is monitored and reported across the UK	<ul style="list-style-type: none"> Number of patients having imaging (and which imaging modality) during therapy
	Investigate surgical management of the axilla following neoadjuvant therapy	<ul style="list-style-type: none"> Percentage of patients having sentinel lymph node biopsy and axillary node clearance before and after neoadjuvant therapy

2.2.1. Phase 1 – national current practice questionnaire

Phase 1 aims to document current stated practice with respect to the use of NST in the UK, and will be delivered via a National Practice Questionnaire (NPQ), applied to all participating MDTs. The NPQ will be developed by members of the steering group. It will assess stated indications for NST, surgical management of the breast and axilla post-NST and systems for monitoring and reporting responses to treatment. The NPQ will be piloted in 2–3 centres and iteratively modified based on feedback to ensure completeness and ease of use.

All breast cancer multidisciplinary teams will be invited to participate in the NPQ phase. A trainee lead at each centre will be identified and will be asked to complete the questionnaire with input from all MDT members.

2.2.2. Phase 2 – multi-centre prospective cohort study of patients treated with neoadjuvant systemic therapy

The aim of Phase 2 is to document the actual practice and outcomes of NST of breast cancer in the UK.

All surgical and oncological units treating patients with breast cancer in the UK will be eligible to participate. Units will be invited by email to participate through the Mammary Fold (MF) Breast Trainees' Association, the Association of Breast Surgery, the Association of Surgeons in Training, the National Trainee Research Collaborative (NTRC), the Breast Cancer Trainees Research Collaborative Group, the NCRI Breast Clinical Studies Group (CSG) and the Reconstructive Surgery Trials Network (RSTN). These professional associations have endorsed the study and will encourage units to participate and support their trainees in recruiting patients and collecting data.

Participating centres will recruit consecutive patients recommended to receive NST into the study. Potential participants will be identified prospectively by the local study team via clinics, local MDT meetings, consultant surgeons and clinical nurse specialists.

Inclusion/exclusion criteria are summarised in [Table 2](#).

Simple demographics, procedure and process data will be collected for each participant. Data will be recorded in an anonymised format using a unique alphanumeric study identification number on a secure web-based database (REDCap) designed by Vanderbilt University to support data capture for research studies [28,29]. The database has been designed using advanced logic, such that only data fields relevant to the treatment modality used (e.g. chemotherapy or endocrine therapy) will appear in the data capture forms. This will minimize the burden of data collection and entry for collaborators, optimizing data quality within the study.

Data regarding treatment, clinical/radiological response and surgical outcomes will be collected prospectively. Indications for NST will be classified, in priority order where possible, as primary and secondary. The required data fields for the prospective study

are shown summarised in the protocol appendices ([Supplementary data files](#)). For the purpose of this study, pCR will be defined as 'no residual invasive disease in either breast or axillary lymph nodes' as this has been shown to have the strongest correlation with event-free and overall survival [31]. Clinical and radiological response will be described using modified RECIST criteria [30] as shown in [Table 3](#).

Pathological response data will be obtained from the formal histological report from local pathology department. Similarly, radiological response details will be obtained from reports of breast imaging by radiologists, clinical response from medical notes/ electronic patient record and details of systemic treatment from notes/electronic patient record/ electronic chemotherapy or drug prescribing systems. Data will also be collected on patients for whom neoadjuvant systemic therapy was recommended by the local MDT but declined by the patient, including reasons for declining treatment.

2.2.2.1. Data validation and management. For quality assurance purposes, the consultant principal investigator at selected sites will nominate an independent individual to validate a percentage of submitted data. Approximately 5% of submitted datasets will be independently validated. Independent assessors will be required to confirm the reliability of data by examining MDT meeting records, theatre logbooks and operating diaries and computer systems to ensure that appropriate cases have been accurately recorded. If concordance between independent assessors and submitted data is <90%, data from that unit will not be included in the analysis. Only datasets with >90% data completeness will be included in the final analysis. This is similar to quality assurance measures utilised in projects of a similar nature [31].

Data collection will adhere to Caldicott II principles [32]. Data for each patient will be anonymised with a unique alphanumeric code. No patient identifiable data will be stored or recorded centrally for the purposes of this study. Anonymised data only will be uploaded to the REDCap database. Patient identifiers will be stored locally at each participating hospital following local institutional approval, and will be held in line with the institution's

Table 2
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age > 16 years	Patients entering "window of opportunity" clinical trials
Histologically confirmed diagnosis of breast cancer	
MDT recommended treatment of neoadjuvant systemic therapy	

Table 3
Modified RECIST response criteria.

Complete Response	No evidence of residual disease on clinical examination or standard routine imaging
Partial Response	Reduction in maximum tumour diameter on clinical examination or routine imaging
Stable Disease	No change in tumour size on examination or imaging
Disease Progression	Increase in the maximum tumour diameter on examination or using imaging

information governance policies. This will be held by the local supervising consultant named on the institutional approval, ensuring continuity of custodianship of the data.

If long-term data are required, proportional ethical approval will be sought centrally by the NeST team to facilitate the central collection of the locally maintained spreadsheets linking study ID to NHS number from participating centres. Only centres with appropriate ethical approval will be able to contribute data at this stage.

2.2.2.2. Anticipated recruitment and sample size. There is a lack of detailed data regarding indications for NST utilisation. Although the UK Systemic Anti-Cancer Therapy Database holds some data in respect of NST use, it does not currently collect the level of detail that will be captured in the NeST study [33]. The majority of the 144 breast units within the UK are likely to consider this treatment for their patients, although it is anticipated that there will be significant variation across the country. Based on a 60% participation rate, it would be anticipated that 100 units may contribute to the study. The study team will approach breast units via both trainees and the professional associations to maximise participation. Based on previous experience with prospective collaborative studies in breast cancer such as iBRA, it is anticipated that closer to 40% of UK breast units may choose to participate in this audit [25]. From our pilot, we estimate accrual of between 2 and 5 patients per month per unit; with 40 centres participating, we would therefore anticipate a recruitment of around 720 patients over a 6 month period (3 patients per month, from 40 centres, for 6 months). However, the study will aim to engage as many UK units as possible. Consequently, and in order to obtain a representative picture of current UK practice, we estimate that it will be necessary to run the prospective audit for a minimum period of 6 months from 1/12/17 until 30/11/18, or at least 600 patients have been registered.

2.2.2.3. Statistical analysis. The study report will be prepared according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for observational studies [34]. All data analysis will occur centrally by the NeST Study Steering Group, with support from Medical Statisticians within the Centre for Public Health at Queen's University Belfast.

Simple summary statistics will be calculated to describe demographic, procedure, process and outcome data overall and at a site level. Categorical data will be summarised by counts and percentages. Continuous data will be summarised by mean, standard deviation and range if data are normally distributed. Median, interquartile range and range will be reported if the data is skewed. No formal statistical testing is planned. Study timelines are summarized in Table 4.

2.2.2.4. Patient and public involvement. Patients have been involved since the inception of this study, and are represented on the NeST Study Steering Group (MG, as a representative of the Northern Ireland Cancer Research Consumer Forum), and there has been patient input into the development of the study protocol and the

Table 4
Study timelines.

Sep – Nov 2017	Pilot study questionnaires
Sep – Dec 2017	Registration of interest from breast units
Sep – Dec 2017	Local approval from participating units
Oct 2017 – March 2018	National Practice Questionnaire Completion
1 Dec 2017 – 30 November 2018	Patient recruitment to prospective audit with pre-operative MDT discussion inside these dates
1 Dec 2017 – 31 Dec 2019	Data collection period to allow time for completion of neoadjuvant therapy and surgery
31 December 2019	Closing date for data submission
1 May – 30 October 2019	Data Analysis – National Practice Questionnaire
1 Jan 2020 – 1 Apr 2020	Data validation and analysis – Prospective audit data
October 2019 – January 2020	Write up and dissemination – National Practice Questionnaire
May – July 2020	Write up and dissemination – Prospective Audit data

Amendment chronology.

There have been no substantial amendments to the study protocol.

data collection instruments. Patient involvement will remain key to data analysis and dissemination as the study continues.

3. Discussion

Use of NST in breast cancer clearly has potential advantages for patients, allowing an increase in the use of breast conserving surgery, and giving accurate information regarding tumour response to treatment. This approach has recently been the subject of some controversy, with some commentators suggesting that the use of neoadjuvant therapy be reconsidered [34].

There remains lack of consensus around optimal patient selection for NST, and around the monitoring and reporting of treatment response. The NeST Study is therefore important in improving our understanding of current patterns of care in this situation. This study will generate much needed novel data, concerning rates of access to and utility of NST in breast cancer, facilitate the design of appropriate randomised controlled trials and may inform best practice, allowing the development of appropriate national guidelines.

In addition, the study will strengthen the existing research collaborative network in breast surgery, created through the iBRA study, and establish new collaborative networks in medical and clinical oncology, radiology and pathology. This will allow the development of multidisciplinary research networks to support future collaborative projects in breast cancer.

The potential challenges for this project warrant consideration. The proposed datasets are complex and there is potential for incomplete data. In order to minimise this, the datasets have been piloted prior to study initiation to ensure they are not cumbersome and to streamline the flow through the online data capture sheets. This also allows the removal of any redundant or ambiguous questions. In addition, REDCap allows the use of logic to ensure that only the appropriate fields relevant to the procedure or indication are displayed during data capture.

There is the possibility that participation will be biased towards the most motivated centres, and that this may not provide a truly representative picture of practice nationwide. To address this, we would seek in future to combine NeST data with additional information from linkage to routinely collected NHS national datasets such as the Systemic Anti-Cancer Therapy Dataset (www.chemo-dataset.nhs.uk) to give a wider picture of UK practice. Furthermore, the NeST Study does not plan to capture information on all cancers

diagnosed in participating units during the time frame of the study, meaning that absolute rates of NST usage cannot be calculated. It is accepted that this is a limitation of this study, but determining rates of usage of NST is not the primary aim of NeST.

Finally, although the project will allow the collection of valuable data around treatment access and selection, surgical decision making and short-term outcomes, it will not provide any information regarding the long-term outcomes of NST in these patients. If long-term data is required, proportional ethical approval will be sought centrally by the NeST team to facilitate the central collection of the locally maintained spreadsheets linking study ID to NHS number from participating centres. Only centres with appropriate ethical approval will be able to contribute data at this stage.

4. Ethics and dissemination

The proposed study will not affect clinical care. Research ethics approval is not required and has been confirmed by the Health Research Authority online decision tool (<http://www.hra-decision-tools.org.uk/research/>). A Trainee Lead will be identified at each participating unit, who will in turn identify a named supervising consultant to act as the principal investigator for registration purposes. The study lead, in consultation with the principal investigator, will be required to register the audit and obtain local audit approvals for study participation prior to commencing patient recruitment. A copy of local approval will be forwarded to the NeST study team. Patient consent is not required, as no patient identifiable data are being recorded and there is no risk to patients.

If long-term data are required, proportional ethical approval will be sought centrally by the NeST team to facilitate the central collection of the locally maintained spreadsheets linking study ID to NHS number from participating centres. Only centres with appropriate ethical approval will be able to contribute data at this stage.

This protocol will be disseminated through the Mammary Fold Academic Research Collaborative (MFAC), the Reconstructive Surgery Trials Network, the Association of Breast Surgery, the British Association of Plastic, Reconstructive and Aesthetic Surgeons and others. Participating units will have access to their own data and information from individual units will be fed back with a comparison to the national data. National results will be fed back to the appropriate professional associations. Collective results will be analysed and the results presented at relevant scientific meetings and published in appropriate peer-reviewed journals. Results will also be made available to relevant patient advocacy groups such as Independent Cancer Patients' Voice. Thus, results will be available to aid in the decision-making for women considering NST.

5. Research registration unique identifying number (UIN)

1. Name of the registry: ISRCTN
2. Unique Identifying number or registration ID: ISRCTN11160072
3. Hyperlink to the registration (must be publicly accessible): <https://www.isrctn.com/ISRCTN11160072?q=&filters=conditionCategory:Cancer&sort=&offset=2&totalResults=2133&page=1&pageSize=10&searchType=basic-search>

6. Guarantor

The corresponding author, Stuart McIntosh, is the guarantor for this study.

Funding

This work was funded by a grant from the Association of Breast Surgery of Great Britain and Ireland.

Ethical statement

Ethical approval was not required for this study, as per the Health Regulatory Authority online decision tool. Institutional approval for participation will be required from each participating hospital.

Author contribution

GI wrote the first draft of the manuscript.

GI, CEC, EC, TIC, RVD, MG, CH SI, COB, ROC, CP, AS, NS, JS and IW all contributed to study design, including design of the data collection instruments, and to the writing and editing of the protocol. FB contributed to study design, methodology and the statistical analysis plan. GI, ROC, SP and IW undertook piloting of the data collection instruments. SMCI and SP were responsible for the conception of the project, and contributed to the design of the project, and to the writing and editing of the protocol.

All authors have read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Trial registration data:

Data category	Information
Primary registry and trial identification number	ISRCTN11160072
Date of registration in primary registry	10th June 2019
Sources of monetary or material support	Supported by a grant from the Association of Breast Surgery
Sponsor	Queen's University of Belfast (for subsequent study phases requiring sponsorship) researchgovernance@qub.ac.uk
Contact for public queries	SMCI (s.mcintosh@qub.ac.uk)

(continued on next page)

Appendix A (continued)

Data category	Information
Contact for scientific queries	SMcI (s.mcintosh@qub.ac.uk)
Public title	A study to help understand the outcomes of pre-surgical treatment for breast cancer
Scientific title	NeST: Neoadjuvant systemic therapy in breast cancer. A national prospective multicentre audit of neoadjuvant systemic therapy in breast cancer
Countries of recruitment	United Kingdom
Interventions	No interventions – anonymised data collection only
Key inclusion criteria	Age > 16 years Histologically confirmed diagnosis of breast cancer MDT recommended treatment of neoadjuvant systemic therapy
Key exclusion criteria	Patients entering “window of opportunity” clinical trials
Study type	Prospective cohort study Observational
Date of first enrolment	December 2017
Recruitment status	Data collection ongoing
Primary outcomes	Investigate variation in practice in the use of neoadjuvant systemic therapy in the UK Assess surgical practice following neoadjuvant therapy Determine pathological response rates after neoadjuvant therapy
Key secondary outcomes	Explored stated indications for use of neoadjuvant systemic therapy Examine treatment regimens in common use Investigate how response to neoadjuvant treatment is assessed/reported across the UK Investigate surgical management of the axilla following neoadjuvant therapy

Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.isjp.2019.10.002>.

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