BMJ Open

Protocol for a mixed-method study to inform the feasibility of undertaking a large-scale multicentre study comparing the clinical and patient-reported outcomes of oncoplastic breast conservation as an alternative to mastectomy with or without immediate breast reconstruction in women unsuitable for standard breast-conserving surgery (the ANTHEM Feasibility Study)

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To cite: Davies C, Holcombe C, Skillman J, *et al*. Protocol for a mixed-method study to inform the feasibility of undertaking a large-scale multicentre study comparing the clinical and patient-reported outcomes of oncoplastic breast conservation as an alternative to mastectomy with or without immediate breast reconstruction in women unsuitable for standard breast-conserving surgery (the ANTHEM Feasibility Study). *BMJ Open* 2021;**11**:e046622. doi:10.1136/bmjopen-2020-046622

► Prepublication history and supplemental material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-046622).

Received 06 November 2020
Revised 09 February 2021
Accepted 18 March 2021

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ABSTRACT

Introduction Approximately 40% of the 55 000 women diagnosed with breast cancer each year in the UK undergo mastectomy because they are considered unsuitable for standard breast-conserving surgery (BCS) due to tumour size or multiple tumour foci. Mastectomy can significantly impact women's quality of life, and only one in four women currently undergo immediate breast reconstruction (IBR). Level 2 oncoplastic breast-conserving surgery (OPBCS) combines removing the cancer with a range of plastic surgical volume replacement (eg, local perforator flaps) and volume displacement techniques (eg, therapeutic mammaplasty) that can extend the role of BCS and may allow some women not suitable for standard BCS to avoid mastectomy. High-quality research to determine whether OPBCS offers a safe and effective alternative to mastectomy±IBR is currently lacking. Preliminary work is needed to ensure a future large-scale study is feasible and well designed and addresses questions important to patients and the National Health Service.

Methods and analysis Mixed methods will be used to inform feasibility and design of a future large-scale study comparing the clinical effectiveness and cost-effectiveness of OPBCS and mastectomy±IBR. It will have four parts: (1) a National Practice Questionnaire to determine current practice and provision of oncoplastic breast and reconstructive surgery in the UK; (2) a pilot multicentre prospective cohort study to explore the proportion of patients choosing OPBCS versus mastectomy, the proportion in OPBCS is successful and clinical and patient-reported outcomes of different techniques at 3 and 12 months postsurgery; (3) a qualitative interview study to explore patients' attitudes to different procedures, rationale for decision-making and perceptions of outcomes; and (4) design of the future study.

All centres offering OPBCS and mastectomy in the UK will be invited to participate. Recruitment is planned to commence winter 2020 and continue for 12 months.

Strengths and limitations of this study

- This mixed-method study will determine whether it is possible to undertake a large prospective cohort study directly comparing the clinical effectiveness and cost-effectiveness of oncoplastic breast-conserving surgery (OPBCS) and mastectomy with or without breast reconstruction in patients considered suitable for both procedures.
- It will determine whether the BREAST-Q core breast cancer modules are an appropriate and meaningful patient-reported outcome measure for use in a future comparative study.
- Qualitative interviews will explore patients' attitudes to different procedures, rationale for decision-making, and perception of outcomes providing the opportunity to improve informed consent in this group.
- Suitability for OPBCS will be assessed by individual surgeons or teams. It is multifactorial with subjective elements and is likely to vary between individuals and centres.
- Patients will only be followed up for 12 months, and the effects of radiotherapy and any revisional surgery are likely to occur at a later time point.

Ethics and dissemination The study has ethical approval from the Wales Research Ethics Committee 6 National Research Ethics Service (REC Ref 20/WA/0225). Results will be presented at national and international meetings and published in peer-reviewed journals. We will work with patients to develop lay summaries and share these through patient groups and breast cancer charities.

Trial registration number ISRCTN18238549.

INTRODUCTION

Despite improvements in treatment, approximately 40%[1] of the 55 000 women[2] diagnosed with breast cancer every year in the UK undergo mastectomy (Mx) as they are considered unsuitable for standard breast-conserving surgery (BCS) due to tumour size or multiple tumour foci. Mx may dramatically impact women's quality of life,[3 4] and although national guidelines[5] recommend that immediate breast reconstruction (IBR) should be routinely offered in this group, only a quarter of women currently receive reconstruction[6] due to a combination of patient-related and treatment-related factors.[7] While some women may chose Mx with or without reconstruction to reduce their risk of recurrence or to avoid the need for radiotherapy, especially in the North American setting,[8 9] BCS is associated with greater patient satisfaction and improved quality of life,[4] and many women would chose this approach if possible.

Level 2 oncoplastic breast-conserving surgery (OPBCS) describes a range of volume replacement and volume displacement techniques that may extend the boundaries of breast conservation and allow some women not suitable for standard BCS to avoid Mx. Volume displacement techniques, often termed therapeutic mammaplasty (TM), combine removing the cancer (wide local excision) with breast reduction and mastopexy techniques to reshape the remaining breast tissue.[10 11] These techniques allow resection of large or multifocal cancers in patients with medium/large or ptotic breasts without compromising cosmetic or oncological outcomes.[12–14] Volume replacement or partial breast reconstruction techniques involve using local flaps to fill the defect left following a wide local excision.[15] These flaps have particular value in patients with small or medium breasts with little ptosis and may offer good cosmetic outcomes without the need for contralateral symmetrisation.[16] Latissimus dorsi miniflaps have been most frequently described, but more recently, muscle-preserving local perforator flaps (LPFs) such as those based on the intercostal artery perforators (ICAPs) (lateral and anterior ICAP flaps), thoracodorsal artery perforator and lateral thoracic artery perforator have gained in popularity[17] and do not compromise shoulder function or future reconstructive options.[18]

There is, however, limited high-quality comparative evidence to support the benefits of OPBCS as an alternative to Mx with or without IBR in women unsuitable for standard BCS. Recent combined analysis of 2540 patients who underwent Mx with or without IBR in the iBRA-2 (immediate breast reconstruction and adjuvant therapy audit) Study[19] and a subgroup of 376 patients who underwent TM to avoid Mx in the TeaM (*Th*e*r*apeutic *M*ammaplasty) Study[20] suggests that although patients in the TM group were 'higher risk' (ie, older, higher body mass index and more likely to be smokers) than those undergoing IBR, rates of major complications requiring readmission or reoperation were significantly lower in the TM group (2.1% TM vs 14.8% implant-based reconstruction; 16.7% free-flap reconstruction).[21] The tumour characteristics were similar in all groups (median whole tumour size 30 mm and multifocality 31.3%), and TM allowed successful breast conservation in almost 90% of cases.[21] Single-centre case series suggests that patients undergoing TM may report better quality of life than those undergoing Mx and IBR,[22 23] and there is emerging evidence to suggest that TM may be a cost-effective alternative to Mx and immediate implant-based[24] and free-flap reconstruction[25] in a North American setting.

While these results are promising, there remains a need for high-quality research to establish the benefits of OPBCS as a safe and effective alternative to Mx±IBR. Randomised trials are ideally needed, but randomised controlled trials in this context have not been possible due to strong patient and surgeon preferences.[26 27] A large-scale multicentre prospective cohort study is therefore required to compare the clinical and patient-reported outcomes (PROs) of OPBCS and Mx±IBR and to evaluate the cost-effectiveness of the approach.

Before such a study can be planned, however, preliminary work is needed to determine whether a comparative study would be feasible, in particular to explore whether sufficient numbers of centres are offering patients OPBCS to avoid Mx; how many patients are offered OPBCS and in what circumstances; of those offered OPBCS, what proportion accepts or declines the procedure and why; and the rate of successful BCS. It is also important to establish whether existing outcome measures capture relevant core outcome domains and are appropriate for use across all patient groups. If not, refinement of existing tools will be needed prior to progression to the main study.

METHODS AND ANALYSIS

Primary aim

The overall aim of the ANTHEM Study is to use mixed methods to assess the feasibility of undertaking a large-scale multicentre prospective cohort study to compare the clinical effectiveness and cost-effectiveness of OPBCS as a safe and effective alternative to Mx±IBR and to determine the most appropriate outcome measures for use in the main study. The study will also explore women's decision-making for particular surgical procedures, rationale for choice, and their perceptions of outcome.

Study design

The ANTHEM Feasibility Study will consist of four parts:

1. National Practice Questionnaire (NPQ)

2. Pilot prospective cohort study
3. Qualitative interview study
4. Design of main study

Patient and public involvement

The protocol for the ANTHEM Study has been codeveloped in collaboration with a patient representative and addresses a key research gap highlighted by patient contributors to the recent Association of Breast Surgery Gap Analysis.[28] Patient representatives will sit on the study steering committee and comment on study documents including patient information sheets and topic guides for the qualitative interviews to ensure that all aspects of the study are patient focused and explore issues that patients' value. During the study, we will also establish a patient group (6–10 women who have undergone a range of surgery for breast cancer including TM, LPF procedures, Mx and immediate or delayed reconstruction using different techniques) to advise on the design of a future main study.

Part 1: National Practice Questionnaire

The NPQ is a nested service evaluation that aims to determine the availability of different approaches to OPBCS (TM and LPFs) and breast reconstruction procedures nationally and understand current practice to inform a future study.

Specific objectives will include the following:

i. To establish the number of centres/surgeons performing OPBCS (volume displacement and volume replacement techniques) to participate in the future study
ii. To determine the approximate numbers of OPBCS (TM/LPF) performed to avoid Mx at a centre level to inform the feasibility of a future comparative study
iii. To determine the indications/contraindications for OPBCS/IBR at the surgeon/centre level and patient/tumour/treatment factors influencing decision-making
iv. To explore patient pathways (neoadjuvant treatments/symmetrisation/day case/follow-up) to inform study design

The NPQ will be developed by members of the steering group using REDCap[29] data management software and will explore current practice at participating centres. This will include the availability of oncoplastic breast-conserving (TM and LPFs) and reconstructive (implant-based and autologous) techniques locally; indications and contraindications for each technique; patient-related, tumour-related and treatment-related factors influencing decision-making; and information regarding patient pathways including the use of neoadjuvant therapy, approaches to contralateral symmetrisation surgery, provision of day case versus inpatient procedures and timing of routine follow-up to inform future study design. The survey will be piloted with surgeons to establish face and content validity and acceptability prior to dissemination.

All breast and plastic surgical units performing breast cancer surgery in the UK will be invited to complete the NPQ via the professional associations (Association of Breast Surgery and British Association of Plastic, Reconstructive & Aesthetic Surgeons (BAPRAS)), collaborative networks including the iBRA-NET group and the Reconstructive Trials Network and social media with the aim of optimising the number of participating sites. One questionnaire will be completed per unit.

Simple summary statistics will be used to describe the provision and practice of oncoplastic and reconstructive surgery. Categorical data will be summarised using counts and percentages. Median, IQR and range will be used for continuous data. Free-response fields will be analysed using a thematic analysis approach.

Part 2: pilot prospective cohort study

The aim of the pilot cohort study is to determine the feasibility of identifying and recruiting patients offered different approaches to OPBCS to avoid Mx and to explore the utility of the BREAST-Q as an outcome measure for the main study.

Specific objectives will include the following:

i. To determine the number of patients offered OPBCS to avoid Mx, the relative numbers of volume displacement and volume replacement procedures offered, the number of patients electing to undergo OPBCS, the success rates of OPBCS and the outcomes for patients in whom further surgery is needed
ii. To establish the clinical outcomes of TM/LPF/Mx±IBR.
iii. To determine whether existing tools (breast cancer core domains of the BREAST-Q) are valid in the OPBCS population and whether these subscales are directly comparable across patient groups.
iv. To explore variability in BREAST-Q Breast Cancer Core Scales to inform sample size calculations for the main study
v. To explore the feasibility of collecting electronic PROs.
vi. To explore the feasibility of collecting multicentre resource-use data using a targeted approach for cost-effectiveness evaluation in the main study

Setting

All UK breast and plastic surgical centres currently performing oncoplastic techniques (therapeutic mammoplasty and chest wall perforator flaps) will be invited to participate in the study through research collaborative networks including the Association of Breast Surgery, BAPRAS, iBRA-NET group and the National Institute for Health Research Clinical Research Network.

Participants

Eligibility criteria

Inclusion criteria will be:

- All female patients 18 years and over

- With invasive breast cancer or ductal carcinoma in situ not considered suitable for standard BCS or simple level 1 techniques
- Who are assessed by the breast cancer (and oncoplastic, if applicable) multidisciplinary team (MDT) and the operating surgeon as being suitable candidates for either OPBCS (either TM or LPF) as an alternative to an Mx with or without an IBR (using any technique)
- Offered both OPBCS and Mx options.

No restrictions will be placed on the size of the tumour as decisions on the suitability of a patient for simple BCS will be based on assessments of the size of the tumour relative to the overall size of the breast and its position within the breast rather than on explicit size criteria.

Exclusion criteria will be women not offered a choice of procedures, those offered OPBCS for reasons other than to avoid Mx (eg, quality of life if large breasted), women offered standard BCS or level 1 procedures only and women who have declined informed consent.

Participant identification and recruitment

Patients who are potentially suitable for either OPBCS or Mx will be identified from the breast cancer and/or oncoplastic MDT meetings. Potentially eligible patients will be assessed by their surgeon in clinic as per standard practice. If the operating surgeon considers the patient to be suitable for either OPBCS or Mx±IBR, they will be offered a choice of procedures. They will be invited to participate in the ANTHEM Study and given a patient information sheet. Patients will have the opportunity to discuss the study with a member of the local clinical or research team as per local practice, and if they elect to participate in the study, they will sign a study consent form.

Data collection and patient pathway

Baseline demographic and pre-operative assessment data will be collected. When the patient has made a decision regarding surgery, they will be asked to complete preoperative PRO measures (PROMs) (BREAST-Q/EQ-5D-5L/ICECAP-A (ICEpop CAPability measure for Adults)) either electronically or on paper as per patient preference.

Patients will undergo surgery according to their preference. Operative and oncological data will be collected. For patients undergoing OPBCS in whom adequate tumour resection as per local policy is not achieved, details of further procedures performed (re-excision of margins/Mx±IBR/chemotherapy followed by further surgery) will be recorded. MDT decisions regarding adjuvant treatment and postoperative complications at 3 months will be collected by clinical or case note review according to local practice. Complications and the need for further surgery will also be collected at 12 months. Patients will be asked to complete PROMs (BREAST-Q/EQ-5D-5L/ICECAP-A) at 3 and 12 months post-operatively.

The feasibility of collecting hospital resource-use data using case report forms (CRFs) developed from NPQ-patient pathway mapping will be assessed.

Outcome measures

Clinical outcomes

Complication rates at 3 and 12 months, in particular rates of readmission and reoperation for complications relating to breast surgery and time to adjuvant therapy defined as the number of days from the last cancer surgery to the first adjuvant treatment (first dose of chemotherapy or first fraction of radiotherapy), will be recorded and compared across surgical techniques. Standardised definitions of complications (listed in online supplemental appendix 1) will be used as per previous studies.[19 20] For patients undergoing OPBCS, rates of successful breast conservation, defined as achievement of adequate resection margins as per local protocol, will be determined.

Patient-reported outcomes

It is anticipated that the primary outcome for the main study will be a PRO included in the reconstructive breast surgery core outcome set.[30] It is vital that a PROM is chosen that is valid and reliable across all patient groups.

The BREAST-Q[31 32] is a validated PROM that has been developed for use in a breast cancer population. It comprises preoperative and postoperative 'core breast cancer modules' in which the developers' report can be used in patients undergoing breast conservation and Mx and IBR procedures, allowing different techniques to be effectively compared. Published evidence of comparability, however, is lacking, and these modules have yet to be used in patients undergoing level 2 oncoplastic breast-conserving techniques (TM and LPF).

Key objectives of the feasibility phase are to determine whether the BREAST-Q subscales can be compared across different patient groups and whether they measure the constructs of interest within the study. Quantitative analysis will be used to explore acceptability (response rates) and construct validity (the extent to which the questionnaire actually measures what it claims to measure) of the BREAST-Q subscales. Face validity (applying a subjective assessment of whether or not a questionnaire measures what it is supposed to measure) will be assessed using qualitative interviews with study participants (part 3, patient interview study). If the BREAST-Q is shown to be useful in this group, variability in BREAST-Q Breast Cancer Core Scales will be explored to inform the sample size for the main study.

For economic evaluation in breast surgery, it is currently unclear whether the EQ-5D-5L (standard approach recommended by The National Institute for Health and Care Excellence (NICE)) or ICECAP-A (a broader measure of capabilities) is best suited to measure differences in outcome following breast surgery. The mixed-method approach used in this study will also provide data on the acceptability and validity (construct and face validity) of these latter two measures.

The feasibility and acceptability of using centrally distributed electronic questionnaires will be assessed.

Exploring the feasibility of using targeted micro-costing to determine the relative costs of OPBCS versus Mx±IBR surgery

The feasibility of using recently described targeted micro-costing[33] to determine the relative surgical costs of OPBCS and reconstructive procedures will be explored. Patient pathways for each surgical procedure will be mapped by the breast and plastic surgeons in the steering group informed by data from the NPQ.

The pathways will be used to identify resources required for each procedure including staff, equipment, consumables, implants and length of patient stay. The lists will be reviewed to identify the main cost drivers for each technique and the key differences in resource use between techniques. These resources will be recorded in detail in the study CRFs. It is anticipated that different centres will have different processes for carrying out each procedure; therefore process maps and lists of resources will differ between centres. We will initially aim to focus on three centres for our targeted micro-costing feasibility study and determine whether it is possible to extend to all centres once the main cost drivers have been identified.

Targeted micro-costing will focus on the period between first preoperative visit and the end of the patient's hospital stay. Additional data such as the number of outpatient visits will be collected from electronic notes/medical records.

Data analysis and sample size

The proportions of patients electing to undergo OPBCS/Mx±IBR will be summarised together with the proportion of patients in whom OPBCS is successful and those in whom further surgery is required, using simple summary statistics and compared between groups. PROMs will be scored according to the developers' instructions and compared at 3 and 12 months across patient groups.

Individual BREAST-Q subscale scores will be compared across each of the study groups. Assessments of construct validity and responsiveness (ability of an instrument to detect change over time in the construct to be measured) of the BREAST-Q to changes in PROs from 3 months to 12 months postsurgery will be explored to determine whether the BREAST-Q is a suitable instrument for use in the future large-scale study.

It is anticipated that patients in the OPBCS groups will be more satisfied with the outcome of their surgery at 12 months than patients undergoing Mx±IBR. To allow the utility of the BREAST-Q for use in the main study to be determined, approximately 50 patients will be recruited in each group (OPBCS—volume replacement/OPBCS—volume displacement/Mx only/Mx and implant reconstruction/Mx and autologous reconstruction). It is anticipated that overall, approximately 250 patients will be recruited over a 12-month period.

Part 3. qualitative interview study

Semistructured qualitative interviews will be used to explore patients' perceptions of choice within the study, rationale for decision-making, perception of outcomes and proposed outcome measures in more depth.

Specific objectives will be to explore the following:

i. Why patients chose different approaches and factors influencing this
ii. Patients' perceptions of the outcomes of their surgery
iii. Whether proposed outcome measures address the issues important to patients and appropriately reflect the key core outcome domains, in particular, satisfaction with breasts, emotional and physical well-being and quality of life, and whether they are adequate or missing key concerns and the acceptability of the individual items
iv. Key aspects of future study design (outcome selection/timing)

Recruitment

All patients consenting to participate in the prospective cohort study will be invited to consent to be contacted regarding participation in the interview study at the time of study entry. Patients who consent to be contacted will be asked to provide contact details (e-mail, telephone or postal address) for this purpose.

If patients agree to be contacted about an interview, they will be invited in batches of 5–10 by their preferred contact method 3–12 months following surgery. Recruitment to the interview study and data collection will be conducted and analysed concurrently and iteratively until data saturation (the point at which no new themes emerge) is considered to have been achieved.

Sampling

Consenting patients will be purposively sampled using a maximum-variation approach based on their procedure choice (OPBCS—volume replacement (LPF)/OPBCS—volume displacement (TM)/Mx only/Mx with IBR/Mx with flaps), outcome (successful OPBCS/not) and participating centre. Theoretical sampling will be used as the study progresses to include individuals whose views may enhance or disprove emerging themes.

Data collection

All interviews will be conducted by telephone by a qualitative researcher using a semistructured topic guide developed by the study steering group based on a review of the literature and clinical expertise. Interviews will explore patients' rationale for decision-making; perceptions of different options/outcomes; detailed views of the appropriateness, adequacy and acceptability of the proposed PROMs and views of the study design.

All interviews will be digitally audio-recorded using an encrypted recording device, transcribed verbatim by University of Bristol staff or a University of Bristol-approved transcription service, checked and anonymised

by the research team against the original recording to protect patient confidentiality.

Data analysis and sample size

Analysis of the interviews will be an ongoing and iterative process commencing soon after data collection and informing further sampling. Transcripts will be systematically assigned codes using the qualitative data analysis package NVivo and analysed thematically[34] using the constant comparison technique of grounded theory.[35] The themes identified from the interviews will be used to iteratively modify the interview topic guides as appropriate to explore emerging areas of interest in-depth. Data collection will continue until saturation is achieved and no new themes emerge from the data.

Part 4: design of main study

Parts 1–3 will inform the feasibility and design of a definitive study, in particular the most appropriate primary outcome and tool by which this can be assessed.

ETHICS AND DISSEMINATION

Ethical approval for the study has been granted by the Wales Research Ethics Committee 6 (ref. number: 20/WA/0225). Written informed consent will be obtained from patients for both the prospective cohort and interview studies prior to study participation. Dissemination strategies will include presentations at scientific meeting presentations and publications in peer-reviewed journals. We will work with our patient and public involvement group to develop lay summaries to disseminate through patient groups and breast cancer charities. Findings will be fed back to the surgical community to promote engagement and recruitment to a future large-scale multicentre prospective cohort study.

Study status

Recruitment is planned to commence winter 2020.

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Acknowledgements The authors express their gratitude to everyone who has contributed to the development of the ANTHEM Feasibility Study.

Contributors SP conceived the study and obtained funding. SP and CD wrote the protocol. SP, CD, CH, JS, LW, WH, CaC, NM, PW, ChC, DM and PF contributed to the study design. PW provided statistical support. CD wrote the first draft of the paper, and SP critically revised the manuscript. All authors read, critically revised and approved the protocol and manuscript before submission.

Funding This study is funded by the Association of Breast Surgery (ABS) and Above and Beyond Charities (ABL-2019-20-02) and supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at the University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol and the Royal College of Surgeons of England Bristol Surgical Trials Centre. SP is an NIHR clinician scientist (CS-2016-16-019).

Disclaimer The views expressed are those of the authors and not necessarily those of the UK National Health Service, National Institute for Health Research or Department of Health.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer-reviewed.

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