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| **FULL TITLE OF THE STUDY**<br>BIOSYM - A Feasibility Randomised Controlled Trial Comparing Biological Matrices with Synthetic Meshes in Women Undergoing One Stage Implant Based Breast Reconstruction | |
| **SHORT TITLE/ ACRONYM**<br>Randomised trial comparing Biological Matrices with Synthetic Meshes | |
| **Version and Date of Protocol:** | V5 28/February/2025 |
| **Sponsor:** | University Hospitals of Derby and Burton NHS Foundation Trust |
| **Chief Investigator:** | Associate Professor Amit Goyal |
| **Sponsor Reference:** | UHDB/2020/078 |
| **IRAS Project ID:** | 315581 |
| **ClinicalTrials.gov:** | ClinicalTrials.gov: NCT05449691 |
| **Funder(s):** | University Hospitals of Derby and Burton NHS Foundation Trust |
| This protocol has regard for the HRA guidance | |

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

## TABLE OF AMENDMENTS:

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

| Amendment number | Date of amendment | Protocol version number | Type of amendment | Summary of amendment |
|---|---|---|---|---|
| 1 | 11/08/2023 | 3.0 | Substantial | The study will be multicentre and supported by Derby CTSU. Addition of 3 centres to achieve sample size of 60. |
| 2 | 21/09/2023 | NA | Non Substantial | Addition of new sites and mNCA added to study. No protocol updates. |
| 3 | 01/11/2024 | NA | Non substantial | New PI at Derby site, no protocol updates |
| 4 | 03/06/2024 | 4.0 | Non Substantial | Addition of remote consent. Clarification surrounding participant withdrawals. Addition of two new centres. |
| 5.0 | 04/02/2025 | 5.0 | Non Substantial | Amendment to progression criteria wording and inclusion of new study logo. |

## SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the collaborators' SOPs, and other regulatory requirements.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**BIOSYM Trial Protocol version 5.0 28 February 2025**

This protocol has been approved by:

| | | | |
|---|---|---|---|
| Name: | Associate Professor Amit Goyal | Trial Role: | Chief Investigator |
| Signature: | _____ | Date: | DD / MON / YYYY |

## KEY STUDY CONTACTS

| | |
|---|---|
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| **Funder:** | Derby & Burton Hospital's Charity (registered charity number 1061812). |

## STUDY SUMMARY

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|---|---|
| **Study Title:** | BIOSYM - A Feasibility Randomised Controlled Trial Comparing Biological Matrices with Synthetic Meshes in Women Undergoing One Stage Implant Based Breast Reconstruction |
| **Sponsor Study Reference:** | UHDB/2020/078 |
| **Study Design:** | A phase III feasibility randomised controlled trial in which participants will be randomised in a 1:1 ratio. |
| **Study Participants:** | Women undergoing mastectomy for breast cancer or risk reduction and immediate one-stage mesh assisted implant breast reconstruction as standard care. |
| **Planner Number of Sites:** | 5 |
| **Planned Sample Size:** | 60 women (30 per arm) |
| **Randomisation:** | Participants will be randomised to biological matrix or synthetic mesh |
| **Blinding:** | Participants will be blinded to the type of mesh (biological or synthetic mesh). |
| **Follow Up Duration:** | 6 months |
| **Planned Recruitment Start Date:** | 01 November 2023 |
| **Planned Recruitment End Date:** | 30 November 2025 |
| **Planned Study End Date:** | 30 May 2026 |
| **Research Question/ Aims:** | To assess patient and clinician acceptance, recruitment rate, compliance with randomly allocated type of mesh and data completeness. |

## FUNDING AND SUPPORT IN KIND

| Funder(s) | Financial and Non-Financial Support Given |
|---|---|
| Derby & Burton Hospital's Charity (registered charity number 1061812). | Financial support |
| Consultant Oncoplastic Breast Surgeons and trainees | Surgeons and trainees participating in the study will undertake research activities. |

## ROLES & RESPONSIBILITIES

**Sponsor**
The Sponsor, University Hospitals of Derby & Burton NHS Foundation Trust, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The sponsor is not providing funds for this study but has taken on responsibility for ensuring finances are in place to support the research.

**Funder**
Derby & Burton Hospital's Charity (registered charity number 1061812). Feasibility study results will be used to apply for NIHR HTA funding for the main study.

**Study Management Committees**

Trial Management Group (TMG)
The TMG will meet regularly to oversee the day-to-day management of the trial, including all aspects of the conduct of the trial. Any problems with study conduct will be raised and addressed during TMG meetings.

The TMG will review recruitment, retention, compliance and data quality to ensure efficient trial conduct according to the research timeline. They will report to the independent Trial Steering Committee (TSC).

Trial Steering Committee (TSC)
The TSC will oversee and supervise the progress of the trial and ensure that it is being conducted according to the protocol and the applicable regulations. The TSC is an independent body that includes a majority of members who are not involved with the running of the trial. They will meet prior to commencement of the study, and then at regular intervals until completion (at least annually). The responsibilities of the TSC are outlined in the TSC Charter which will be signed by all members.

Data Monitoring and Ethics Committee (DMEC)
This is a small feasibility study and therefore will not require a DMEC.

**Protocol Contributors**

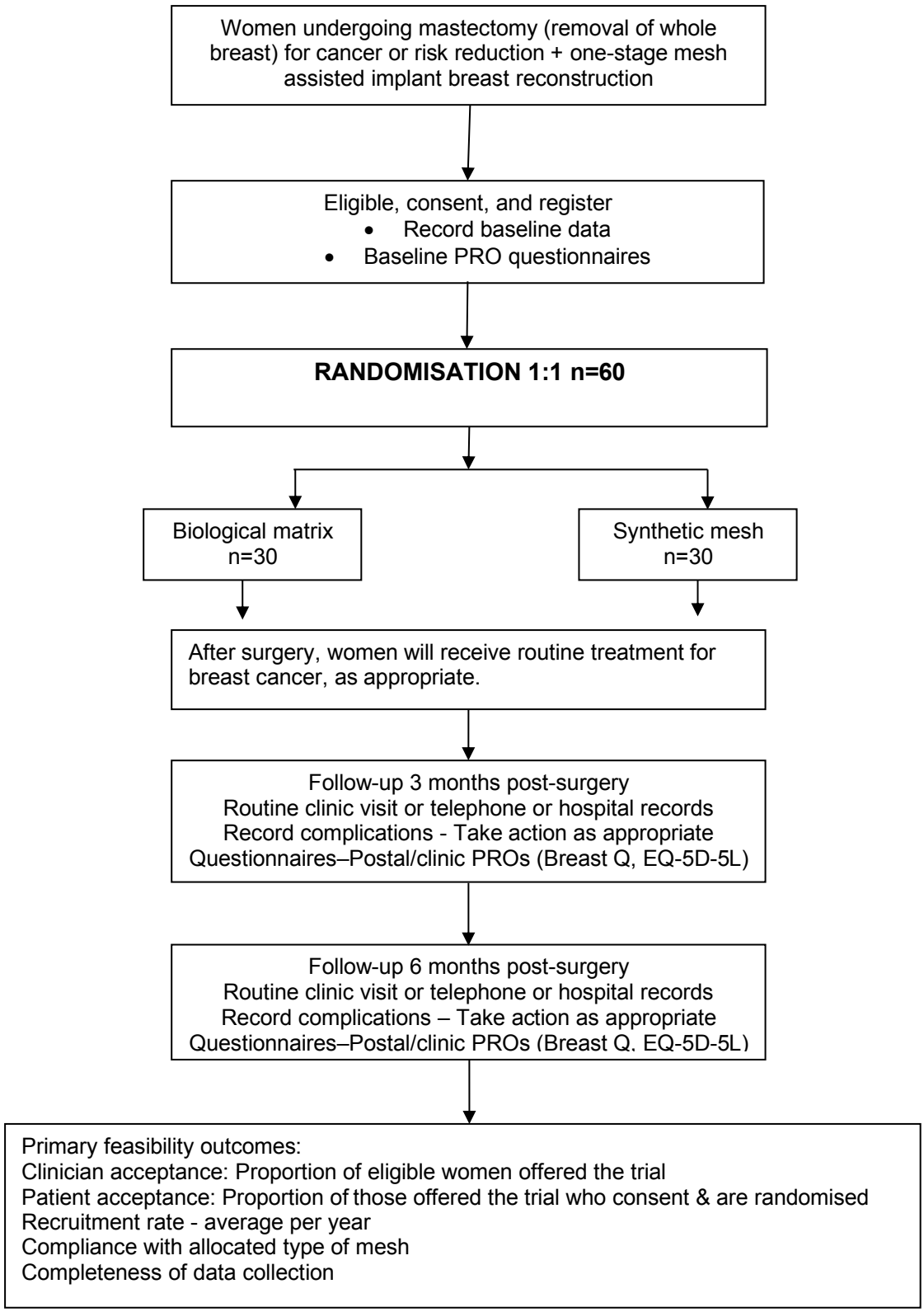
A number of protocol contributors have been involved in the development of this protocol, these include; Chief Investigator, Co-Investigators (including patient and public representatives) and the Trial Management team. Protocol contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

## CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| CI | Chief Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| DMEC | Data Monitoring and Ethics Committee |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. |
| ICPV | Independent Cancer Patient's Voice |
| ICJME | International Committee of Medical Journal Editors |
| IRAS | Integrated Research Application System |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trials |
| NCRI | National Cancer Research Institute |
| NICE | National Institute for Health Care Excellence |
| NHS R&D | National Health Service Research & Development |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PPI | Patient Public Involvement |
| QA | Quality Assurance |
| QALY | Quality-adjusted Life Year |
| QoL | Quality of Life |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SOP | Standard Operating Procedure |
| SSDL | Site Signature and Delegation Log |
| TMG | Trial Management Group |
| TMF | Trial Master File |
| TNO | Trial Number |
| TSC | Trial Steering Committee |
| UHDB | University Hospitals of Derby and Burton NHS Foundation Trust |

## STUDY FLOW CHART




PROs, patient reported outcomes; BCN, breast care nurse, QoL, quality of life

## 1. BACKGROUND

Immediate breast reconstruction in women undergoing removal of the whole breast (mastectomy) for cancer or risk reduction is most commonly performed using breast implants[1]. A sheet of mesh is used as standard treatment in majority of implant reconstructions[2] to cover the implant partially or completely like an internal bra to support the weight of implant and re-create a natural looking breast. The mesh enables one-stage breast reconstruction and avoids a second procedure for the patient[3].

Two types of meshes that are used routinely in the NHS are – biological and synthetic. Biological matrices are derived from animal tissue e.g. pig or cow, treated to remove animal cells and are costly (around £2500 per sheet). Synthetic meshes are made from net-like absorbable or non-absorbable fabric with open spaces between the strands and cost less (around £500 per sheet). The two types of meshes have different acceptability issues amongst women because of personal beliefs and concerns on animal welfare.

The UK iBRA audit[4] has collected information on the use and outcomes of different meshes at 3-months. The audit showed that use of mesh does not put patients at any higher risk of adverse post-operative outcomes, and both meshes may be equally safe. The quality of data is poor as it was an audit that did not directly compare the two types of meshes. It did not assess the long-term safety, lacks patient reported outcomes and suffers from numerous selection (e.g. women undergoing reconstruction using synthetic meshes may have been healthier and different before surgery than those who had biological meshes) and other biases (e.g. incomplete reporting and differences in surgical experience between surgeons contributing data). In contrast to iBRA, US and Canadian MROC study[5] showed significantly higher major complications with some biological matrices that has led FDA to issue a safety warning[6]. There are no trials directly comparing the two types of meshes. We do not know how safe each type of mesh is beyond 3-months. This is important as there can be side-effects that only appear in the long-term as they have for some other types of surgery.

A randomised study directly comparing the two types of meshes is needed to address the long-term safety, clinical effectiveness and cost effectiveness of the biological and synthetic meshes. It would allow women and surgeons make shared informed decisions on breast reconstruction.

Before starting a large study, we will run a feasibility study to find out whether women and surgeons are willing to take part in such a study. Women undergoing reconstruction will be randomly allocated to receive biological or synthetic mesh and followed up-to 6-months initially. Feasibility study will establish whether random allocation of type of mesh is acceptable to women and clinicians and explore what outcomes are important to capture. This will help us design the follow-on main trial that will measure women's satisfaction with reconstructed breasts, quality of life (QoL), complications and costs over 5 years.

## 2. RATIONALE

Breast and cosmetic implant registry data shows that in 2019, 2885 implant reconstructions were performed and 2075 meshes were implanted in England &Scotland[2]. This is an underestimate as figures from Hospital Episodes Statistics and the Private Healthcare Information Network suggests that half of all people that had breast implant surgery in 2019 are not recorded in the registry[2]. Women are living longer with more effective cancer treatment. Reconstruction is a part of cancer treatment and women have to live with the outcome for the rest of their lives. National Mastectomy and Reconstruction Audit[1] and iBRA audit[4] show that 9% women suffer implant loss at 3-months. The number of women requiring repeat surgery for complications has increased from 5%[1] to 18%[4] in the last few years. The complications can be serious and unpleasant to women trying to adapt to life after breast cancer and are costly to NHS in terms of hospital related and primary care costs.

Although mesh assisted implant breast reconstruction has become standard treatment and the most widely used procedure[4], we do not know patient outcomes and how safe each type of mesh is in the long-term to guide patient choices or surgeon decision-making. The choice of mesh is currently guided by surgeon preference and availability.

Mesh surgery for urinary incontinence and vaginal prolapse has seen many women complain of devastating side effects. The NICE (National Institute for Health and Care Excellence) guidelines have been revised and advise mesh surgery as the last resort for these symptoms and recommend 5 year follow-up[7].

Therefore, it is important to conduct a study comparing the two types of meshes in breast reconstruction and generate long-term patient outcome and safety data. The BIOSYM research question has been identified as a key research gap by Association of Breast Surgery[8]. The research output will reduce the risk of avoidable harm in the future as recommended by the independent review report 'First do no harm'[9] and inform specialist and NICE guidelines.

The NCRI Living With and Beyond Cancer Initiative highlights what is important to cancer patients to live better with and beyond cancer. The number one priority concerns looking at long-term side effects of cancer treatment, confirming the importance of this study to women[10].

# 3. AIMS, OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

## 3.1. Objectives

To assess patient and clinician acceptance, recruitment rate, and compliance with randomly allocated type of mesh. We will explore views of women and healthcare professionals about the study; evaluate appropriateness and completeness of data on proposed future main study outcomes. The standard deviation (SD) of patient reported 'satisfaction with breasts' score on Breast Q questionnaire will inform sample size calculations for the main study.

Feasibility study will assess:

- Clinician acceptance: Proportion of eligible women offered the trial
- Patient acceptance: Proportion of women offered the trial who participate in the trial
- Recruitment rate (average per year )
- Completeness of data on proposed definitive trial study outcomes
- Compliance with allocated type of mesh

The follow-on main study will assess long-term (5 years) patient reported 'satisfaction with breasts' measured using Breast Q questionnaire, quality of life measured using Breast Q and EQ-5D-5L questionnaires, complications and economic evaluation.

## 3.2. Outcomes

### 3.2.1. Feasibility study primary outcomes:

- Clinician acceptance: Proportion of eligible women offered the trial
- Patient acceptance: Proportion of women offered the trial who consent & are randomised in the trial
- Recruitment rate (average per year)
- Compliance with allocated type of mesh
- Completeness of data on proposed definitive trial study outcomes

### 3.2.2. Feasibility study secondary outcomes:

- Sample size estimation: Estimate the sample size for the main study.
- Completeness of data on proposed definitive trial study outcomes
    - **a.** Surgical complications such as infection, wound breakdown, readmission, reoperation, unplanned surgery, skin flap necrosis, implant loss, seroma, pain, capsular contracture and haematoma recorded at routine NHS clinic visits (or by nurse led telephone call or from hospital records) at 3- and 6-months post-surgery.

b. Patient reported outcomes (PROs) questionnaires: Breast Q and EQ-5D-5L completed at randomisation in the clinic or at home, 3- and 6-month post-surgery (postal or clinic).

# 4. STUDY DESIGN

Pragmatic phase III randomised, feasibility trial with of biological matrices compared with synthetic meshes in women undergoing immediate one-stage mesh assisted implant breast reconstruction as standard care.

# 5. ELIGIBILITY CRITERIA

## 5.1. Inclusion Criteria

Eligible participants will be/should have:

- Female age ≥ 18
- Women undergoing mastectomy and immediate one-stage mesh assisted implant breast reconstruction as standard treatment

## 5.2. Exclusion Criteria

Participants will be excluded if they have any one of the following:

- Revision reconstruction surgery
- Delayed reconstruction surgery, i.e. when reconstruction surgery is NOT performed at the same time as mastectomy.

# 6. STUDY PROCEDURES

## 6.1. Screening and Consent

### 6.1.1. Participant Identification

The target population are women undergoing mastectomy for breast cancer or risk reduction and immediate one-stage mesh assisted implant breast reconstruction as standard care.

Potential trial participants will be identified at the routine multi-disciplinary meetings and reconstruction clinics, where patients' eligibility will be assessed. The trial will be introduced and discussed with the patient by the treating clinician at the clinic appointment. Screened patients will be entered onto the screening log which will record whether they were eligible for the trial or not and the reasons why non-eligible patients were not eligible. Eligible patients will be approached by their treating clinician. If a treating clinician decides not to approach an eligible patient, the reasons for not approaching them must be recorded in the screening log.

### 6.1.2. Patient Information Sheet (PIS)

The aim of the PIS is to provide information about the research study to potential BIOSYM participants Patients will be encouraged to take the information sheet home and discuss the trial with their family ahead of making an informed decision. Patients will be given sufficient time to consider the information and reach a decision, this may include coming back to the centre for another clinic visit.

### 6.1.3. Informed Consent

If a patient has read the PIS, and is happy to participate in the trial, they will be consented and enrolled in the study. The patient must be given the opportunity to ask questions and to be satisfied with the responses, prior to written consent being given. Patients can refuse consent without giving a reason, but if they do say why they do not want to take part this should be recorded in the screening log. Consent may be taken remotely using the same version of the consent form. Participants should be provided

with a PIS and the consent form should be completed by a delegated individual via a telephone or video conference call. The delegated individual will mark that the consent was taken remotely. At the next routine visit to the hospital, , the same consent form should be countersigned by the participant and a copy given to them for their record.

#### 6.1.3.1 Responsibilities

It is the responsibility of the Principal Investigator (PI) at each site, or trained delegate, to obtain informed consent for each participant, prior to performing any trial related procedure. The PI may delegate responsibility for obtaining informed consent to other appropriate members of the site research team, for example Clinical Nurse Specialists and Research Nurses, who must be appropriately trained in obtaining informed consent and in Good Clinical Practice (GCP). Delegation of responsibility for obtaining informed consent must be indicated appropriately on the Site Signature and Delegation Log (SSDL). Participant eligibility should be confirmed by the PI or Investigator(s) who are delegated this task on the SSDL. Other members of the Research Team (e.g. Research Nurse) may assist with this process but responsibility remains with the PI.

#### 6.1.3.2 Process for obtaining informed consent

Full consent can be obtained in writing at a face to face clinic visit or remotely.
The local PI, or designee receiving consent, must countersign the consent form.

If a participant is not available to consent face to face, consent may be taken remotely via a teleconference or video call. The same consent form will be used by the delegated individual who will sign the form and document on the form that consent was completed remotely. At the next routine visit to the hospital, the participant will be requested to sign the same consent form.

A patient cannot be randomised to the trial without informed consent (remote consent is acceptable for randomisation). Completed informed consent forms should be kept at site.

A copy of the fully signed consent form must be given to the patient. The site must ensure that the patient's participation in the trial is recorded in the patient notes and is communicated to the patient's GP.

Original ICFs must be retained on site (the original should be retained in the trial site file, with a copy filed in the relevant participant's hospital notes and a copy given to the participant).

If the PIS and/or ICF are modified during the course of the trial, sites will be notified of the procedure to follow for participants already consented and for prospective participants.

### 6.1.4. Screening Log

Participating sites will be expected to maintain an electronic screening log of all potential study candidates. This log will include limited information about the potential candidate (e.g. date of birth and initials), the date and outcome of the screening process (e.g. enrolled into study, reason why not approached for consent, reason why candidate declined to participate).

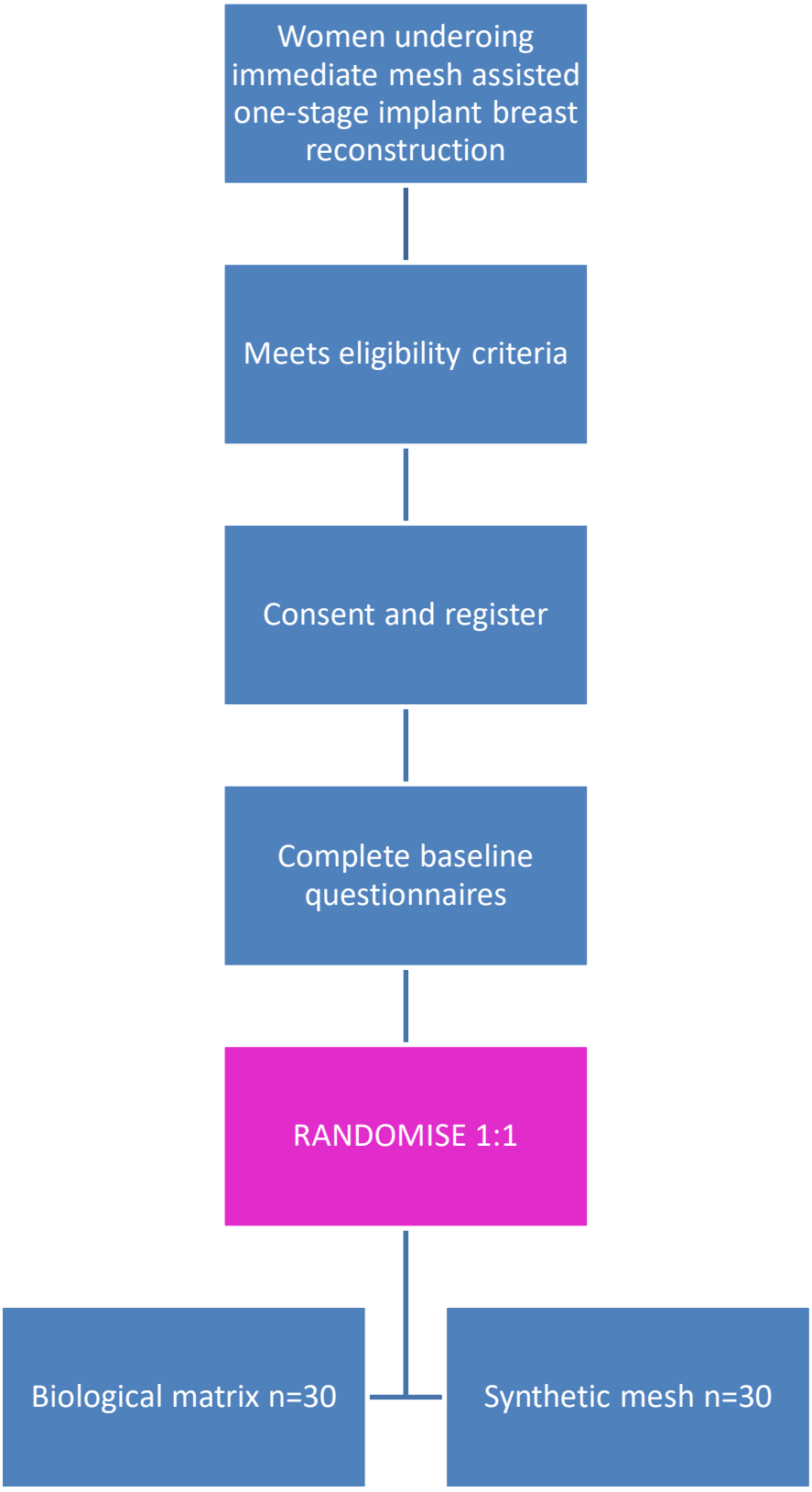
As part of the screening process, the participant will be assigned a unique trial number (TNO) generated sequentially by the EDC system that should be used to identify the participant and be recorded on all eCRFs and on any correspondence.

No identifiable information about patients who are not eligible or who do not consent will go out of the clinical team.

## 6.2. Trial Entry

### 6.2.1. Pathway for Trial Entry

Eligible participants will be approached prior to surgery. If patients give their informed consent to participate, they will be enrolled and randomised on to the study.



## 6.3. Enrollment and Randomisation Procedure

Before randomising a participant, written informed consent must have been obtained and confirmation of trial eligibility documented in the patient's medical notes. Following consent, participants will be enrolled and complete the baseline Breast Q and EQ-5D-5L questionnaires. They will be randomised to biologic matrix or synthetic mesh to allow sufficient days to order the allocated mesh for surgery. Participants will be blinded to the type of mesh (biological or synthetic mesh).

### 6.3.1. Method of Implementing the Treatment Arm Allocation

Participants will be randomly allocated using permuted block randomisation stratified by site via a web-based randomisation form in the Electronic Data Capture (EDC) system. Access to the EDC system will be via personal username and password, and specific to role.

Patients will be randomly allocated to the techniques in a 1:1 ratio. Women undergoing bilateral surgery will receive the same mesh on both sides.

## 6.4. Interventions

Participants will undergo ALL treatments as per standard local practice.

### 6.4.1. Surgery

Breast surgery will be performed as per standard local practice.

**Surgery quality assurance (QA):** The use of mesh for implant breast reconstruction has embedded into surgical practice[2]. For QA, only surgeons who have performed at least 25 mesh assisted implant reconstructions previously with implant loss of <10% will be eligible to participate.

### 6.4.2. Pathology

The histology specimens should be examined and reported according to standard local practice.

## 6.5. Study assessments

### 6.5.1. Randomised participants

Participant demographics, medical history, and indication for surgery will be collected at randomisation. Operative details such as procedure time, placement of implant under or over the muscle, and hospital stay will be collected during the in-patient stay for surgery. Details of any treatment given after surgery will also be collected during follow-up. We are using validated questionnaires for participant reported outcomes that have been used previously.

| Study Assessments | Baseline visit | Surgery admission | Month 3 post surgery | Month 6 post surgery |
|---|---|---|---|---|
| Consent | X | | | |
| Randomisation | X | | | |

| | | | | |
|---|---|---|---|---|
| Participant Demographics | X | | | |
| Medical History | X | | | |
| Indication for Surgery | X | | | |
| Operative Details | | X | | |
| Post-Surgery Histology | | | X | |
| Post-Surgery Treatment Details | | | | X |
| Questionnaires (Breast Q, EQ-5D-5L) postal or clinic | X | | X | X |
| Follow-Up (Surgical Complications data collection; via clinic, telephone or hospital records) | | | X | X |

**Complications:** such as infection, wound breakdown, readmission, reoperation, unplanned surgery, skin flap necrosis, implant loss, seroma, pain, capsular contracture and haematoma recorded at routine NHS clinic visits (or by nurse led telephone call or from hospital records) at 3 and 6 months post-surgery.

**Patient reported outcomes (PROs) questionnaires:** Patient-reported outcome data will also be collected in this feasibility study. We will assess aesthetic outcome and QoL with the widely used and validated reconstruction module of the Breast-Q questionnaire[11, 12]. This questionnaire has become the gold-standard measure of QoL for breast surgery, and was used in the National Mastectomy and Breast Reconstruction Audit[1]. It is comprised of independently functioning scales that measure outcomes and patient's experience of care (i.e. satisfaction with the surgeon, information and medical team). The QoL domain consists of three subdomains: physical, psychosocial and sexual wellbeing. The satisfaction with outcome domain also consists of three subdomains: satisfaction with breasts, satisfaction with overall outcome and satisfaction with care. A total Breast-Q score will be calculated (ranging from 0-100), with higher scores indicating greater satisfaction or better QoL. A minimum difference score of 4 points on the transformed 0 to 100 scale is clinically important when assessing an individual patient's outcome using the reconstruction module of the Breast-Q[13].

The EQ-5D-5L questionnaire is recommended to estimate utility values and quality-adjusted life years (QALYs) in economic evaluations in the UK[14]. This is a validated generic QoL tool and the responses to this questionnaire administered at randomisation, 3- and 6-months post-surgery will be summarised by randomised arm as completion rates and descriptive statistics (mean and median with their associated measure of uncertainty). QALYs will be estimated using the area under the curve approach[15] and summarised descriptively.

If the scores suggest any concerns, we will arrange rapid access back to the patient's breast care nurse.

**Patient Photographs:**
Patient photographs, both before and after surgery, will be recorded in accordance with routine local guidelines. Patients will be asked to provide consent for the use of these photographs for publication purposes, as per routine NHS practice.

## 6.6. Withdrawal Criteria

In the event of a participant's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the participant wishes to withdraw and record the details on the eCRF. For participants withdrawing from all aspects of the trial, the investigator should ascertain from the participant if they continue to consent to collecting routine information from hospital records.

Participants may withdraw from the allocated trial treatment only; this may be at the discretion of the investigator due to safety concerns. If a participant is withdrawn from the allocated trial treatment prior to surgery, they must be followed-up in accordance with the protocol and standard of care.

Participants who are randomised, but subsequently found not to meet the eligibility criteria, should be withdrawn from the trial, continue with standard care and a replacement patient should be recruited.

For patients who are lost to follow-up, follow-up data should continue to be collected from hospital or GP records, these patients should not be automatically withdrawn from the trial.

Participants who withdraw prior to randomisation will be replaced. Participants who withdraw from the study after randomisation will not be replaced.

### 6.7. End of Study

The end of study will be defined as last data capture for the last participant, allowing 1 month after the last visit to upload data and answer data queries. The CI will notify the Sponsor, participating site/s and REC within 90 days of the end of study, or within 15 days if the study is ended prematurely (please see Section 9.6 for the criteria for premature study termination). The clinical study report will be written within 12 months of the end of study.

## 7. ADVERSE EVENT MANAGEMENT

### 7.1. Definitions

| Term | Definition |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, where or not related to the investigational medical device and whether anticipated or unanticipated. |
| **Adverse Device Effect (ADE)** | An adverse event related to the use of an investigational medical device.<br><br>*NOTE: this definition includes:*<br>• *AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.*<br>• *Any event resulting from use error or from intentional misuse of the investigational medical device.*<br>• *'Comparator' if the comparator is a medical device.* |
| **Serious Adverse Event (SAE)** | An adverse event that led to any of the following:<br>• death<br>• serious deterioration in the health of the subject, users, or other persons as defined by one of more of the following<br>○ a life-threatening illness or injury, or |

| | |
|---|---|
| | ○ a permanent impairment of a body structure or a body function including chronic diseases, or<br>○ in-patient of prolonged hospitalisation, or<br>○ medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure of a body function,<br>• foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.<br><br>*NOTE: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP without a serious deterioration in health, is not considered a SAE.* |
| **Serious Adverse Device Effect (SADE)** | An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| **Unanticipated Serious Adverse Device Effect (USADE)** | A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.<br><br>*NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.* |
| **Device Deficiency** | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.<br><br>*NOTE: This definition includes:*<br>• *Malfunctions, use errors, and inadequacy in the information supplies by the manufacturer including labelling.*<br>• *Device deficiencies related to the investigational medical device or the comparator.* |
| **Serious Health Threat** | Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.<br><br>*NOTE: this would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.* |

## 7.2. Reporting Requirements

### 7.2.1. Adverse Events and Adverse Device Events

Data about relevant AEs or adverse device events are collected through routine data capture (i.e. on the Follow-up Form and through participant reported outcomes on questionnaires). Recurrence of and/or death from breast cancer and the diagnosis of new cancers in participants are outcome

measures of the trial that will be collected via the CRF and are treated as expected events. Further separate collection of adverse event data is not required for trial analysis.

### 7.2.2. Serious Adverse Events and Serious Adverse Device Events

Whilst it is not anticipated there will be any serious adverse events or serious adverse device events directly related to the study, it is important that this protocol includes a process for dealing with any serious adverse events in the unlikely event they occur. All participants in this study will receive standard NHS treatment. Both types of meshes – biologic matrix and synthetic mesh are used routinely in the NHS. This protocol does not contain investigational agent(s). Therefore, events related to the natural course of the disease and its treatment are expected and not required to be reported as outlined below.

For the purpose of this study, the following are regarded as expected SAEs and should not be recorded as an SAE.

- Haematoma, wound infection, seroma or other surgical complication of breast surgery
- SAEs relating to radiotherapy
- SAEs relating to breast reconstruction
- SAEs relating to adjuvant treatment for breast primary cancer or recurrence
- SAEs relating to lymphoedema events

For the purposes of this study, the following events also constitute expected SAEs and should not be reported to Research ethics.

- Hospitalisations for:
  - Surgical complications related to breast reconstruction, as this information is captured elsewhere in the CRF
  - Pre-planned elective procedures unless the condition worsens.
  - Treatment for progression of the patient's cancer
- Progression or death as a result of the patient's cancer.

For medical devices that are CE marked and being used for their intended use(s) all USADEs must be reported to the REC and the manufacturer.

### 7.2.3. Reporting Procedure

**Site**

Events that meet the criteria for a SAE or SADE per the protocol, should be reported on the SAE form on the Electronic Data Capture (EDC) system by the investigator or a member of the research team. When completing the form, the Investigator will be asked to confirm the following information:

- full details in medical terms and case description
- event duration (start and end dates and times, if applicable)
- action taken
- outcome
- grade of severity
- causality (i.e. relatedness to type of mesh), in the opinion of the investigator
- expectedness

On becoming aware that a patient has experienced a SAE, the Investigator (or delegate) must complete, electronically sign and date the SAE Form on EDC.

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE form.

**Trial Office**

On receipt of an SAE Form, the Chief Investigator will perform an independent assessment of relatedness. The Chief Investigator will also assess all related SAEs for expectedness. If the event is deemed unexpected (i.e. is not defined as an expected event in Section 7.2.2) it will be classified as an Unexpected and Related SAE.

**Reporting to the REC**

The Chief Investigator/Trial co-ordinator will report all events that are categorised as Unexpected and Related SAEs to the REC within 15 days of receipt. Details of all Unexpected and Related SAEs and USADEs will also be reported to Principal Investigators at recruiting sites.

All related and unexpected SAEs must be reported by the investigator using the 'non-CTIMP safety report to REC form' from the HRA website. The completed form should be submitted to the Sponsor and REC within 15 days of the CI becoming aware of the event. Safety information will be reviewed during trial management group meetings.

| **UHDB contact information**: |
| --- |
| **Email**: uhdb.randdsae@nhs.net |

#### 7.2.4. Reporting Period

The PI is responsible for checking for SAEs and SADEs when participants attend for treatment and follow-up. Details of all related SAEs (except those listed in Section 7.2.2) will be documented and reported from randomisation until 6 months post randomisation. This reporting period should be sufficient to capture all SAEs associated with the trial protocol however, if a related SAE is identified after this period, the event should be reported to the Trial Office.

#### 7.2.5. Reporting Urgent Safety Measures

If any urgent safety measure is taken the research team should inform the Sponsor with 24 hours using the Sponsors safety incident reporting form. The Sponsor will inform the REC and participating sites of the measures taken and the circumstances giving rise to those measures within 3 days on implementation of the urgent safety measure.

## 8. DATA HANDLING

### 8.1. Data Collection Tools

Study data will be entered at site into electronic case report forms (eCRF) directly by study personnel. The study will use an electronic data capture (EDC) system to store all data securely. The database will be a cloud-based EDC hosted by a fully validated 3rd party vendor. The database will be compliant with ICH-GCP and MHRA guidelines for computerised systems. Derby CTSU will be responsible for database design, build and data validation while the provider of the software will be responsible for hosting and storage of the study data. Access to the EDC will be assigned based on study roles.

After data entry is performed, validation checks will be applied to the data to ensure accuracy and consistency according to the data validation plan. All data queries generated as a result of these checks will be available online for resolution by the site. Processing of study data and monitoring for consistency, validity and quality will be undertaken by study statisticians, data and trial manager on an

ongoing basis during recruitment. After data entry is complete and all data queries have been resolved, the database will be locked and released for statistical analysis.

Participants will be identified only by their unique study number assigned by the Electronic Data Capture system. The NHS numbers will be linked to the study numbers and this information will be stored securely locally at each hospital with restricted access.

Participant reported outcomes will be captured via a series of participant questionnaires (outlined in Section 3.2). Paper questionnaires will be issued to participants at the required time points by site staff in clinic or posted to the participants. Participants will complete their responses within the questionnaire booklet, and return the completed document to site, for entry onto the trial database.

## 8.2. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concomitant medication may be summarised into the eCRF), and correspondence.

| Outcome | Source |
|---|---|
| Participant Demographics | Patient case records |
| Medical History | Patient case records |
| Indication for Surgery | Patient case records |
| Operative Details | Operation notes |
| Post-Surgery Histology | Histology report |
| Post-Surgery Treatment Details | Patient case records |
| Questionnaires (Breast Q, EQ-5D-5L) | Paper or scanned questionnaires |

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

Investigators should keep records of all participating patients andall original signed informed consent forms. It is necessary for investigators to provide access to source document for monitoring and audit purposes to Sponsor, any monitoring or regulatory authorities as deemed necessary.

## 8.3. Data handling and reporting

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

## 8.4. Access to Data

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

## 8.5. Archiving

At the end of the study, following completion of the end of study report, UHDB will securely archive all centrally held study related documentation for a minimum of 10 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure

that data and all essential documents relating to the study are retained securely for a minimum of 10 years after the end of study, and in accordance with national legislation. All archived documents must continue to be available for inspection by appropriate authorities upon request.

# 9. STATISTICS AND DATA ANALYSIS

## 9.1. Sample Size Calculation

The sample size is 60. Sample sizes between 30 and 50 are recommended for a feasibility study[16, 17]. By recruiting 60 (out of 120) we will be able to estimate a participation rate of 50% of women offered the trial to within a 95% confidence interval of +/-9% and a completion rate of 90% (54 of 60) within a 95% confidence interval of (80%, 95%).

## 9.2. Statistical Analysis

Descriptive statistics will be presented to summarize the distribution of demographic and baseline variables across each of the randomisation groups. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients/ participants:

- Assessed for eligibility and reasons for not eligible,
- Approached and reasons for not approached
- Confirmed as eligible
- Consented and reasons for not consented
- Excluded before randomisation (and the frequency of each reason for exclusion),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated type of mesh,
- That did not receive each allocated type of mesh,
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each randomisation group,
- Analysed for each randomisation group,
- Not analysed (and the frequency of each reason for not being analysed) for each randomisation group.

Primary analysis will be intention-to-treat. Clinician acceptance (proportion of eligible women offered the trial), patient acceptance (proportion of women offered the trial who participate in the trial), randomisation rate and recruitment rate (average per year) will be presented overall as proportions along with 95% confidence intervals. Compliance with allocated type of mesh and completeness of data (primary and secondary endpoints) will be presented overall and by study group using summary statistics along with 95% confidence intervals.

Secondary outcome measures will be presented overall and by study groups, as summary statistics at each assessment point. The standard deviation and effect size of Breast Q will be estimated using an Independent T-Test. Safety outcomes (AEs, SAEs, complications) will be presented with summary statistics by the treatment that has been received.

Missing data will be excluded from analysis and will not be imputed.

## 9.3. Criteria for the Premature Termination of the Study

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants or serious repeated deviations from the protocol/ regulations). If this occurs the Sponsor shall justify its

decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

### 9.4. Progression criteria to main trial

The feasibility study will identify the challenges with study implementation and delivery. This will help us design the main trial that will measure women's satisfaction with reconstructed breasts, quality of life (QoL), complications and costs over 5 years. We will progress to writing the grant application for the main trial if ALL the criteria below are met:

- Clinician acceptance (proportion of eligible women offered the trial) - 50% and above
- Patient acceptance (proportion of those offered the trial who consent & are randomised) - 20% and above
- Average recruitment rate, 30 per year (overall)
- Compliance with allocated treatment (treatment acceptability) – 80% and above

## 10. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors or the Research Ethics Committee (REC). Authorised representatives of the Sponsor may visit the participating sites to conduct audits/ inspections.

## 11. ETHICAL AND REGULATORY CONSIDERATIONS

### 11.1. Public and Patient Involvement

Patient & Public Involvement (PPI) has been key in the planned research for the BIOSYM trial. Patient representatives were approached for collaboration and involvement in the trial design from the outset. An extensive consultation process was undertaken across a number of patient advocate groups, including Independent Cancer Patient's Voice (ICPV) and the National Cancer Research Institute (NCRI) Consumer Forum.

Jan Rose (NCRI) has joined the research team as lay co-investigator. She was involved in the development of the trial design and the protocol. Their feedback underlined that there is currently a lack of involvement of breast cancer patients in the decision making regarding the type of mesh used in their reconstructive surgery. They also highlighted that to make an informed decision, more information should be available to those diagnosed with breast cancer on outcomes for patients, quality of life and the long-term safety of the different types of mesh. The patient representatives further contributed to the development of the proposal by advising and reviewing the plain English summary of the study protocol to ensure that the study rationale and procedures were explained in an accessible language.

A Patient & Public Involvement (PPI) group will be formed to ensure that the BIOSYM trial remains centred on patients' needs. This is important so that they can engage better and they've got somebody else there with them that they can connect with, and they don't feel like they're there by themselves. We will follow the 'outreach' model of PPI, in which the named lay representatives will be linked to patient advocates from breast cancer charities or support groups.

Representatives of the above group will be members of the protocol development group and (after the trial has launched) the trial management group. They will provide advice at different stages of the planned research. Main activities will involve:-

a.) Contributing to and reviewing of the study protocol; (we will also ask members of Independent Cancer Patient's Voice (ICPV) to review the study protocol);

b.) Reviewing the content of the patient information leaflet to protect patient rights and ensure that the research rationale, procedures and risks will be fully explained and in an accessible language. (we will also ask members of ICPV to advise on the patient information leaflet);

c.) Providing insight in the ethical approval application, and assisting with communications with the NHS Research Ethics Committee;
d.) Assisting with the dissemination of the planned research, including advising on conference proceedings and how to share the research findings to a wide audience in a way the public can understand;
e.) Contributing to the trial design, agreeing which outcomes would be most important to measure and the grant application of the main study.
The PPI group will engage throughout the study with the other members of the research team via email, remote video meetings (MS Teams/Zoom) and teleconferences.

### 11.2. Research Ethics Committee (REC) & Regulatory Considerations

The study will be conducted in compliance with the approved protocol, GCP, the Declaration of Helsinki and the Sponsor SOPs. The protocol and all related documentation (e.g. ICF, PIS, and questionnaires) will be reviewed and receive approval by a REC. The investigator will not begin any participant activities until approval from the HRA and REC has been obtained and documented. All documentation and correspondence must be retained in the trial master file/investigator site file. Substantial amendments that require HRA and REC (where applicable) review will not be implemented until the HRA and REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

It is the responsibility of the CI to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The CI is also responsible for notifying the REC of the end of study within 90 days. Within one year of the end of study, the CI will submit a final report with the results, including any publications/abstracts to the REC.

The CI is also responsible for ensuring that the publicly available databases on which the trial is registered (i.e. ISRCTN or clinicaltrials.gov) are updated with the results of the trial.

Before any site can enrol a participant into the study confirmation of capacity must be sought from the site's research and development (R&D) department. In addition, for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is ongoing.

### 11.3. Protocol Compliance

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations (known as non-compliances) may happen and as such these must be reported within the eCRF via a non-compliance form on the EDC by the PI or a delegated staff member. Within this form the non-compliance will be categorized and classified as minor, major, or a serious breach, and will be reviewed by the trial manager and the TMG to identify any trends. Corrective and preventative actions will be identified and actioned.

### 11.4. Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or
(b) The scientific value of the study.

If a serious breach is confirmed by clear and unequivocal evidence, the study Sponsor must notify the REC within 7 days of the matter coming to their attention.

### 11.5. Data Protection and Patient Confidentiality

The study will be conducted in accordance with the General Data Protection Regulation (GDPR). The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. Participants will be identified on all study specific documents (except for the informed consent form and enrolment log) by only the participants study specific identifier (and initials if deemed necessary). This identifier will be recorded on documents and the database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

All documents will be stored securely with access restricted to study staff and authorised personnel.

To preserve the participants' anonymity, only their allocated trial number and initials will be required on the eCRFs. Participants should be assured that their confidentiality will be respected at all times

UHDB will act as data controller of the data generated in the study.

### 11.6. Financial and Other Competing Interests

At the time of protocol writing, there are no known financial or other competing interests of the Chief Investigator or their team.

### 11.7. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

### 11.8. Amendments

Changes to the protocol will be documented in written protocol amendments; the Sponsor is responsible for deciding if an amendment should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendments will only be implemented after approval and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

### 11.9. Access to Final Study Dataset

Access to the trial datasets will be limited to the CI and to the trial statisticians. The datasets will be provided to the sponsor at the end of the trial for archiving purposes.

Access to all data at site will be restricted to personnel approved by the local Principal Investigator and recorded on a delegation log. Access will also be given to the sponsor and regulatory authorities.

### 11.10. Data Sharing Statement

Any requests for access to the trial data should be sent to the CI who will inform the data custodians and agreement will be made through the data access committee which will comprise of the principal investigators from the trial management group. For each data sharing request, it is essential that a proforma is completed which will describe the purpose, scope, data items requested, analysis plan and acknowledgment of the trial management team. Requestors who are granted access to the data will be required to complete a data sharing agreement which will be signed by the requester, sponsor and principal investigator(s). We anticipate that data sharing will be possible after the publication of the primary endpoint of the trial.

## 12. DISSEMINATION POLICY

The dissemination of the study results will be via a study report and research papers for publication in peer reviewed journals, and presentation at relevant conferences. Reporting will be in compliance with CONSORT recommendations. Publication of the results will be based on outcomes at least 6 months following the last recruited participant. No interim publication of results is planned.

A summary of the results will be publicised through Independent Cancer Patients' Voice, Cancer Research UK and Breast Cancer Now.

### 12.1. Policy for Publication and Authorship

Authors and Contributors will be defined as per The International Committee of Medical Journal Editors (ICJME) recommendations. The publication and authorship policy shall be agreed with the collaborators. The first author will be the CI of the study. Authorship will be named authors on behalf of a collaborative group; the named authorship is for those who have made a significant contribution. Additional authors will be those who have contributed to the overall success of the study. These will include team members who have randomized at least 10 participants to the study.

Citable collaborators: Citable collaborators will have made a considerable contribution to the study but will not have met the ICMJE criteria for authorship (non-author contributors). All citable collaborators will be listed at the end of the paper and their roles identified.

Acknowledged collaborators: Acknowledged collaborators will include team members and trainees who have made a lesser contribution to patient recruitment and data collection than that required for citable collaborator status. Trainees who are acknowledged contributors will also receive a certificate of participation for inclusion in their portfolios.

## 13. REFERENCES


1. Jeevan, R., et al., *Findings of a national comparative audit of mastectomy and breast reconstruction surgery in England.* J Plast.Reconstr.Aesthet.Surg, 2014. **67**(10): p. 1333-1344.
2. *Breast and Cosmetic Implant Registry - January 2019 to December 2019, Management Information.* https://digital.nhs.uk/data-and-information/publications/statistical/mi-breast-and-cosmetic-implant-registry/2020, 2020.
3. Hallberg, H., et al., *Benefits and risks with acellular dermal matrix (ADM) and mesh support in immediate breast reconstruction: a systematic review and meta-analysis.* J Plast Surg Hand Surg, 2018. **52**(3): p. 130-147.
4. Potter, S., et al., *Short-term safety outcomes of mastectomy and immediate implant-based breast reconstruction with and without mesh (iBRA): a multicentre, prospective cohort study.* Lancet Oncol, 2019. **20**(2): p. 254-266.
5. Sorkin, M., et al., *Acellular Dermal Matrix in Immediate Expander/Implant Breast Reconstruction: A Multicenter Assessment of Risks and Benefits.* Plast Reconstr Surg, 2017. **140**(6): p. 1091-1100.
6. FDA. *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication*. 2021 [cited 2021 11/07/2021]; Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication.
7. *Urinary incontinence and pelvic organ prolapse in women: management [NG123].* https://www.nice.org.uk/guidance/ng123, 2019.
8. Cutress, R.I., et al., *Opportunities and priorities for breast surgical research.* Lancet Oncol, 2018. **19**(10): p. e521-e533.
9. *First Do No Harm: The report of the independent medicines and medical devices safety review.* https://www.immdsreview.org.uk/Report.html, 2020.
10. *NCRI The UK Top living with and beyond cancer research priorities.* https://www.ncri.org.uk/lwbc/all-questions/, 2018.
11. Pusic, A.L., et al., *Patient-Reported Outcomes 1 Year After Immediate Breast Reconstruction: Results of the Mastectomy Reconstruction Outcomes Consortium Study.* J Clin Oncol, 2017. **35**(22): p. 2499-2506.
12. Eltahir, Y., et al., *Outcome of Quality of Life for Women Undergoing Autologous versus Alloplastic Breast Reconstruction following Mastectomy: A Systematic Review and Meta-Analysis.* Plast.Reconstr.Surg, 2020. **145**(5): p. 1109-1123.
13. Voineskos, S.H., et al., *Giving Meaning to Differences in BREAST-Q Scores: Minimal Important Difference for Breast Reconstruction Patients.* Plast.Reconstr.Surg, 2020. **145**(1): p. 11e-20e.
14. *National Institute for Health and Care Excellence (NICE): Guide to the methods of technology appraisal 2013.* https://www.nice.org.uk/article/pmg9, 2013.
15. Whitehead, S.J. and S. Ali, *Health outcomes in economic evaluation: the QALY and utilities.* Br Med Bull, 2010. **96**: p. 5-21.
16. Lancaster, G.A., S. Dodd, and P.R. Williamson, *Design and analysis of pilot studies: recommendations for good practice.* J Eval.Clin Pract., 2004. **10**(2): p. 307-312.
17. Sim, J. and M. Lewis, *The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency.* J Clin Epidemiol., 2012. **65**(3): p. 301-308.
18. Voineskos, S.H., et al., *Giving Meaning to Differences in BREAST-Q Scores: Minimal Important Difference for Breast Reconstruction Patients.* Plast Reconstr Surg, 2020. **145**(1): p. 11e-20e.