A Mesh SAfety Platform for Immediate Implant based BReAst Reconstruction (MAP-BRA)

Project: A multicentre prospective cohort study to evaluate the safety and effectiveness of Fortiva porcine acellular dermal matrix in immediate implant based breast reconstruction

MAP-BRA Project 1 Protocol
V4.0, 15/06/2021

Study Sponsor:
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EudraCT number: N/A

CTA Reference Number: N/A

ISRCTN: 16902075

Research Ethics Ref: 19/NW/0352

Sponsor Ref: 5862

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Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: J Henderson **Date:** 12/7/21

Ms Julia Henderson
Consultant Oncoplastic Breast Surgeon

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature: See accompanying email approval confirmation **Date:** 30/06/2021

James Boateng
R&D Clinical Research Monitor

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: See accompanying email approval confirmation **Date:** 12/07/2021

Dr Richard Jackson
Senior Statistician

General Information

This document describes the MAP-BRA Project 1 study including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre, Liverpool Clinical Trials Centre to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Julia Henderson, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 0.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Relationship Statements

Liverpool University Hospitals NHS Foundation Trust is the Sponsoring organisation and will formally delegate specific sponsoring roles to the Chief Investigator, Research Sites and the Clinical Trials Centre (CTC), but remains legally responsible for the trial.

The LCTC of the University of Liverpool in collaboration with the Chief Investigator, Mrs Julia Henderson will have overall management responsibility for the trial from a CTC perspective and will be responsible for the co-ordination of centres.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

iBRA Net is an innovative network of research interested breast, reconstructive and plastic surgeons established with the aim of enabling safe and effective innovation in breast surgery. The network is supported by the Association of Breast Surgery to promote ‘no innovation without evaluation’. The role of the network is to provide shared learning and support for breast, plastic and reconstructive surgery research, promote the development of high quality research and encourage participation and recruitment to clinical trials. This project has been developed with support from the iBRA net group.

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Mesh Supplier:**
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Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Co-Investigator:**
Mrs Heather Rodgers RD&I Governance Manager The Liverpool University Hospitals NHS Foundation Trust Royal Liverpool Hospital Prescot Street Liverpool L7 8XP **Tel:** 0151 706 3702 **Email:** RGT@RLBUHT.nhs.uk	**Ms Julia Henderson** Consultant Oncoplastic Breast Surgeon The Liverpool University Hospitals NHS Foundation Trust Royal Liverpool Hospital Prescot Street Liverpool L7 8XP **Tel:** 0151 706 3452 **Email:** Julia.henderson@liverpoolft.nhs.uk	**Prof Chris Holcombe** Consultant Oncoplastic Breast Surgeon The Liverpool University Hospitals NHS Foundation Trust Royal Liverpool Hospital Prescot Street Liverpool L7 8XP **Tel:** 0151 706 3459 **Email:** Chris.holcombe@liverpoolft.nhs.uk
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Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File

2 Glossary

AcoRD	Attributing the costs of health and social care Research and Development
ADM	Acellular Dermal Matrix
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DVT	Deep vein thrombosis
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
GA	General Anaesthesia
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
IBBR	Implant Based Breast Reconstruction
iBRA Study	The iBRA study34 (ISRCTN37664281) is a NIHR funded multicentre prospective cohort study that aims to explore the outcomes of new approaches to IBBR
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LA	Local Anaesthesia
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
MDT	Multi-Disciplinary Team
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
NRES	National Research Ethics Service
PE	Pulmonary Embolism
PI	Principal Investigator
PIS	Patient Information Sheet
PPIBR	Pre-Pectoral Implant Breast Reconstruction
PROMS	Patient Reported Outcome Measures
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCA	Root Cause Analysis
REC	Research Ethics Committee

RN	Research Nurse (Registered)
RSA	Research Site Agreement
RSI	Reference Safety Information
RSO	Research Support Office
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPIBR	Sub-Pectoral Implant Breast Reconstruction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VAS	Visual Analogue Score

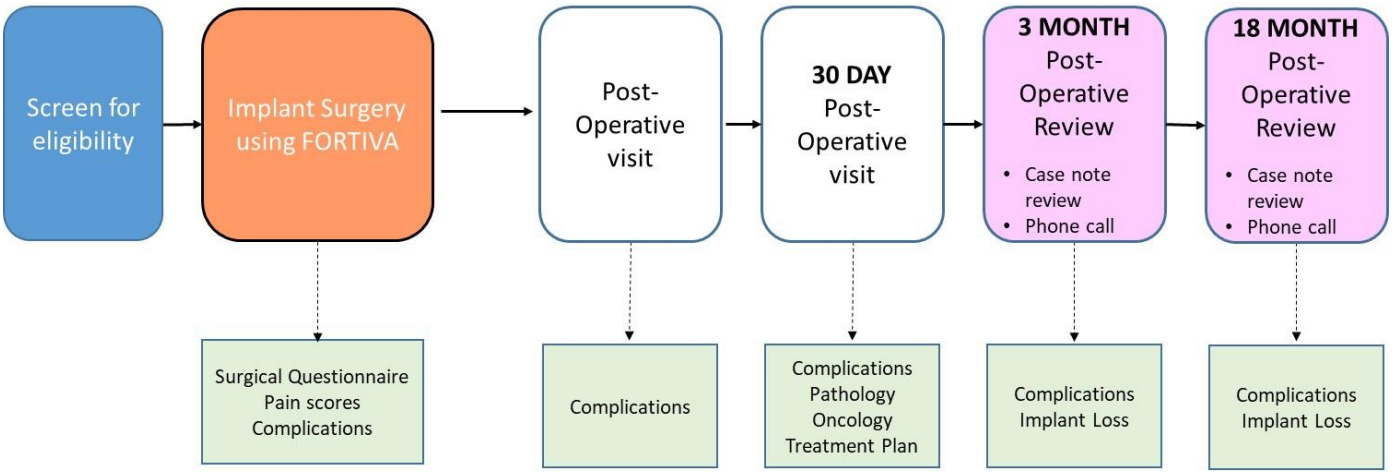
3 Protocol Overview

Study Full Title:	A **M**esh S**A**fety **P**latform for Immediate Implant based **BR**e**A**st Reconstruction – Project 1. A multicentre prospective cohort study to evaluate the safety and effectiveness of Fortiva porcine acellular dermal matrix in immediate implant based breast reconstruction.
Study Short Title:	MAP-BRA Project 1.
Phase:	N/A.
Target Condition:	Implant based breast reconstruction with mesh.
Sample size:	79 patients.
Inclusion Criteria:	1. Female patients age 18 or over electing to undergo immediate implant based reconstruction with mesh for invasive or pre-invasive cancer or for risk reduction. 2. Written and informed consent obtained from the participant and agreement of the participant to comply with the requirements of the study.
Exclusion Criteria:	1. Women undergoing revisional or delayed reconstruction. 2. Women who have undergone previous breast surgery or mantle radiotherapy. 3. Women who currently smoke cigarettes or e-cigarettes. 4. Women with a BMI of 35 or above. 5. Women in whom it is anticipated that an implant volume of greater than 500cc will be required.
Number of Sites	10 UK sites.
Patient Study Duration:	Each patient will be followed up for 18 months post-surgery.
Study Duration:	36 months - 6 months set-up, 9 months recruitment, 18 months follow-up and 3 months close out and reporting.
Intervention:	Implant based breast reconstruction using Fortiva mesh.

Objectives and Endpoints		
Primary:	To robustly evaluate the safety and effectiveness of Fortiva in implant based breast reconstruction by comparing standardized clinical and	Implant loss rate at 3 months.

	patient-reported outcomes with data from the NIHR funded iBRA study. Refer to section **Error! Reference source not found.** for further details on endpoint/outcome measures.	
Secondary:	As above.	Implant loss rate at 18 months.
		Complications of implant based breast reconstruction with Fortiva mesh at 3 months.
		Complications of implant based breast reconstruction with Fortiva at 18 months.
	To evaluate product handling and surgeons experience of using Fortiva in subpectoral and prepectoral reconstruction.	Surgeon self-report feedback form.
Exploratory:	To establish a platform for the evaluation of new mesh products in breast reconstruction.	

3.1 Schematic of Study Design



4 Roles and Responsibilities

Sponsor

The Liverpool University Hospitals NHS Fondation Trust is legally responsible for the study. They will formally delegate specific sponsoring roles to the Chief Investigator (CI) and Liverpool Clinical Trials Centre (LCTC).

Funder

This study is funded by the Association of Breast Surgery and RTI Surgical Holdings, Inc.

Funders	Role
RTI Surgical Holdings, Inc	An Educational Grant has been awarded by RTI Surgical Holdings, Inc to iBRA net to conduct this study. The trial design and management is completely independent of RTI Surgical Holdings, Inc who will have no ownership of data and no control over publication of the findings.
Association of Breast Surgery	Additional funding has been awarded by the Association of Breast Surgery after the application and peer review.

Chief Investigator: Julia Henderson is the Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of eCRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: The LCTC at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, safety reporting, data management, registration, statistical analysis and participating site coordination.

Oversight Committees

The MAP-BRA Project 1 study is subject to oversight from the following committees:

Trial Management Group (TMG)
A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial, as well as the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

Trial Steering Committee (TSC)

The TSC will provide independent oversight of the study and make all the key decisions regarding the continuation of the study. The TSC will consist of representatives from the TMG, an independent chairperson, 2/3 independent experts in the field of breast surgery, a biostatistician, a Principal Investigator and a comsumer (laymember) representative. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

5 BACKGROUND INFORMATION

5.1 Introduction

Implant based breast reconstruction (IBBR) is the most commonly performed immediate reconstruction for UK patients undergoing mastectomy[1]. This procedure has evolved from a 2 stage technique using complete subpectoral coverage of a tissue expander following the introduction of biological and synthetic mesh. Mesh is used to create a pocket allowing the placement of a fixed volume implant[2]. It may avoid the need for uncomfortable expansion[3] and improve lower pole projection leading to more acceptable cosmetic outcomes[4-8].

Mesh has been widely and rapidly adopted despite a limited evidence base to support is safety and efficacy[9-10]. Biological products may be derived from human tissue or animals (acellular dermal or collagen matrices ADM/ACM) or, synthetic products including titanium coated polypropylene mesh and silk. The largest studies are from North America where human derived dermal matrix is the most commonly used product. This is not licensed in the UK and less data is available on the animal derived [11-19]and synthetic meshes[23-28] which are more commonly used in UK practice. Some concerns have been raised regarding excessive early complication rates with mesh products[29-33]. High quality prospective outcome data is needed to inform patients and surgeons about the safety and efficacy of these products.

The iBRA study[34] (ISRCTN37664281) is a NIHR funded multicentre prospective cohort study that aims to explore the outcomes of new approaches to IBBR. This innovative trainee collaborative study has collected robust standardised clinical and patient reported outcome data[35] on over 2000 patients undergoing IBBR at over 70 centres between 2014 and 2016. The iBRA cohort is currently the largest prospective evaluation of new approaches to IBBR world-wide and will provide the best available evidence for the safety and effectiveness of biological and synthetic meshes in IBBR. It will establish the current standard of care and allow benchmarking of new products and procedures.

Mesh based implant reconstruction has continued to evolve with the development of the 'pre-pectoral' implant reconstruction (PPIR). A fixed volume implant is placed on top of the pectoral muscle and completely covered in biological or synthetic mesh. Proposed benefits of this 'muscle-sparing' technique are reduced post-operative pain, more natural results and prevention of the 'implant animation' sometimes seen with subpectoral reconstruction (SPIR) [36-39.] Whilst it would seem likely that postoperative pain would be reduced by not disrupting the muscle this has not been demonstrated in all studies[40]. Implant rippling and palpability may have a negative impact on cosmetic outcomes[40]. The 'PreBra' Study has been designed to evaluate this technique with the aim to inform the design of a randomized clinical trial of prepectoral and subpectoral implant reconstruction.

Fortiva is a novel porcine acellular dermal matrix produced by RTI Surgical. It is perforated unlike standard ADMs. As a larger sheet it is marketed for both PPIR and SPIR and may offer patients and surgeons a more effective and cost-effective alternative to other xenogenic ADMs (e.g. Strattice, SurgiMend, Braxon) in the UK and human products (e.g AlloDerm) in North America. Robust evaluation, however, is necessary to demonstrate safety and effectiveness of the product before it is introduced into routine practice.

We propose an IDEAL stage 2a/b prospective observational study. IDEAL is a framework for evaluation of surgical innovation (ideal, development, evaluation, assessment and long-term study) [41]. Phases 2a and 2b establish the risks and benefits of a technique, ensuring stability of the procedure and evaluating the learning curve before proceeding to formal evaluation. We plan to evaluate the safety of Fortiva mesh in both SPIBR and PPIBR using data from the iBRA study cohort for comparison. Safety will be measured by implant loss and complication rate at 3 months and 18 months post operatively.

Patients undergoing both SPIBR and PPIBR will be recruited to the study. After recruitment of 46 patients there will be an interim analysis to confirm the safety of the product. If the rate of implant loss is considered acceptable (less than 5 implant losses) the trial will continue to recruit a total of 79 patients. The interim analysis will also allow a pause for group learning and transparent reporting of technique modifications. Root cause analysis will be conducted for every implant loss prior to proceeding to the next phase.

The iBRA study has established a network of research interested breast surgeons experienced in the use of MESH based breast reconstruction. This is now being formalised through iBRANet, supported by the

Association of Breast Surgery. Using this network centres with an acceptably low implant loss rate of <10% at 3 months will be approached as suitable centres to recruit to test this new product.

Once established the aim of this study would be to provide a framework for the evaluation of future products, in a similar manner to a platform study[41]. A platform study aims to evaluate multiple treatments using the same master protocol. This enables trials to be completed over a shorter time period with earlier identification of futile treatment strategies and fewer patient failures. With regard to implant mesh evaluation this protocol could be modified to allow a comparative evaluation of similar products using data from the iBRA study as a robust comparative standard. This accommodates the desire for surgeons to innovate and assess the safety of new products whilst providing a safety monitoring process and standardised evaluation. Gathering surgeon feedback on technique modification and product handling will also facilitate shared learning and collaboration.

5.2 **Objectives**

The aim of this study is to robustly evaluate the safety and effectiveness of Fortiva in implant based breast reconstruction by comparing standardized clinical and patient-reported outcomes with data from the NIHR funded iBRA study.

Stage 1: Recruitment of 46 patients to IBBR including SPIBR and PPIBR with Fortiva

There will be an interim analysis at this point

- Implant loss and complications will be assessed for all cases
- All implant losses will undergo root cause analysis
- Surgeon feedback and technique modification will be reviewed in a joint learning group.

Stage 2: If safety is confirmed recruitment will continue until 79 patients have been recruited.

- Implant loss and complications will be assessed for all cases
- All implant losses will undergo root cause analysis
- Surgeon feedback and technique modification will be reviewed in a joint learning group.

The specific end points will be:

1. Implant loss at 3 months with Fortiva implant based breast reconstruction compared with complication rates observed in the iBRA study
2. Complications at 3 months with Fortiva implant based breast reconstruction compared with complication rates observed in the iBRA study
3. Implant loss at 18 months with Fortiva mesh immediate implant based breast reconstruction compared with complication rates observed in the iBRA study
4. Complications of implant based breast reconstruction with Fortiva mesh immediate implant based breast reconstruction at 18 months in comparison those observed in the iBRA study
5. Evaluation of product handling and surgeons' experience of using Fortiva in subpectoral and prepectoral implant reconstruction using a self-report questionnaire
6. Establish the principal of a platform for the evaluation of new mesh products marketed for IBBR.

5.3 **Potential Risk and Benefits**

Porcine acellular dermal matrices (ADM) have been used for subpectoral breast reconstruction for a number of years and this is a well-established technique. Risks of using a new product include a higher rate of complications including implant loss, poorer cosmetic outcome and patient reported outcome. We aim to reduce the risk of complications by requiring participating surgeons to demonstrate that they have a low incidence of complications (<10% 3 month implant loss over 12 month period). By excluding patients shown by the iBRA study to be at increased risk of complications (Smokers, patients with previous radiotherapy, high implant volumes, BMI above 35) we hope to further reduce the risk of implant loss.

Many meshes are introduced into the surgical market without adequate evaluation, higher rates of complication may be missed and if a product is unsafe this can take a long period of time to come to light. Evaluating this new product within a clinical trial provides reliable standardised safety data whilst allowing surgeons to assess whether Fortiva is as effective as other products on the market and whether they find it technically more or less usable. There will be shared learning from surgeon feedback on product handling. There may be cost savings if Fortiva is shown to be a suitable alternative to current ADMs.

By building in an initial evaluation after 46 cases any safety concerns can be detected at an early stage and the study can be stopped. All implants that are lost during the study will undergo a root cause analysis (RCA) see appendix G.

The purpose of the IDEAL2a/b design is to allow transparent reporting of changes and modifications to surgical technique and device use. In order to harness this group learning there will be a review of surgeon feedback (appendix A) for each centre after 10 cases. This information will be shared jointly with participating centres via email. At completion of stage 1 a summary document of surgeon experience will be produced including the results of all RCA undertaken for implant loss. This will inform decision making including any procedural modifications prior to proceeding to stage 2. Surgeon feedback will continue to be collected for each case and to be shared throughout stage 2.

5.4 **Lay Summary**

Breast reconstruction is offered to patients having a mastectomy and can be done at the same operation (an immediate reconstruction) or at a later date (delayed reconstruction). Silicone implants are the most common way of reconstructing breasts in patients having immediate reconstruction. This is commonly done using a mesh. Meshes can be made from man-made material (synthetic mesh) or from human or animal tissue that has been treated (biological mesh). A pocket is created to hold the implant in place underneath the skin. The upper part of the pocket is often formed by lifting the pectoral (chest wall) muscle. The lower part of the implant is supported by a mesh. This is called sub-pectoral reconstruction. Another alternative is to make the whole pocket from mesh and place this on top of the muscle, known as pre-pectoral reconstruction. This is a newer technique and is also being assessed in this study.

Many new mesh products continue to be developed to try and improve the results of implant reconstructions. These products need to be assessed to ensure that they are safe and effective.

The purpose of this study is to monitor and collect information about a new mesh designed for breast reconstruction with implants. Information about complications that occur as a result of the surgery will be collected. The main way of measuring the safety of the mesh will be the number of patients who need to have their implant removed because of a complication from the surgery. Details of complications after the surgery will be collected at 3 months and 18 months. This will be compared with results from a group of 2000 patients who have had breast reconstruction with mesh and implants. Patients and surgeons will be asked for their feedback on the result of the operation.

This study design could then be used to test new meshes that are produced for implant reconstruction to ensure that every new product has reliable safety information before it is widely used.

6 STUDY DESIGN

MAP-BRA Project 1 is a multicentre prospective cohort study to assess the safety of Fortiva in immediate implant-based breast reconstruction.

6.1 Blinding

This is an open label study with no blinding requirements. All participants receive the same intervention and so all researchers and participants know the intervention that is being administered.

6.2 Study Setting

6.2.1 Selection of Participating Sites & Principal Investigators

Each participating centre (and Principal Investigator) has been identified and selected for their expertise in performing breast surgery. Each of the centres must have the required support to undertake their delegated roles in the study. Each centre will complete a MAP-BRA feasibility questionnaire which will ensure that the centre has the appropriate facilities, qualified personnel and capacity to set up and run the study to the current approved protocol and Good Clinical Practice (GCP) standards. This feasibility questionnaire will also ensure that there are no operational concerns that were not previously considered.

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for MAP-BRA Project 1 and will be opened to recruitment upon successful completion of all global (e.g. REC) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the CTU. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

The study will be adopted on to the NIHR Portfolio. All staff working on the study must be qualified by education, training and experience to perform their respective tasks and have the applicable employment contact and status within the research site.

Given the influence of individual surgical technique on complication and implant loss rates, and the concern over the high implant loss rates demonstrated in the iBRA study, we will set markers of quality based on previous implant based breast reconstruction for entry in to this study: Implant loss rate of less than or equal to 10% over a 3 month period for individual surgeons participating. Implant loss rate of less than or equal to 10% for units over a 12 month period. For surgeons undertaking PPIBR a minimum of 10 cases must have been performed with the above implant loss criteria

Local study delivery in a geographical regions may be required to take place across multiple centres to facilitate the treatment and surgical requirements of the trial.

7 STUDY POPULATION

The MAP-BRA Project 1 study aims to recruit 79 patients based on sample size calculations described in Section **Error! Reference source not found.**. All patients must provide written, informed consent before any study procedures occur (see Section 9.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

7.1 Target Population

The target population for the study is patients undergoing an implant based breast reconstruction with mesh. All patients must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of informed consent. Under no circumstances can there be exceptions to this rule.

7.2 Inclusion Criteria

Patients eligible for the trial must comply with all of the following prior to registration:

1. Women over the age of 18 undergoing mastectomy for invasive or pre-invasive breast cancer or risk reduction who elect to undergo a sub-pectoral or pre-pectoral immediate implant based reconstruction with mesh.
2. Written and informed consent obtained from the participant and agreement of the participant to comply with the requirements of the study.

7.3 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1. Revisional surgery.
2. Delayed breast reconstruction.
3. Previous breast surgery or mantle radiotherapy.
4. Patients who are allergic to pork or unwilling to have a porcine product.
5. Patients unable or unwilling to give informed consent.
6. Patients considered by their surgeon to be unsuitable for mesh reconstruction.
7. Patients who currently smoke cigarettes or e-cigarettes.
8. Patients with a BMI of 35 or above.
9. Patients in whom it is anticipated that an implant volume of greater than 500cc will be required.

7.4 Co-enrolment Guidelines

Patients who agree to participate on the study may also be eligible for recruitment to other studies.

Recruitment to a Clinical Trial of an Investigational Medicinal Product (CTIMPS) or experimental treatments would not be compatible with entry into MAP-BRA.

It would be acceptable for MAP-BRA participants to be recruited to non-interventional /observational studies.

8 TRIAL INTERVENTIONS

8.1 Introduction

Eligibile patients will be registered to MAP-BRA Project 1. All patients who have given Informed Consent and have been found to comply with the study inclusion and exclusion criteria will be registered to the study. This study is not randomised and all registered patients will receive the same intervention (Fortiva mesh). The study intervention is implant based breast reconstruction using Fortiva mesh.

The Fortiva mesh will be provided by RTI Surgical and will be sourced at site via the usual NHS procurement arrangements according to local Trust policy.

8.2 Intervention Description

All patients registered to the MAP-BRA Project 1 trial will undergo implant based breast reconstruction using Fortiva mesh (a CE-marked device)

Name of Device	FORTIVA® 1mm Porcine Dermis
Formulation:	Mesh
Manufacturer:	RTI Surgical
Packaging, storage and stability:	No special storage instructions, as per package instructions
Supplier's name:	RTI Surgical
Regulatory Status:	CE-marked device

8.3 Manufacturing and Distribution

Fortiva Mesh is manufactured and distributed by RTI surgical. Site should source the Fortiva Mesh from RTI Surgical via the usual NHS procurement arrangements according to local Trust policy.

Sites do not need to document Fortiva Mesh stock on accountability logs for the purposes of the study.

8.4 Administration of Trial Intervention

Patients will undergo implant based breast reconstruction using Fortiva mesh. Surgery will take place according to the patient's standard care treatment timelines.

Surgical procedure instructions can be found in Section 9.7. These instructions should be followed for all patients registered on the MAP-BRA Project 1 study.

8.5 Treatment Modifications

Not applicable (no treatment modifications are permitted for this study).

8.6 Accountability Procedures

MAP-BRA Project 1 sites are not required to document accountability of Fortiva Mesh or completed any accountability logs for the study. The Fortiva Mesh used for the study will be from local supplies and ordered by the NHS site according to the usual NHS procurement arrangements.

8.7 Assessment of compliance

Not applicable (patients will undergo implant based breast reconstruction using Fortiva mesh at time of surgery, surgery details will be recorded on CRF)

8.8 Concomitant medications

Concomitant medications required as part of the patients' treatment pathway are permitted.

8.9 Unblinding

Not applicable as this is a non-randomised open-label study.

9 PARTICIPANT TIMELINES AND ASSESSMENTS

9.1 Participant Identification and Screening

Start of screening is defined as when a patient has been provided with the Patient Information Sheet (PIS) and Informed Consent Form (ICF) and has had a discussion with their clinical care team regarding their surgery and the possibility of entry into a study requiring additional assessments.

A screening-log of patients who are assessed for eligibility for the study will be maintained as this will provide important information for monitoring purposes and details on the patient uptake on to the study and the reasons for declining. At the start of screening as defined above, the patient details must be documented on the LCTC web portal ***"Screening Log".*** Screening details should be entered into the portal and this will automatically generate a screening number and a confirmation email with these details will be sent to site staff. The screening log can be printed at any time from the Portal to allow for storage in the Investigator Site File. The screening log **WILL NOT** collect any patient identifiable information e.g. date of birth.

A step-by-step guide to using the log will be issued to research site staff prior to green light and the process will also be demonstrated during site initiations.

The potential eligibility of patients will be assessed at the earliest opportunity following referral of patients requiring breast reconstructive surgery. Depending on other eligibility criteria being met, the patient will undergo an informed consent discussion and then be registered for the study.

Patient hospital notes should be screened by the research team prior to the patient being approached to ensure no obvious ineligibility criterion is apparent. The patient`s written informed consent must be obtained before any trial related procedures are undertaken.

9.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in CTU coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason.

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any assessments that are not conducted as standard of care and before patient registration on study. Patient Information Sheets will be provided to facilitate this process. Trial information is also available on the LCTC website and the UK Clinical Trials Gateway.

Investigators must ensure that they adequately explain the aim, trial procedures, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (at least 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the Research Team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

Informed consent will be taken by the local Principal Investigator/Co- Investigator, who will be a medically qualified person who is named on the study delegation log and has undergone study specific training. They will go over the risks and benefits of the study and be given time to ask questions about the trial. A research

nurse will also be available to go through the trial or ask questions to. Informed consent will take place in the hospital clinic.

After verbal and written information has been provided, the invidual seeking consent will ensure that the patient has fully understood all the information and will ask if they are happy to consent to participation in the trial.

Where this is the case, written informed consent will be obtained by means of a dated patients signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the patient for their information,
- One copy transferred to the CTU (uploaded to the portal)
- One copy filed in the patient's medical records paper

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records

9.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until fully informed consent is documented. Eligibility criteria are described in detail in Section **Error! Reference source not found.**.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's Eligibility eCRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally registered onto the study.

9.4 Registration

Patients who have given Informed Consent and have been found to comply with the study inclusion and exclusion criteria will be enrolled and registered onto the study by site staff. Site staff should log in to the REDCap database, add a new patient and complete the 'Eligibility Checklist' form. If the patient is eligible, once the 'Eligibility Checklist' form is saved, access to the 'Registration Form' will be granted. Site staff should complete and submit this form to confirm registration.

When a patient has been registered on the REDCap system, an email confirmation will be sent to the research site and LCTC, detailing the participant's REDCap ID, study number and date of registration. Successful registration will activate the eCRF for the Preoporative Data visit and all subsequent study visits for site staff to enter.

Trial Registration
Website: https://www.lcturedcap.org.uk/redcap/

If site staff have any queries while registering a patient, the LCTC is available 9am-5pm Monday-Friday, excluding weekends, bank holidays and university holidays.

Following registration of a patient, a copy of the completed Informed Consent Form should be sent to the LCTC via portal upload. If you do not have access to the LCTC portal and require access, please contact the MAP-BRA study team.

The MAP-BRA study team at the LCTC will review the informed consent form and eligibility/registration data within 1 month of each patient being registered. If it is discovered that a patient was registered incorrectly, the site will be contacted for further information and the patient withdrawn from the study. If there are queries regarding the data or consent form, these will be sent to the site.

9.4.1 Registration System Failure

If the REDCap system is down for an extended period of time, a completed paper copy of the Eligibility Checklist workbook may be submitted to the LCTC for central data entry onto REDCap when the system is available again. This should be discussed with the MAP-BRA study team.

In the event of REDCap/complete server failure at both the research site and the LCTC, registration will be performed by the MAP-BRA Project 1 study team at the LCTC.

9.5 Schedule for Assessments and Follow-up

It is anticipated that patients entering the study will be followed up for 18 months.

Baseline assessments (pre-operatively) at Pre-Operative visit

- Baseline CRF (patient demographics)

In-patient

- Procedure information
- Operative CRF
- Post-operative pain assessment at 24 hours or point of discharge
- Immediate in hospital complications
- Length of stay
- Surgeon questionnaire

1 week clinical follow up (+/- 2 days)

- Assessment of complications (clinical review)
- Post-operative pain

2 weeks clinical follow up (+/- 2 days)

- Assessment of complications (clinical review)
- Post-operative pain

30 days (+/- 2 days)

- Assessment of complications (from clinical notes)
- Oncological data and planned adjuvant treatment

3 months

- Assessment of complications (medical records review) including readmission and re-operation

18 months

- Assessment of complications (medical records review) including readmission and re-operation and implant removal.

9.6 Schedule of assessments

Procedures	Screen	Baseline	In patient	1 week (+/- 2 days)	2 weeks (+/- 2 days)	30 days (+/- 2 days)	3 months [1]	18 months [1]
Inclusion/Exclusion criteria met	X							
Informed consent	X							
Patient Registration		X						
Baseline CRF: Demographics, medical history		X						
Surgery – Mesh reconstruction			X					
Operative CRF			X					
Assessment of pain on VAS			X	X	X			
Immediate in hospital complications			X					
Length of stay			X					
Surgeon Questionnaire			X					
Assessment of complications			X	X	X	X	X	X
Assessment of implant loss							X	X
Oncological outcome and planned adjuvant						X		

[1] This can be done by research nurse via case note review and/or phone call

9.7 Surgical Procedures

The following tables contain the mandatory and non-mandatory steps for sub-pectoral and pre-pectoral procedures to standardise between centres

Table 1: MAP-BRA Mandatory and Non-Mandatory **Prepectoral** Reconstruction Steps

Component	Step	Type	Conditions	Surgeons Discretion	Flexibility
Before Incision	Antibiotics	Mandatory	Surgeon's Practice Risk factors Local guidelines	Yes	Number of doses Type of antibiotic
Intraoperative - Resectional	Mastectomy	Mandatory	Type of mastectomy depends on tumour, nipple preservation, type of reconstruction	Yes	Skin sparing Nipple sparing Skin reducing
	Raising or damaging Pectoralis major, pectoralis minor or serratus anterior	Prohibited	N/A	N/A	N/A
Intraoperative - reconstruction	Planned 1 or 2 stage	Optional	Patient factors, mastectomy weight, skin flaps	Yes	Flexible
	Prepectoral pocket created using Fortiva	Mandatory	Pocket size depends on implant volume and dimensions	Yes	
	Dermal Sling	Prohibited	N/A	N/A	N/A
	Implant insertion	Mandatory	Surgeon's choice	Yes	Fixed volume/tissue expander/ Becker
	Glove change	Mandatory	Surgeon's choice	Yes	Flexible

Strategies to minimise infection	Re-prep and drape	Mandatory	Surgeon's choice	Yes	Flexible
Postoperative	Use of drain	Mandatory	Surgeon's choice	Yes	Number of drains and duration of use
	Antibiotics	Optional	Surgeon's choice/local policy	Yes	Y/N Type, duration

Table 2: MAP-BRA Mandatory and Non-Mandatory **Subpectoral** Reconstruction Steps

Component	Step	Type	Conditions	Surgeons Discretion	Flexibility
Before Incision	Antibiotics	Mandatory	Surgeon's Practice Risk factors Local guidelines	Yes	Number of doses Type of antibiotic
Intraoperative - Resectional	Mastectomy	Mandatory	Type of mastectomy depends on tumour, nipple preservation, type of reconstruction	Yes	Skin sparing Nipple sparing Skin reducing
	Raising Pectoralis major, pectoralis minor or serratus anterior	Mandatory	N/A	N/A	N/A
Intraoperative - reconstruction	Planned 1 or 2 stage	Optional	Patient factors, mastectomy weight, skin flaps	Yes	Flexible
	Pectoral muscle detached from chest wall and	Mandatory	Pocket size depends on implant volume and dimensions	Yes	Pectoralis major, Pectoralis Minor, Serratus Anterior

	sutured to Fortiva Mesh				
	Dermal Sling	Prohibited	N/A	N/A	N/A
	Implant insertion	Mandatory	Surgeon's choice	Yes	Fixed volume/tissue expander/ Becker
Strategies to minimise infection	Glove change	Mandatory	Surgeon's choice	Yes	Flexible
	Re-prep and drape	Mandatory	Surgeon's choice	Yes	flexible
Postoperative	Use of drain	Mandatory	Surgeon's choice	Yes	Number of drains and duration of use
	Antibiotics	Optional	Surgeon's choice/local policy	Yes	Y/N Type, duration

9.8 Withdrawal

Participants will be free to withdraw from the study at any point upon request.

An investigator **may** terminate participation in the study if:

- The participant meets an exclusion criteria.
- Any clinical adverse event occurs such that continued participation in the study would not be in the best interest of the participant.

All data collected up until the point of withdrawal will be retained and analysed, so that the integrity of the project is not compromised.

9.9 Loss to Follow-up

A participant will be considered lost to follow up if they fail to return for scheduled visits and are not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit (be conscious of acceptable windows for collecting valid data) and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the End of Study eCRF.

9.10 Patient Transfers

For patients moving from the area or transfer to the care of another physician, every effort should be made for the patient to be followed-up at another (the closest) participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient CRFs should be provided to the new site. The patient remains the responsibility of the original site until the new site PI has signed the Transfer CRF. The LCTC should be notified in writing of patient transfers and the planned arrangements.

9.11 Premature Termination or Suspension of the study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for the study termination or suspension will be provided by the suspending or terminating party to Liverpool Clinical Trials Centre. If the study is prematurely terminated or suspended the PI will promptly inform the Research Ethics Committee and will provided the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include but are not limited to:

- Determination of unexpected, significant or unacceptable risks to the patient
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and the REC.

9.12 **End of Study Definition**

Unless early termination is required, the end of trial is defined as once all patients have completed a minimum follow-up of 18 months or have died /come off study for other reason, together with sufficient time to collect outstanding data and resolve queries. The final statistical analysis will not be triggered until the end of study is reached (whether this is planned or early termination).

Trial Management Group (TMG) or Trial Steering Committee (TSC) may recommend that the trial be stopped prematurely for safety. Such premature termination or suspension of the trial will be notified to the REC as required. Ongoing patients must be contacted to notify them of the end of the study.

9.13 **Long Term Follow-up**

The study will collect patient NHS numbers to allow the possible long term follow-up and entry in to follow-up trials. This will be subject to a separate protocol and ethics application.

10 CRITERIA FOR ASSESSMENTS

10.1 Procedures for assessing safety

Post-operative complications will be assessed clinically at 1 week, 2 weeks and 30 days to determine the initial safety of the technique and by a medical records review at 3 months. A further case note review will take place at 18 months to confirm any further complications, revisional surgery or implant loss.

The primary outcome of safety is assessed by implant loss at 3 months.

Implant loss will be defined as any unplanned removal of the implant ***without replacement of the prosthesis*** (implant or expander) for infection, wound problems or other indication within the first 3 months following surgery. This will not include implants that are salvaged e.g. by debridement and replacement with a tissue expander/implant.

The remaining 3 primary outcomes from iBRA will also be reviewed to determine the safety of Fortiva mesh in IBBR.

These are

- Infections at 3 and 18 months.
- Unplanned re-operation for complications relating to the implant reconstruction at 3 and 18 months.
- Re-admission for complications related to the implant reconstruction at 3 and 18 months.

These are defined as:

Implant salvage – return to theatre for debridement of wound/resuturing/drainage of infection/washout/or other indication in which the implant is removed and immediately replaced either with the same device or a tissue expander with primary closure of the wound.

Infection - A hot, red swollen breast associated with one of the following; a temperature, pus at the wound site, a raised white cell count and/or; a positive wound swab within the first 3 months following surgery. This will be further classified as:

- Minor – requiring oral antibiotics only.
- Major 1 – requiring admission for IV antibiotics and/or debridement.
- Major 2 – requiring surgical drainage/debridement.

Re-admission to hospital – any re-admission to hospital in the 3 months following surgery directly related to the procedure (e.g. with infection requiring antibiotics).

Return to theatre – Return to the operating theatre at any time during the first 3 months following surgery to deal with any complication of the reconstruction. This will not include any secondary oncological procedures such as axillary clearance or planned procedures including exchange of expander for a fixed volume implant or lipomodelling.

Other complications will also be assessed at 1 and 2 weeks; 30 days and 3 months and are defined as follows:

Seroma - A symptomatic collection of fluid around the reconstructed breast following surgery requiring aspiration. The total number of aspirations will be collected at 3 months.

Haematoma - A collection of blood in the reconstructed breast.

- Minor – managed conservatively or by aspiration in clinic.
- Major – requiring surgical evacuation.

Mastectomy skin flap necrosis - Any area of skin loss on the reconstructed breast.

- Minor – managed conservatively with dressings.
- Major 1 – requiring debridement (in clinic or theatre) under local anaesthetic (LA).
- Major 2 – requiring surgical debridement under general anaesthesia (GA).

Nipple necrosis – Any area of necrosis of the nipple areolar complex (NAC) (if nipple preserving mastectomy).

- Minor – managed conservatively with dressings.
- Major 1 – requiring surgical debridement under LA in clinic or theatre.
- Major 2 – requiring surgical debridement under GA in theatre.

Wound dehiscence – separation of the skin edges at the wound site.

a) Minor – treated conservatively.
b) Major – requiring return to theatre for re-suturing under GA.

Displaced implant requiring repositioning under GA – any implant displacement that requires surgical correction to restore its position.

In hospital complication – any complication that occurs during the patient's initial hospital stay at the time of their reconstructive surgery. This includes systematic complications such as DVT/PE and procedure specific complications such as haematoma.

Major complication - Any complication requiring readmission to hospital or return to theatre.

Minor complication - Any other complication.

10.2 Other assessments

Assessment of pain

Post-operative pain will be assessed on a visual analogue scale (VAS) from 1 to 10 at 24 hours post-operatively or prior to discharge if the patient is a day case and at 1 and 2 weeks at clinical follow up.

10.3 Safety oversight

Safety oversight will be under the direction of a Trial Steering Committee (TSC) composed of individuals with the appropriate expertise who are independent of the study. An implant loss rate of >13% is considered unacceptable. Initially 46 patients will be recruited the TSC will review the data at this point and the trial will be halted if 5 or greater patients have an implant loss at 3 months. If implant loss is 4 or less the trial will continue to recruit to 79 patients.

11 SAFETY REPORTING

11.1 Terms and Definitions

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Related Adverse Event (Related AE)
An AE which resulted from administration of any of the research procedures – i.e. assessed as "probably", "possibly" or "almost certainly" related to the trial procedures.

Related Unexpected Adverse Event (RUAE)
A Related AE which is not expected, i.e. not consistent with the known effects of the research procedures.

Serious Adverse Event (SAE)
An adverse event which meets the definition of "serious".

Related Serious Adverse Event (Related SAE)
A SAE which is assessed to be "probably", "possibly" or "almost certainly" related to the trial procedures.

Related Unexpected Serious Adverse Event (RUSAE)
A Related SAE which which is not expected, i.e. not consistent with the known effects of the trial procedures.

11.2 Event Reporting Procedures

All safety events which are reportable for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" related events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

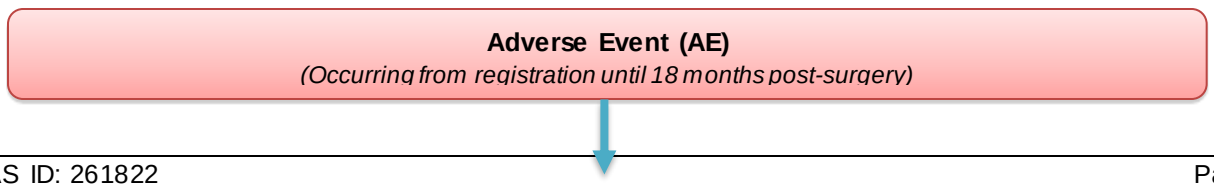
The FORTIVA MESH is a CE-Marked device being used in its approved indication, and the procedures carried out during this trial are standard of care for patients in this population. Therefore, safety reporting from sites will be limited to Related SAEs, and only Related Unexpected Serious Adverse Events (RUSAEs) will be reported to REC in an expedited manner.

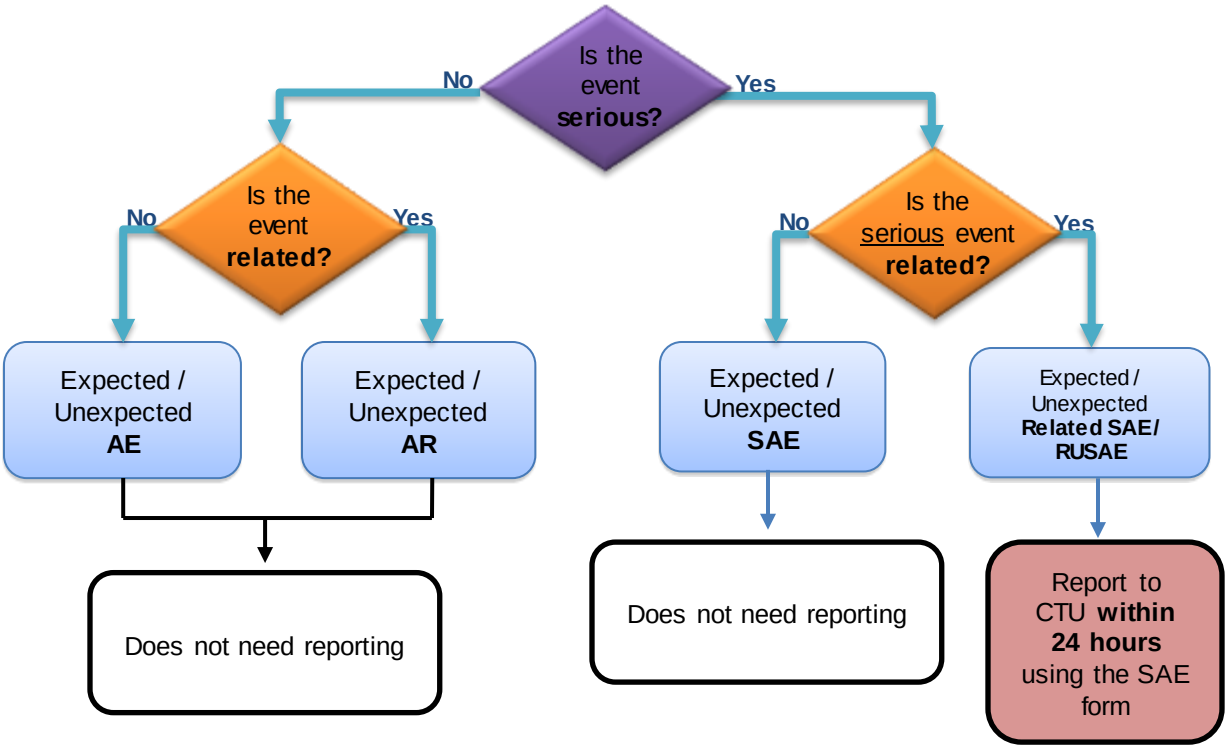
Adverse Events that do not meet the criteria of serious (see Section 10.4) do not need to be reported to the LCTC. Serious Adverse Events that are deemed by the Principal Invesitgator to be ***unrelated*** or ***unlikely to be related*** to the Fortiva mesh or study procedures do not need to be reported to the LCTC.

All Related SAEs must be reported to the LCTC within 24 hours of site becoming aware of this event.

Related SAEs will be reported for each patient from registration until 18 months post-surgery.

11.2.1 Flowchart for Site Reporting Requirements of Adverse Events





11.2.2 Reporting Events to the LCTC

- To report a Related SAE, a paper SAE Form should be completed. This should then be scanned and emailed to **lctcsafe@liverpool.ac.uk** within 24 hours of becoming aware of the event.
- The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
- The patient must be identified by trial number, age/ month & year of birth and initials **only.** The patient's name must not be used on any correspondence
- Reportable SAEs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised (see Section 11.7.4). N.B. Follow-up may continue after completion of protocol treatment if necessary.
    - Follow-up information is noted on a new SAE form to be transferred securely to the CTU as soon as more information becomes available
    - Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.
- Extra, annotated information and/or copies of pseudonymised test results may be provided separately.

11.2.3 Follow-up After Adverse Events

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)

- not resolved/ongoing
- fatal or unknown.

11.3 Investigator Reporting Responsibilities

Safety events which meet the definition of "serious" and possibly, probably or almost certainly related must be reported in more detail to the LCTC on an SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware** they will be appropriately processed.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person/dentist . Minimum reporting information must be provided in initial reports for all studies.

Minimum information required for reporting:

- Patient study number
- Study site number
- Reporting site research team member (PI/delegate)
- A description of the event
- Date of onset
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study procedures/device

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the the site R&D team in accordance with local policy.

11.3.1 Yellow Card Reporting

It is the responsibility of sites to report device incidents via MHRA yellow card reporting:

https://yellowcard.mhra.gov.uk/devices/?type=hcp

These incidents do not need to be reported to the LCTC but the report should be filed in the patient file.

11.4 LCTC Responsibilities

The trial Sponsor has delegated to LCTC the duty of onward reporting of safety events to REC. SOPs will be followed to ensure appropriate reporting as detailed below.

All reportable serious safety events will be forwarded to the Chief Investigator or Medical Reviewer by LCTC within 24 hours of receiving the minimum information from site. The CI or Medical Reviewer will review information provided by site and for all reportable events assessed as "related" will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" and "unexpected" (RUSAEs), will be onward reported by LCTC to the ethics committee within 15 days of the LCTC receiving the minimum information.

Additionally, RUSAEs will be reported to the trial Sponsor, the device manufacturer and Principal Investigators of participating sites.

A list of all safety events recorded for the trial will also be reported annually by LCTC to the ethics committee and Trial Steering Committee.

Any concerns raised by the TSC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported Related SAEs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

11.4.1 **Safety Reports**

Safety reports will be generated during the course of the trial which allows for monitoring of safety event including reporting rates and safety events by site. The LCTC will send Annual Progress Reports (APRs) containing the number of all Related SAEs to the main REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

11.4.2 **Urgent Safety Measures**

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC.

The LCTC will notify the REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC. If the study is temporarily halted it may not recommence until authorised to do so by the REC. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC), the Sponsor should notify the REC within 15 days of the date of termination by submitting the formal End of Trial Notification.

11.5 **Assessment of Seriousness**

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event / reaction is assessed as serious if it:

a) Results in death;
b) Is life-threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
c) Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation);
d) Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
e) Consists of a congenital anomaly or birth defect (in offspring of trial participants, or their partners, regardless of time of diagnosis), or
f) Is otherwise considered medically significant by the investigator.

Note: Planned hospitalisation for pre-existing conditions, or a procedure required by the study protocol, without a serious deterioration in health is not considered a Serious Adverse Event.

11.6 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 3: Clavien-Dindo classification of surgical complications

<table>
<tr><th>Grade</th><th colspan="2">Definition</th></tr>
<tr><td>Grade I</td><td colspan="2">Any deviation form the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions.
Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.</td></tr>
<tr><td>Grade II</td><td colspan="2">Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
Blood transfusions and total parenteral nutrition are also included</td></tr>
<tr><td rowspan="2">Grade III</td><td colspan="2">Requiring surgical, endoscopic or radiological intervention</td></tr>
<tr><td><u>Grade IIIa</u>
Intervention not under general anaesthesia</td><td><u>Grade IIIb</u>
Intervention under general anaesthesia</td></tr>
<tr><td rowspan="2">Grade IV</td><td colspan="2">Life-threatening complication (including CNS complications)* requiring IC/ICU management</td></tr>
<tr><td><u>Grade IVa</u>
Single organ dysfunction (including dialysis)</td><td><u>Grade IVb</u>
Multiorgan dysfunction</td></tr>
<tr><td>Grade V</td><td colspan="2">Death of a patient</td></tr>
</table>

**Brain haemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transent ischemic attacks.*
CNS = central nervous system, IC = intermediate care, ICU = intensive care unit

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 10.4. Hence, a severe safety event need not necessarily be a “serious” safety event.

11.7 Assessment of Causality

The assignment of causality should be made using the definitions in the table below:

Table 4: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after surgery/study procedures). There is

	another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after surgery/study procedures). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the REC will be informed of both points of view.

11.8 Assessment of Expectedness

The Chief Investigator for the MAP-BRA Project 1 trial is responsible for determining whether a safety event is expected or unexpected. However, the Chief Investigator will not assess their own patients, these patients will be assessed by a Medical Reviewer. There is no requirement for a reporting investigator to make an assessment of expectedness.

An event will be considered unexpected if it is not listed within the current and approved protocol (see Table 5) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that of the event listed in the protocol, the event should be assessed as unexpected.

The information to be used for expextedness assessment for the MAP-BRA Project 1 trial is the list of events in Table 5 below.

Table 5: Expected Events

Event
Implant loss
Infection – a hot red swollen breast associated with one of the following: • A temperature • Pus at the wound site • Raised white cell count • Positive wound swab
Implant salvage – return to theatre for: • Debridement of wound • Resuturing • Drainage of infection • Washout • Any other indication in which the implant is removed and immediately replaced either with the same device or a tissue explander with primary closure of the wound

Seroma – A symptomatic collection of fluid around the reconstructed breast following surgery requiring aspiration
Haematoma – A collection of blood in the reconstructed breast
Mastectomy skin flap necrosis – Any area of skin loss on the reconstructed breast
Nipple necrosis – Any area of necrosis of the nipple areolar complex (NAC) (if nipple preserving mastectomy)
Wound dehiscence – separating of the skin edges at the wound site
Displaced implant

11.9 Time Period for Active Monitoring of Safety Events

Active monitoring of safety events which require reporting (see Section 10.3) experienced by participants will be from patient registration until 18 months post-surgery.

11.10 Notes on Safety Event Recording

The following should not be recorded as a safety event:

- Medical or surgical procedures (the condition that led to the procedure should be recorded as the event)
- Pre-exisiting disease or condition present before treatment that does not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication **without signs or symptoms**
- The disease being treated or associated symptoms/sings unless more severe than expected for the patient's condition

11.11 Reporting of Pregnancy

Pregnancies occurring during the study do not need to be recorded. This decision was made in discussion with the TMG and CI as the study is low risk, the procedures carried out during this study are the same as standard care procedures and the device is CE-marked. This was determined by the TMG and CI and is documented in the TMF.

11.12 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate eCRF within 24 hours of becoming aware.

11.13 Contact Details and Out-of-hours Medical Cover

As the intervention used in the trial is a CE-marked device, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for MAP-BRA participants. All participants will be provided with a copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

12 STATISTICAL CONSIDERATIONS

12.1 Introduction

The study is designed as a single arm phase II study to assess the safety of Fortiva in immediate implant-based breast reconstruction.

Aims:

The main aim of the study is to demonstrate that Fortiva is safe for further evaluation. Secondary aims will be to compare outcome measures against the cohort of patients from the iBra study.

Outcomes:

The primary outcome will be the implant loss rate at 3 months following surgery.

Secondary outcomes include

- Complications at 3 months
- Complications at 18 months
- Implant loss at 18 months

12.2 Sample Size

Sample size calculations are based on the primary outcome of implant loss rate at 3 months using Simons' two-stage design. A target rate for implant loss (p_0) is considered to be 6% with an unacceptable implant loss rate (p_1) being 13%. Using a one-sided alpha level of 0.1 and a Power of 80% an Optimal 2-stage design is chosen with a maximum of 79 patients is required using the 'minmax' approach.

The design incorporates an inbuilt interim assessment which will occur after 46 patients have had 3 months of follow-up. Recruitment will continue only if 5 or fewer patients have had an implant loss. If ≥ 6 implant losses are observed, the study will stop due to an unacceptable implant loss rate. At the point of final analysis, the mesh will be deemed safe and suitable for further investigation if ≤ 7 implant losses are observed. If >8 implant losses are observed then it will be determined that the null hypothesis cannot be recruited.

As this is a relatively small study with a short follow-up for the primary analysis, no inflation to the sample size is included to account for patient attrition. The study will however allow for patient replacement for any patients that prematurely withdraw consent for the study.

12.3 Recruitment

Recruitment is planned to take place over 10 contributing sites selected as being good recruiters from the iBRA cohort study. It is estimated from the iBRA study that sites should recruit at a rate of 24 patients/year (2 patients/month). Assuming that sites will be opened to recruitment at a rate of 2 sites per month then 9 months are sufficient to obtain the full cohort of 79 patients (Figure 1 below)

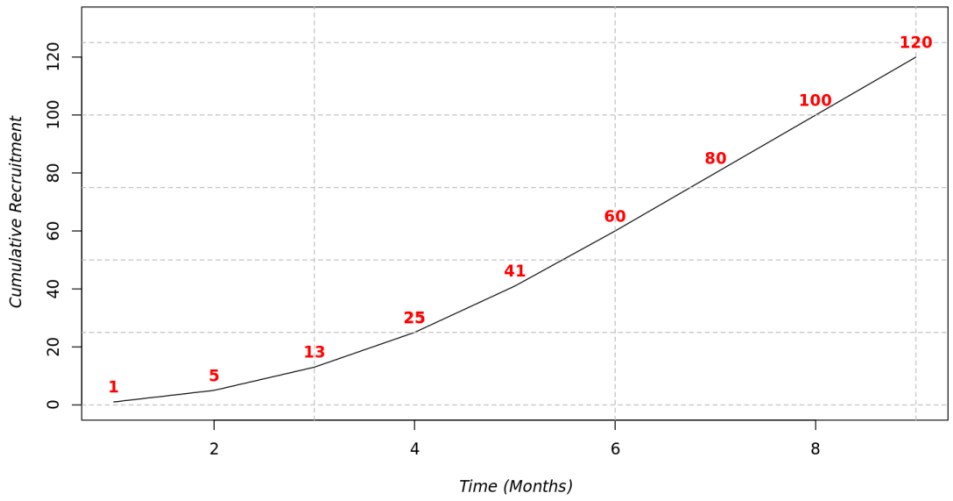


Figure 1: Predicted recruitment rate for MAP-BRA study

12.4 Analysis methods

Data Summaries

Continuous data shall be presented as medians with associated inter-quartile ranges and ranges. Categorical data shall be presented as frequencies and percentages.

Patient Groups for Analysis

The study will be analysed on an Intention To Treat (ITT) basis retaining all patients irrespective of any protocol violations. Secondary analysis will be performed removing any major protocol deviations which are deemed to have an impact on the primary outcome.

Significance Levels/Success Criteria

The primary outcome of 3 month implant loss rate shall be assumed to follow a binomial distribution and shall be presented as the estimated percentage alongside a one-sided 90% confidence interval. Formal assessment of the primary outcome will be assessed based on the exact number of events as laid out in the sample size section. If the number of implant losses is exceptionally rare then exact confidence intervals shall be used.

Further within-study comparisons

Comparisons of the primary endpoint as well other categorical implants shall be compared across clinical/demographic subgroups using Chi-Square/Fishers test as appropriate. PROMS measures will be compared across clinical/demographic studies using Wilcox/t-tests as appropriate.

Comparisons against iBRA patients

Outcomes from this study will be compared against the iBRA study by matching patients based on clinical/demographics factors. Comparisons of implant loss rate will be carried out using conditional logistic regression. If events are sparse then propensity score methods will be applied to match patients and exact method used to compare outcomes between studies.

12.5 Interim Analyses

After recruitment of 46 patients there will be an interim analysis to confirm the safety of the product. If the rate of implant loss is considered acceptable (less than 5 implant losses) the trial will continue to recruit a total of 79 patients. The interim analysis will also allow a pause for group learning and transparent reporting of technique modifications. Root cause analysis will be conducted for every implant loss prior to proceeding to the next phase.

12.6 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any analysis of the treatment arms. As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

13 DATA MANAGEMENT AND TRIAL MONITORING

For the MAP-BRA Project 1 study the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

13.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical study.

The eCRF will be considered the source document where no prior record exists and which is recorded directly into the bespoke eCRF.

Each participating site should maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating site should identify any data to be recorded directly on the CRFs (i.e. no prior electronic or written record of the data), and to be considered to be source data.

13.2 Data Collection Methods

The study electronic case report form (eCRF) is the primary data collection instrument for the study. These will be made available electronically via the REDCap database. Data are to be entered into the REDCap database by members of the research team at site. Paper worksheets will be available for download from the portal to aid data collection.

All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

13.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted inaccordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

13.3.1 **Central Monitoring**

There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per CTU processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to the CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

13.3.2 **Clinical Site Monitoring**

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

13.4 **Risk Assessment**

A structured risk assessment will be carried out in accordance with the LCTC standard operating procedure to determine the overall risk of the study, the required mitigations and monitoring strategy.

13.5 **Confidentiality**

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

eCRFs will be labelled with a unique REDCap ID. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed Informed Consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the Patient Information Sheet.

N.B. Consent forms must be transferred separately to any other study documentation to ensure the pseudonymisaiton of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of the University of Liverpool will preserve the confidentiality of participants taking part in the study. The Liverpool University Hospitals NHS Foundation Trust is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the study Sponsor and the Liverpool University of Liverpool Data Protection Officer and appropriate processes followed.

13.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The MAP-BRA Project 1 study team at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the study specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The study will be conducted in accordance with procedures identified in the protocol.
- Independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, registration and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

13.7 Records Retention/Archiving

Study archiving will be divided in two sections the sponsor/CTC documentation and data and the research site documentation and data.

Sponsor/LCTC

The paper elements of the Trial Master File (TMF) will be archived by the University of Liverpool.

The study data in the REDCAP database will contain all the case report form data from the study participants.

The TMF (paper and data) as described above will be stored for **15 years**. Reference to location and arrangement for the site documentation (see below) storage will be included in the sponsor/CTC archive records to allow full reconstruction.

Research Sites

The per patient source data and the research sites Investigator Site Files (ISF) will be archived by the individual research sites in accordance with their local policies as outlined in the research site agreement Schedule 2 point 8 of the Research Site Agreement. On study closure the site MUST inform the sponsor of the location of this archive and the name of the assigned archivist for their records.

14 REGULATORY AND ETHICAL CONSIDERATIONS

14.1 Statement of Compliance

The trial involves the use of a CE marked medical device which is utilised for the intended purpose therefore this trial is not within the remit of the Medical Devices Regulation.

14.2 Ethical Considerations

The use of mesh in sub-pectoral implant based breast reconstruction is well established and is the most commonly performed immediate breast reconstruction technique in the UK[1]. Patients who have been offered a mesh assisted implant based breast reconstruction would be considered eligible to participate in this study. This includes patients who are planned to have sub-pectoral (implant under the muscle) or pre-pectoral (implant on top of the muscle) techniques.

Fortiva mesh is CE marked and has been used in ventral hernia repair and in breast reconstruction however there has been no data collected regarding this. The product is similar in composition and processing to other porcine mesh products. There is a risk that this mesh will lead to a higher rate of complications including seroma formation, infection, wound problems and implant loss. Participants will have this risk clearly explained and it will be documented in the patient information leaflet and consent form. Patients and service users will be involved in the design of these documents. Patients who do not wish to take part in the trial will be offered implant based breast reconstruction with the mesh selected by their surgeon.

Fortiva mesh is a porcine product derived from pig skin. Patients need to be aware of that this is an animal product and this may not be acceptable for cultural or religious reasons. This is part of the standard discussion and consent in patients undergoing breast reconstruction with a biological mesh.

Patients who have been have chosen to enter the study and have pre-pectoral reconstruction with Fortiva need to be aware that this is a new and evolving technique with limited data on safety and efficacy regardless of the mesh used. Early limited data supports successful outcomes in expert hands. Only surgeons with experience of performing prepectoral reconstruction would be considered suitable to recruit to the prepectoral reconstruction with Fortiva. Patients who did not want to enter the study would be offered prepectoral reconstruction with the mesh selected by their surgeon.

Patients will be approached regarding study participation at the time when breast reconstruction is discussed with them. Many patients will have a new cancer diagnosis at this time. As per standard unit practice and NICE guidelines, patients will be offered all appropriate forms of breast reconstruction (implant based, pedicled and free-flap), dependant on co-morbidities and treatment factors. If patients are considered suitable for mesh assisted implant-based reconstruction and fulfil the entry criteria to the study, the study will introduced at the time of the discussion and the PIS given in addition to the unit's standard breast reconstruction information. Potential participants will then be given time to consider their options as per individual unit practice. This may include a meeting with a specialist nurse to receive more information and see photographs or a further meeting with the surgeon.

If the patient elects to undergo implant-based breast reconstruction using Fortiva mesh, they will be asked to sign a consent form prior to entering the study. Patients will be made aware that they are able to change their mind about the procedure at any time up until the surgery.

Following surgery, patients will be seen for clinical review at 1 week, 2 weeks. No additional visits will be required. Data at 3 and 18 months data be collected from medical records.

14.3 Approvals

The trial protocol and patient documents has received the favourable opinion of the North West Liverpool Central Research Ethics Committee (REC) but all participating sites must undergo site specific assessment of capacity and capability. A copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to LCTC before patients are entered. The LCTC should receive a confirmation of capacity and capability for each new centre via the site's R&D department.

14.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and REC requirements are handled based on their nature and severity.

Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committee (TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to REC.

Breaches confirmed as 'serious' will be reported to REC within 7 days by the LCTC, on behalf of the Sponsor and notified to the TMG and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

15 **INDEMNITY**

In the event of a patient being harmed by taking part in this research project, there are no special compensation arrangements. If this is due to someone's negligence, patients may have grounds for legal action for compensation against the NHS Trust where the patient was treated. The normal National Health Service complaints procedures is available to patients.

In the event of a defective product patients may have grounds for legal action for compensation against the manufacturer, but they may have to pay for their legal costs.

16 PUBLICATION AND DISSEMINATION

16.1 Study Publications

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

16.1.1 **Authorship**

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the MAP-BRA Project 1 study Consortium which will also be named at the manuscript head.

16.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to REC. The results of MAP-BRA Project 1 will be published regardless of the magnitude or direction of effect.

17 CHRONOLOGY OF PROTOCOL AMENDMENTS

17.1 Substantial Amendment 02 – Version 4.0 (01/03/2021)

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
N/A	**N/A**	Protocol moved onto new Protocol Template
N/A	**General Information**	"The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system." Added
N/A	**Contact Details: Individuals**	Email addresses updated
4	**Roles & Responsibilities**	Section added
8	**Trial Interventions**	Section added
9.2	**Informed Consent**	"Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in CTU coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason." Added
9.3	**Eligibility Assessment & Confirmation**	Section added
9.4	**Registration**	Registration section amended to reflect change in process – site staff will now register patients using REDCap database rather than this being carried out centrally at the LCTC. A post-registration check will be performed by the LCTC trial team.
11	**Safety Reporting**	Previously the protocol stated that only device incidents would be reported. This has been amended to reflect that RUSAEs will be reported to REC and so related SAEs must be reported by sites to the LCTC, and appropriate sub sections added relating to safety

		reporting. Yellow card reporting will be the responsibility of the sites.
11.5	**Interim Analysis**	Section added
12.6	**Analysis Plan**	Section added
13.7	**Records Retention/ Archiving**	Archiving period updated from 25 years to 15 years in line with study contract

17.2 Substantial Amendment 01 - Version 3.0 (21/MAR/2020)

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Page 1	**N/A (p1)**	ISRCTN number updated to 16902075 as this previously was unknkown.
Page 1	**N/A (p1)**	University of Liverpool was previously listed as Sponsor due to an administrative error but the Sponsor is now listed correctly as The Liverpool University Hospitals NHS Foundation Trust.
2, 3, 5 & 6	**N/A – Sponsor details are listed before the protocol sections begin**	Protocol updated to reflect the change in trust name (see above for reason).
Pages 1, 2, 3, 7, 10, 17, 18, 22, 23, 31, 33, 34, 35 & 38	**Please review page numbers for sections**	All references of LCTU have been updated to LCTC to reflect the new name since the University of Liverpool Clinical Trials Units have merged to form the LCTC.
Page 2	**Study Protocol Approval**	Job title of Sponsor Representative has been added in Study Protocol Approval signature box.
N/A (p5 & p6)	**Contact Details**	Trial contact details updated.

17.3 Version 2.0 (10/JUL/2019)

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**

N/A as this refers to the entire document		Minor grammatical changes to the wording of the protocol were made throughout the document.
Page 2	**Study Protocol Approval**	Address update for LCTC representatitives approving the protocol.
3.1	**Centre/Clinician Inclusion Criteria**	Additional inclusion criteria *'Approval to purchase the FORTIVA MESH through the sites local procurement processes for devices'* added.
6	**Patient Enrolment**	Section 6.1 - Updated to state that the patient will undergo an informed consent discussion if they are eligible for the study and then be registered. - Timeframes of screening assessments removed as no time restricted tests are completed prior to registration. Section 6.2 (previously detailed as section 8.2 in v1 of the protocol but this section was deleted) - Updated to inform of the process of informed consent from the PIs/Co-Investigators. Section 6.3 - Instructions to site on how to upload the ICF to the portal added.
8	**Device Incident Reporting**	Section added to detail the process sites should follow if a patient experiences any events relating to fortiva mesh malfunctions and/or inadequecies while on the study.
10	**Trial Monitoring**	Section 10.4 - A statement was adding confirming that the LCTU will provide a final copy of all CRF after the data lock to each centre for archiving with their ISF Section 10.7 - Updated to provide the process for sponsor/CTU to follow for records retention/archiving and the process for research sites.

17.4 **Version 1.0 (dd/mon/yyyy)**

Original Approved version

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19 **DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL**

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to Ethical review are submitted as separate version controlled documents.