Comparison of patient reported outcome measures in patients undergoing pre versus sub-pectoral implant based reconstruction

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Non-CTIMP trial

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2. Abbreviations

AE	Adverse Event
ABS	Association of Breast Surgery
BRCA	Breast Cancer Gene
BREAST-Q	BREAST-Q questionnaire
CI	Chief Investigator
CNST	Clinical Negligence Scheme for Trusts
CRF	Case Report Form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
IBR	Immediate Breast Reconstruction
ICF	Informed Consent Form
LTHT	Leeds Teaching Hospitals NHS Trust
MDT	Multi-Disciplinary Team
NACT	Neo-adjuvant chemotherapy
NMBRA	The National Mastectomy and Breast Reconstruction Audit
NHS	National Health Service
NIHR	National Institute of Health Research
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
ppm	Patient Pathway Manger (electronic patient record system - Leeds Teaching Hospitals)
PRO	Patient Reported Outcomes
PROMs	Patient Reported Outcome Measures
QoL	Quality of Life
R&I	NHS Trust Research and Innovation Department
REC	Research Ethics Committee
RGF	Research Governance Framework
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences (statistical package)
TMF	Trial Master File

3. Background and Rationale

Breast cancer affects around 55000 women per year in the UK (2015-2017; Cancer Research UK) and 5 year survival for all breast cancer is favourable at 86.6% in the UK as a result of advances in locoregional and systemic treatment. Nationally approximately 40% of women undergo mastectomy to treat breast cancer[1]. All eligible women are offered immediate breast reconstruction (IBR), with the UK National Mastectomy and Breast Reconstruction Audit (NMBRA) showing that up to 43% of women opted for immediate breast reconstruction[1], and that the rate of IBR is increasing in UK over time[2]. There is also an increasing number of patients who opt to undergo risk reducing mastectomies and reconstruction due to high family history risk or germline genetic mutations[3] (e.g. BRCA).

Given this increased uptake of IBR, it is important to study the patient's quality of life after mastectomy and reconstruction. When compared to mastectomy alone, current research shows improved quality of life in patients who opt to receive reconstruction[4]. Women opting for reconstruction reported positive effects on their self-esteem, body image, sexuality and psychological health.

Currently there are two well established methods of breast reconstruction after mastectomy: autologous 'flap' reconstruction or implant reconstruction. Whilst autologous reconstruction utilises tissue transfer from the patient themselves, implant reconstruction uses a silicone implant device or a saline tissue expander to re-create the breast mound. Implant reconstruction is the commonest form of breast reconstruction and in Leeds Teaching Hospitals NHS Trust (LTHT), 60% of patients receiving IBR opt for implant based reconstruction. The breast surgery unit at LTHT is a national oncoplastic fellowship centre and perform around 100 IBR of all types per year (personal communication and analysis; author BK).

Traditionally immediate implant based reconstructions were not technically possible as implant size required to recreate breast shape was usually too large and raising pectoralis major and serratus anterior muscle was insufficient to cover and stabilise the implant position[5]. Therefore, smaller expanders were commonly placed under both muscles and gradually inflated. This was then later exchanged to an implant. The aesthetic outcome from such procedures was sub-optimal with increased risk of pain and implant malposition.

More recently, acellular dermal matrices [6] has led to an improvement in implant based breast reconstruction. Acellular dermal matrix is sutured to the lower part of pectoralis muscle that is raised. This enables full coverage and stabilises the implant and therefore avoids the need for raising the serratus anterior muscle or routine use of expanders. As a result, this reduces the number of surgeries the patient requires, as well as improve aesthetic outcome. This technique is defined as sub-pectoral implant based breast reconstruction. It has been adopted widely [7] and has become established as standard practice.

In the last 5 years, surgical techniques and technologies have advanced further to enable the implant to be placed above the pectoral muscle. This avoids the need to raise the pectoral muscle and therefore has advantages in reducing post-operative pain and length of the operating time. This has been made possible with larger acellular dermal matrices that are able to stabilise implant position without needing to raise the pectoral muscle to cover the implant device. This technique is defined as pre-pectoral implant based breast reconstruction[8] and has been adopted widely in UK given the perceived advantages for the patient. There is currently a national study [9] that is examining patient outcome in pre-pectoral implant based breast reconstruction. Figure 1 clearly demonstrates the difference between pre- and sub-pectoral implant reconstruction.

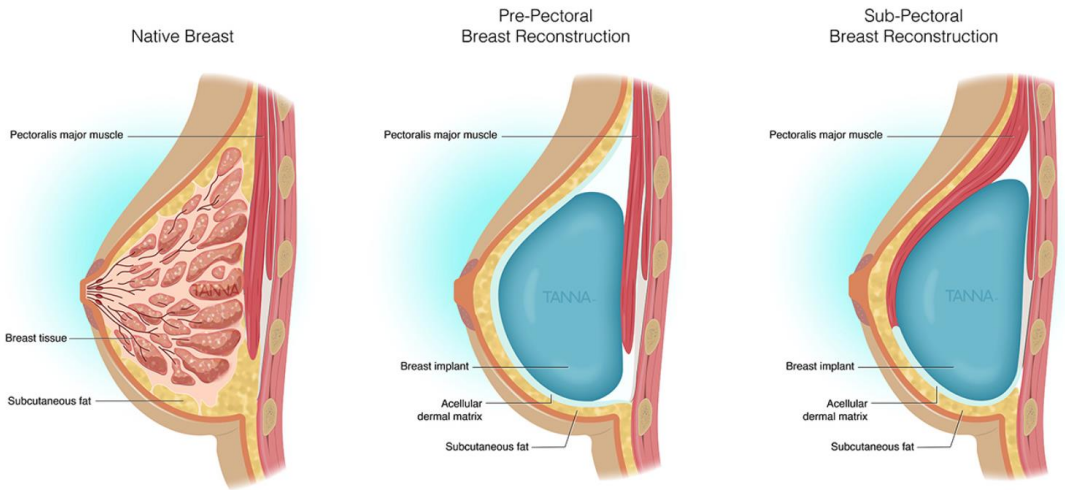

Figure 1. Pre- versus sub-pectoral breast reconstruction [10]

Both surgical techniques have proven safety for the patient in demonstrating low complication rates such as implant loss rate due to infection. There are potential advantages as well as disadvantages for each surgical technique as demonstrated by the table 1.

Sub-pectoral	**Pre-pectoral**
Raising the pectoral muscle can result in excess upper pole fullness of the reconstructed breast.	More predictable aesthetic result as the pectoral muscle is not raised.
Animation deformity, which is defined as visible twitching of the pectoral muscle (under the skin) with certain arm or shoulder movements. Patients may find this unsightly.	No animation deformity.
Potentially greater pain due to partial division of the pectoral muscle resulting in slower recovery to normal function.	Potentially less pain and therefore shorter hospital stay and quicker recovery to normal function.
Additional tissue coverage over the implant resulting in less likelihood of implant palpability, rippling, or capsular contracture.	Thin tissue coverage over the implant. This may increase the risk of rippling which may be treated with further revisional surgery (e.g. lipomodelling to improve tissue coverage over the implant).

Table 1. Potential advantages and disadvantages of pre- vs. sub-pectoral implant based breast reconstruction.

Given the equipoise and proven safety of both surgical techniques, eligible patients are counselled about their surgical options when opting for implant based breast reconstruction. Implant based reconstruction includes a fixed volume silicone implant device as well as an expander device which has an outer silicone shell with an internal saline chamber which can be inflated gradually once the surgical wound has healed. Expanders can be used for both pre- and sub-pectoral reconstruction and is used in cases where there are potentially higher wound healing risks (e.g. patients with smoking history). This is fully discussed between the surgeon and the patient as part of a standard informed consent.

At LTHT, we are able to offer patients both pre- and sub-pectoral implant based reconstruction. The current practice shows that equal proportion of patients opt for pre- versus sub-pectoral implant based IBR (BK: personal communication and preliminary data). However, it is unclear how much of this decision making is influenced by the patient or the surgeon. There is no current research of national guideline suggesting recommendation of one surgical technique versus the other.

Therefore, it becomes even more important to examine and compare patient reported outcome measures (PROMs) in both patient groups. This is an important research question as if PROMs are significantly higher in one patient group versus the other, this has significant implications for future patients when counselled with regards to their surgical options. Decision making for breast reconstruction is complex for the patient and the healthcare professionals involved. Therefore, further research such as this study is required to aid this process.

BREAST-Q is a validated questionnaire specific for breast patients undergoing reconstruction [11-13]. It is able to assess multiple pertinent PROMs including the patient's expectation of breast reconstruction, the level of pain, physical function after surgery, satisfaction with shape of the reconstruction, and satisfaction with the treating medical team and the level of information provided. Importantly, it has questions specific to implant based breast reconstruction and has specific questions relating to the potential issue of animation deformity [14]. It is also validated for use at multiple time points after surgery (including longer term PROMs at 12 months). Therefore, assessing PROMs using the BREAST-Q in patients undergoing pre- or sub-pectoral implant based IBR at the Leeds Breast Unit, a high volume reconstructive surgery centre, provides an ideal setting to answer this important research question.

4. Objectives and Outcome Measures

Does the difference in the surgical technique for immediate implant breast reconstruction (pre- versus sub-pectoral) influence patient perceived outcomes?

Aims:

The current lack of research evidence and guidelines on the topic signifies that the type of operation undertaken usually comes down to surgeon or patient preference. By completing this project we aim to provide better:

- Patients with curated information regarding short and longer term post-surgical patient reported outcomes.
- Healthcare professionals with a more extensive understanding of the advantages and limitations of both types of surgery from the patient's perspective.

This will equip the patient and the healthcare professional to make more informed decisions regarding the optimal surgical technique.

Objectives:

- Compare aesthetic outcome of pre- and sub-pectoral reconstructions using Patient Reported Outcome Measures (PROMs)
- Compare potential difference in pain between pre- and sub-pectoral reconstructions as reported by PROMs
- Compare potential difference in functionality between pre- and sub-pectoral reconstructions using PROMs

Outcome Measures:

We will collect PROMS on a prospective cohort of patients undergoing immediate implant based reconstruction after mastectomy for cancer or for risk reduction. The Association of Breast Surgery (ABS) guidelines for oncoplastic breast surgery [15] states that patients undergoing breast reconstruction should have PROMs data collected on a routine basis. We will utilise the BREAST-Q questionnaire (BREAST-Q, 2017), which is a validated PROMs survey that has been published widely.

5. Trial Design

5.1 Research Design

A prospective non-randomised longitudinal cohort study with data collection for patients undergoing mastectomy with immediate implant based reconstruction surgery for early breast cancer or risk reduction using repeated measures and mixed methods.

5.2 Study Measures

a) Clinical Outcomes and process of care measures

e.g. anaesthetic blocks used, number of hospital contacts, unplanned admissions, clinic appointments, phone calls with hospital staff, medications prescribed and taken, any changes to treatment plan. Details will be obtained via the individual electronic patient records.

b) Patient Reported outcomes

PROs using validated questionnaires

The BREAST-Q utilises PROMs to evaluate outcomes for various types of breast surgeries. Two of its 'modules' are relevant to this study; 'Reconstruction' and 'Reconstruction Expectations'. Each module contains multiple independently scored 'scales' with overarching themes of psychosocial and physical quality of life. To establish a baseline pre-operatively, we will use the 'Reconstruction Expectations' module. To explore the change in PROMs over time, the 'Reconstruction' module will be given to patients post-operatively (BREAST-Q, 2017). The main strength of using BREAST-Q is that it allows for comparison to other work in the same field of research. Furthermore, the outcome of the study could aid in designing and setting up of future multi-centre studies.

The questionnaires will be collected at four time points; pre-surgery, 2 weeks post-surgery and at 3 and 12 months post-surgery. This is in line with current clinical follow up for patients undergoing implant based reconstruction in Leeds. Therefore, patients will not require any additional clinical visits. The PROM scores may also be influenced by their surgical outcome (e.g. complication after reconstructive surgery). Therefore, routine clinical data regarding the patient's treatment outcome (e.g. any return to theatre or re-admission) will be collected alongside sociodemographic, relevant medical history data and the questionnaire.

5.3 Study Duration

Patients will be a participant in the study for approximately thirteen months. Thirteen months following surgery is completion of the patient's involvement in the study.

5.4 Findings

The overall findings will determine the feasibility of using this approach to support the care of patients undergoing immediate implant based reconstructive surgery for breast cancer or risk reduction. All data and opinions will inform the future development of information which aims to improve patient choice, experience and outcomes.

6.0 Participant Identification

6.1 Trial Participants

The sample of patients will include all prospective patients who undergo immediate implant based breast reconstruction in the Leeds Breast Unit between August 2020 and September 2021.

6.2 Inclusion criteria

- Female age ≥ 18 years
- Skin or nipple sparing mastectomy with immediate implant based reconstruction for cancer or for risk reduction (e.g. BRCA mutation)
- Unilateral or bilateral mastectomy
- Implant or expander based immediate reconstruction
- Able to read and understand questionnaire in English

6.3 Exclusion criteria

- Male or transgender
- Skin or nipple sparing mastectomy alone with no reconstruction
- Delayed reconstruction
- Autologous reconstruction
- Cognitive impairment or inability to provide informed consent

6.4 Participants in the local service evaluation

Patients who have already completed the questionnaires through their participation in a local service evaluation, will also be approached to ask to participate. They will be provided with a separate patient information sheet which explains the difference between the service evaluation and the study. Retrospective consent will be sought to use this information as part of this study.

7.0 Trial Procedures

7.1 Recruitment

All eligible patients will be identified at the Leeds Breast diagnostic MDT meetings and through clinics. Those planned for a mastectomy and implant based reconstruction are offered the option of completing the BREAST-Q as part of routine care. The direct clinical team will discuss this with the patient and this will not impact on routine care of decision making for either pre- or sub-pectoral implant based reconstruction (i.e. non-randomised). All patients deemed eligible will be offered the study patient information sheet and given a minimum of 24 hours to consider the study. As common practice is for surgery to be 2-3 weeks after the clinic appointment, there will be sufficient time for the patient to consider the information and ask any questions they may have about participation.

7.2 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. It is the responsibility of the Chief Investigator (or designee as listed on the Site Responsibilities Form) to obtain written informed consent in compliance with national requirements from each patient prior to entry into the study. On the day of surgery, the clinical team will confirm if the patient wishes to participate and if yes, will arrange for consent to be taken. Written informed consent will be taken by an appropriately trained member of the team and may include experienced research nurses or trials assistants, as per the delegation log. This is in accordance with Good Clinical Practice (GCP) guidelines and will have been documented and approved by the Chief Investigator on the delegation log. Patients will be reminded that participation is voluntary and that they can withdraw at any time point without this affecting their care. This process will be clearly documented in the patients' medical notes.

A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained in the trial site file and a copy will be placed in the patient's notes.

There will be two study PIS's; one for prospective patients and one for retrospective patients who participated in the local service evaluation and have already completed BREAST-Q questionnaires. There will be two ICFs for the study, one for those entering as prospective patients who have not yet had their surgery and a separate ICF for those who participated in the local service evaluation.

On consent, all participants will be allocated an anonymised sequential trial identification number which will be used on all trial data collection.

7.2.1 Patients who withdraw consent

Patients are free to withdraw from the study at any time.

7.3 Baseline Assessments

Once written informed consent is obtained, participants will be asked to complete the baseline questionnaire. Clinical data will be obtained from medical notes by the clinician and/or research team and will include (but not limited to) gender, age, diagnostic details, co-morbidities, smoking status, previous surgical and planned treatments.

Timepoint 0

<u>After consent but prior to surgery</u>

Following written informed consent and prior to the planned surgery, the baseline BREAST-Q questionnaire will be completed by every patient.

The following data items will be collected during the study:

- Reason for surgery (cancer or risk reduction)
- Uni or Bilateral surgery
- Type of mastectomy (skin and nipple preserving or nipple sacrificing, skin reducing)
- Pre- or sub-pectoral reconstruction
- Any axillary surgery
- Breast implant size
- Details of any anaesthetic block used (to reduce post-operative pain)
- Any additional cancer treatments (e.g. chemotherapy, radiotherapy)
- Any complications (e.g. haematoma, infection)
- Unplanned hospital re-admission
- Unplanned further surgery
- Implant loss at 3 months due to infection
- Expectation of pain after surgery
- Expectation of appearance after surgery
- Expectation of breast symmetry
- Expectation of change in sensation
- Satisfaction of breast shape and implant
- Psychosocial well-being
- Physical well-being related to chest
- Satisfaction with the information and care provided by the clinical team
- Sociodemographic information

7.4 Subsequent Timepoints

Timepoint 1
On completion of surgery and discharge from hospital

All study participants will be asked to complete the BREAST-Q questionnaire 2 weeks (+1 week) after having surgery. Patients will be due to be seen at a routine outpatient appointment and will be offered the opportunity to complete the questionnaires whilst in clinic. Due to COVID-19, the clinician and the patient may decide that a telephone clinic consultation is more appropriate rather than a face-to-face consultation. Participating in this study will not influence this decision making. For these cases where the follow up consultation is not face-to-face, a letter will be sent asking them to complete the questionnaire along with a pre-paid envelope to return the questionnaire.

Timepoint 2
All participants will be asked to complete the BREAST-Q questionnaire 3 months post-surgery (+ 6 weeks). Patients are routinely seen in a follow up clinic, so they will be offered the opportunity to complete the questionnaires whilst in clinic. If they are missed or if the clinic consultations are via telephone (as explained above), a letter will be sent to the participant asking them to complete the questionnaire booklet along with a pre-paid envelope to return the questionnaires.

Timepoint 3
All participants will be asked to complete the BREAST-Q questionnaire 12 months post-surgery (+ 6 weeks). Patients are routinely seen in a follow up clinic, so they will be offered the opportunity to complete the questionnaires whilst in clinic. If they are missed or if the clinic consultations are via telephone (as explained above), a letter will be sent to the participant asking them to complete the questionnaire booklet along with a pre-paid envelope to return the questionnaires.

7.5 Patient Outcome Measures (see appendix)

Participants in the study will complete the same measures on paper to ensure comparison between the timepoints. The questionnaire will be completed at baseline, 2 weeks and 3 and 12 months post-surgery.

7.6 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Withdrawal of Consent
- If surgery not undertaken as planned at time of consent

Any data acquired prior to withdrawal will be included in the final analysis (unless consent is withdrawn by the participant). The reason for withdrawal will be recorded.

8 Statistics

As we are exploring patient perceived outcomes and not evaluating a new intervention, a power calculation is not required to calculate sample size. Based on the rate of immediate implant based reconstructions performed in the Leeds Breast and Reconstructive unit, we

estimate that approximately 60 patients will be available to complete the questionnaire per year. We have set a pragmatic target of 60 patients to be recruited over the study period. This is especially relevant given the current coronavirus pandemic which has had an impact on routine patient care during 2020.

8.1 Sample size and recruitment rate

This is a single centre study with a planned minimum sample size of 60 participants. We have allowed a 2 year period for recruitment.

8.2 General Considerations

Statistical analysis of the recruitment and attrition rates, data collection, measures and outcome data is the responsibility of the Chief Investigator (assisted by the study team). The questionnaire score for each participant will be converted into a Rasch scale (scores 0-100) as per BREAST-Q score conversion protocol. Simple comparative statistical analysis will be performed with the aid of SPSS to compare BREAST-Q scores between participants undergoing pre-pectoral implant reconstruction and sub-pectoral reconstruction. Each sub-module PROMs category within the BREAST-Q will also be directly compared between the two groups. The matched BREAST-Q scores over the four time periods for each participant will also be analysed to explore the potential change in scores over the study follow-up period. Patient outcome (e.g. complication rates, re-admission, additional cancer treatment) will also be correlated with the BREAST-Q scores to examine their potential impact on PROMs.

8.3 Recruitment, Follow up and Attrition

The feasibility of the recruitment process will be evaluated by using the screening logs, eligibility and consent processes. If reasons for ineligibility and non-participation have been provided, these will be summarised. Follow up retention, including the number of participants who withdraw and any reasons for withdrawal will be described.

8.4 Clinical Measure and Processes

Telephone calls and contact with hospital staff to report problems such as pain or infection symptoms will be summarised.

8.5 Patient Outcome Measures

Patient outcome measures will be summarised for each time point. Any differences between the two groups will be analysed where possible. All analyses will be used to help plan a future advice and information for patients undergoing implant based reconstruction.

9 Data Management

Data collection will occur in accordance with GCP, Caldicott principles and the General Data Protection Regulation (GDPR) 2018, and will work in line with NHS confidentiality guidelines and codes of conduct. All questionnaires will be fully anonymised and contain no patient identifiable details. Anonymised data will be manually inputted into an excel spreadsheet which will be held on a password protected location within a secure NHS departmental drive.

9.1 Source Data

Source documents are where data is first recorded, and from which participants' data are obtained. These will 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, diaries, microfiches, radiographs, ppm (patient pathway manager - the Leeds electronic patient record) and correspondence.
Source data verification will be monitored to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996. Monitoring by the Chief Investigator or authorised authorities will be to ensure

- Sufficient data is recorded to enable accurate linkage between hospital records and CRFs
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit
- Staff working on the trial will meet requirements of the EU Directive

9.2 Access to Data

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.

9.3 Data Recording and Record Keeping

General

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Leeds Teaching Hospitals NHS Trust. The Leeds Breast Unit will comply with all aspects of the Data Protection Act 1998 and operationally this will include:

- consent from patients to record personal details including name, date of birth, address and telephone number, email address, NHS ID and hospital ID
- appropriate storage, restricted access and disposal arrangements for patient personal and clinical details

- consent from patients for access to their medical records by responsible individuals from the research staff, the sponsor or from regulatory authorities, where it is relevant to trial participation
- Consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.

Data Collection

Data collected on each patient must be recorded by the Chief Investigator, or his/her designee, as accurately and completely as possible. The Chief Investigator is responsible for the timing, completeness, legibility, accuracy and signing of the CRF and he will retain a copy of each completed form. The Clinical Investigators must allow study staff access to any required background data from hospital records (source data e.g. medical records) on request.

All fields MUST be completed. If a test or measurement was not done, please indicate why that was omitted on the CRF. Entries must be made in **black ballpoint pen**. Errors must be **crossed out with a single line** leaving the original data un-obscured (i.e. without overwriting), the correction inserted and the change initialled and dated. An explanatory note should be added if necessary. Correction fluid/tape/labels must not be used. All data submitted on CRFs must be verifiable in the source documentation. These may 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, diaries, radiographs and correspondence. All documents will be stored in confidential conditions. Any deviation from this must be explained appropriately.

Data Completeness

Data completeness is an integral part of any trial. A CONSORT style will be used to monitor data completeness from eligibility screening, approach, study acceptance through to the final follow-up visit. This information will be made available to the TMG as regular reports. The team will also report the number of:

- Patients screened per month
- Patients approached per month (and reasons why not approached)
- Patients recruited per month
- The number of patients who complete each follow up visit or are lost to follow-up
- The number of patients who complete the trial.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

10. Safety

There are no pre-defined safety end-points for this study. However, any adverse events which occur as a result of normal care will be reported to the study team.
The majority of the research will involve completion of a simple and well validated questionnaire, so there will be no physical pain, discomfort or distress caused by these. However, questionnaires take time to complete and so can be seen as an inconvenience. Some of the questions refer to personal matters, so can be perceived as being intrusive. This study may add to the current knowledge of patient experience of implant based reconstruction techniques.

Burden will be minimised using the following approaches:

- The study pathway has been designed to avoid the need for extra visits as will be undertaken in conjunction with all standard of care appointments**.**
- The chosen assessment is widely used and is validated and has been found to be generally acceptable in use with patients.
- Experienced staff used to dealing with patients with cancer, will be involved.
- If a patient indicates that they wish to stop during the completion of the questionnaires this will be respected and they will be offered an opportunity to continue them later.

11. Ethical and Regulatory Considerations

11.1 Approvals

This study is a single centre research study taking place at Leeds only.
The protocol, informed consent forms and participant information sheets will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) 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.

11.2 Reporting

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

11.3 Patient Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

12. Public and Patient Involvement

Discussions were had with local patients who have undergone breast reconstruction regarding their experiences of the procedure and how they made their choice of type of reconstruction. One patient has reviewed all the study paperwork including the protocol, information sheet and consent form. Patient involvement with this study is vital to its success and as such, their involvement has been key since inception.

13. Archiving

In line with the principles of GCP/UK Clinical trial Regulations guidelines, at the end of the trial, data will be securely archived at the centre for a minimum of 15 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately. No records may be destroyed without first obtaining written permission from the Sponsor.

14. Insurance

NHS indemnity through the Clinical Negligence Scheme for Trusts (CNST).

15. Publication Policy

Credit for the main results will be given to all those who have collaborated in the trial, as its success depends on collaboration and participation. Requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published

- and that all these conditions must be met (www.icmje.org).

The Chief Investigator will be named as main author in any publications. In addition, all collaborators will be listed as contributors for the main trial publications, giving details of roles in planning, conducting and reporting the trial. All publications will acknowledge gratitude to the women who have taken part in the study.

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