Perf-Act Brecon

Perf-Act BreCon: A Prospective Case-control Study to Compare Tissue Perfusion between RetrActors and Non-retractors during Immediate Breast ReConstruction

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Perf-Act Brecon Clinical Study Protocol

Study title:	Perf-Act BreCon: A Prospective Case-control Study to Compare Tissue Perfusion between RetrActors and Non-retractors during Immediate Breast ReConstruction
Protocol version:	Version 1.1

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Addenbrooke's Charitable Trust

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1 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	18/Dec/2023	Amit Agrawal, Perf-Act BreCon Study Co-ordinator & Nikos Demiris	Sections 5, 6, 10.2 and 12.2.2 revised to change the pain score collection for each breast to 18hr post-surgery and at Follow-ups week 1, week 2 and week 4-6. Section 5 updated to include an Overall Purpose of this study. Section 7 updated to include more information, explaining the relationship between the current study and the development of the new tool. Section 12.2.1 updated to provide further clarification on the surgical procedure and clarified the beginning of the surgery as the pre incision on table and the end of mastectomy as post mastectomy before wound closure. Section 15 updated with further clarification on the data capture system. Section 17.1 updated to include the direction of the one-sided t-test. Administrative clarification: previous version of the protocol there was a typo on the footer, it was given version 1.1, dated 11/Oct/2023 when it was intended to be version 1.0, dated 11/Oct/2023. This version 1.1, dated 18/Dec/2023 is considered the updated version of the protocol.

2 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
..../...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):
.....

3 STUDY MANAGEMENT GROUP

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LIST OF CONTENTS

4 LIST OF ABBREVIATIONS

AE/AR	Adverse event/Adverse Reaction
ACT	Addenbrooke's Charitable Trust
BREAST-Q	Patient Reported Outcome Measure designed to evaluate outcomes among women undergoing different types of breast surgery
CCTU-CT	Cambridge Clinical Trials Unit – Cancer Theme
CI	Chief Investigator
CTCAE	Common Terminology Criteria for Adverse Events
(e)CRF	(Electronic) Case Report Form
DIEP	Deep Inferior Epigastric Perforator
EU	European Union
GP	General Practitioner
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HES	Hospital Episode Statistics
Hr(s)	Hour(s)
HRA	Health Research Authority
ICF	Informed Consent Form
ICG	Indocyanine Green
ID	Identification
ISF	Investigator Site File
LD	Latissimus Dorsi

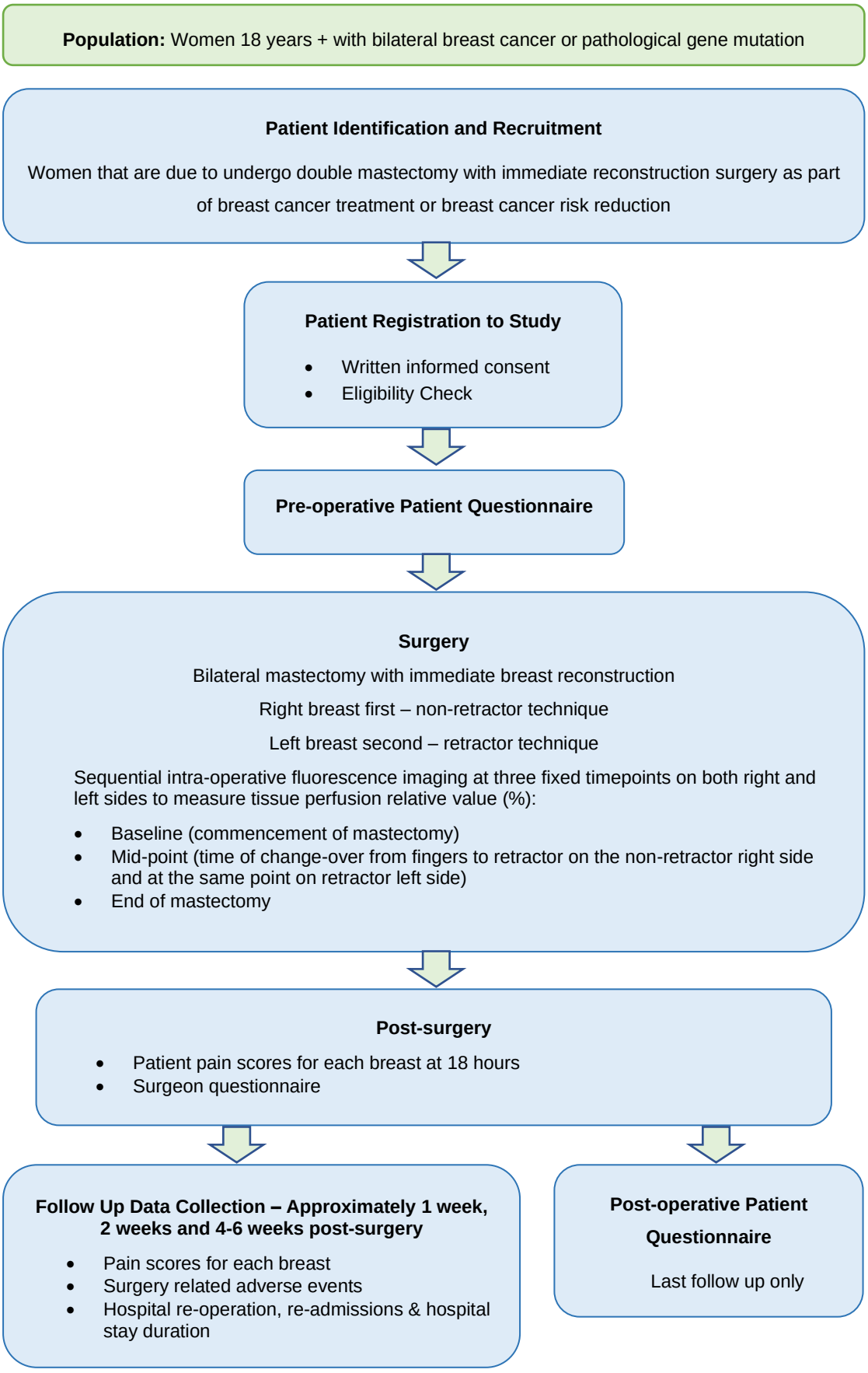
MDT	Multi-Disciplinary Team
NCI	National Cancer Institute
NHS	National Health Service
NIHR	National Institute for Health and Care Research
PI	Principal Investigator
PIS	Participant Information Sheet
PROMS	Patient Reported Outcome Measures
R&D	Research and Development
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SoC	Standard of Care
SOPs	Standard Operating Procedures
SMG	Study Management Group
SPY-PHI	SPY Portable Handheld Imaging
SPY-QP	Intraoperative and surgeon-controlled fluorescence assessment software designed to allow surgeons to objectively assess the intensity of the fluorescence signal through Relative Values (%)
TMF	Trial Master File
TMG	Trial Management Group
UK	United Kingdom
ULN	Upper Normal Limit

5 SYNOPSIS

Study Title	**PerfAct BreCon** Study: A prospective case-control study to Compare Tissue **Perf**usion between Retr**Act**ors and non-retractors during Immediate **Bre**ast Re**Con**struction
Internal ref. no.	A096761
Study Design	Prospective case-control study
Study Participants	Women 18 years of age and over undergoing bilateral mastectomy with immediate reconstruction.
Planned Sample Size (if applicable)	A total of 30 evaluable participants
Follow-up duration (if applicable)	Up to 42 days
Planned Study Period	12-15 months
Overall Purpose of this study	To collect clinical evidence to demonstrate the difference in trauma caused to the breast tissues due to current surgical practices.
Primary Objective	To determine if there is a difference in blood perfusion (Relative Value %) in the breast where the non-retractor technique is used during surgery versus the breast where the retractor technique is used, in the same patient.
Secondary Objectives	To assess whether there are differences in the post-surgical complications, post-surgical recovery and post-surgical pain scores associated with the breast where the non-retractor technique is used during surgery, versus the breast where the retractor technique is used; in the same patient.
Exploratory Objectives	1. To evaluate the surgeons experience of each different operative technique, retractors and non-retractors. 2. To assess the differences in overall operative times between the breast where the non-retractor technique is used during surgery, versus the breast where the retractor technique is used.
Primary endpoint	The relative difference (%) in blood perfusion between each breast in the same patient. Blood perfusion will be measured at 3 time-points (T1: baseline, T2: mid-point, T3: end) during the mastectomy procedure. The relative difference is defined as the difference, D, of Blood perfusion at T2-T1. The t-test will be applied on the between-breast difference on D.

Secondary endpoints	To compare the following post-surgical outcomes, as associated with the breast where the retractor technique is used during surgery, versus the breast where the non-retractor technique is used, within the first 30 days post-surgery: o Patient hospital re-admission, where applicable o Patient hospital stay duration, where applicable o Patient re-operation required, where applicable o Patient reported post-surgery pain scores assessed at the following time points: 18hr, follow-up week 1, week 2 and week 4-6 o Incidence, type and severity of surgery related adverse events, where applicable Comparison of patients pre- and post-surgery outcomes, as measured by Modules 7, 8, 9 and 14 of the BREAST-Q Recon version 2.0 questionnaire.
Exploratory endpoints	1. Comparison of surgeons self-reported scores of the following between retractor and non-retractor technique: o Operative comfort o Operative difficulty/complexity o Operative visibility o Safety of technique o Physical demand of technique 2. Comparison of: o Overall operative time in breast where the non-retractor technique is used, versus the breast where the retractor technique is used, in the same patient. o Proportion of time before the retractor is used in the breast where non-retractor technique is employed.

6 STUDY FLOWCHART



7 BACKGROUND AND RATIONALE

In the UK, 55,000 cases of breast cancer are diagnosed every year. It will remain the commonest cancer in women until 2035 (1). Worldwide, two million new breast cancers were diagnosed in 2018 (2). Surgery remains the mainstay of breast cancer treatment, and any surgery associated adverse outcome affects a sizeable population.

Post-operative complications can delay chemo or radiotherapy (3) and potentially contribute to systemic cancer recurrence (4). This can also negatively impact patients psycho social status, besides adding to the existing burden on both primary (5) and secondary care resources such as staffing and beds (6).

In the UK, 35-40% (7) of breast cancer patients undergo mastectomy (~20,000), 40% of which (~8,000) undergo immediate breast reconstruction (3, 8). An NIHR-funded UK national audit (9) revealed that complication rates associated with mastectomy and immediate reconstructions remain high; with infection being the leading cause of patient re-admissions, potential re-operation and loss of the implant (25% infection, 18% re-admission, 18% re-operation, 9% implant loss rates respectively). In line with National Quality Standards, if just infection were to reduce from 25% of 8,000 reconstructions (n-2000) to below 10% (n-800), 1200 NHS patients annually would benefit from a reduction in this one complication.

Extrapolation of UK statistics (8, 9) to global data will need to be conservative since global reconstruction rates are likely lower than in the UK.
The vital component of mastectomy and immediate breast reconstruction is the viability of the preserved skin envelope (with a healthy blood supply) once the underlying breast tissue is excised (10, 11). Any trauma and compromise of skin vascularity can lead to complications such as infection, skin necrosis and reconstruction failure.

To reduce complications, different interventional methods in mastectomy and immediate breast reconstruction have been tried to prevent post-surgery infections, but none have been widely adopted. Attempted solutions have included the use of Nitro-glycerine (vasodilator) ointment that improves the vascularity to some extent but was not adopted in practice due to systemic side effects (12). A RCT compared the complication rates between standard electrocautery and high-frequency radiosurgery where the study found that both methods had equal complication rates of 23% (13). Another NIHR-funded RCT of patients (n=141) at higher risk of complications such as diabetes and smoking, showed 26% skin necrosis in heat preconditioned (pre-operative skin warming to increase skin blood flow) breast tissue, with 11% of the patients requiring surgical intervention. Conversely, the control group revealed 35% skin necrosis, with 17% needing reoperation (14). One technique that could help

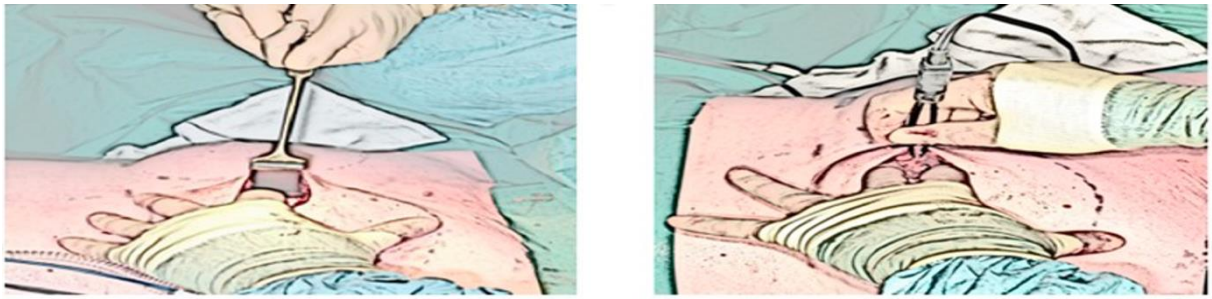
decrease post-surgery infection and potentially reduce patient re-admission and re-operation is using a gentle technique to lift the tissue.

Using a gentle technique to lift the soft tissue could decrease post-surgery infection and reduce patient re-admission and re-operation. To enable a clear view of the operative field during surgery, surgical tools called retractors are used to forcefully lift tissue to allow access for the surgeon. The forceful lift can contribute to tissue injury and consequent complications. Eighty per cent of breast surgeons believed that retractors were the leading cause of injury to breast skin during immediate reconstruction (15).

There is thus ample scientific literature on the association of retractors (hard metal instruments) with trauma to the soft tissue that surgeons have discussed in various publications as referenced. However, since there are no solutions, surgeons spread fingers apart to minimise trauma to the tissues.

The surgeon's non-dominant hand is spread apart (like a 'V'), and the dominant hand is used to operate the instruments in between the fingers of the 'V' as an alternative to the assistant pulling firmly on the skin (Figure 1). However, fingers get tired soon and/or cannot reach the depth of the surgical dissection field and then they have to resort back to retractors.

Figure 1: Left side panel shows pull by Retractor, right side panel show Finger dissection



Surgeons currently employ both intra-operative dissection techniques; therefore, this is not a new intervention; yet, importantly, there is no such novel study design known in the literature.

Therefore, CI with a team of engineers has been working on a device that surgeons can wear that will spread surgeons passively (without fatigue and trauma to their fingers) and at the same time, the extenders will increase reach where fingers can’t. This will be an alternative to the retractors.

Whilst seeking funds for the development of the potential solution, it was suggested to gather some objective clinical evidence to demonstrate the difference in trauma caused to the tissues due to both of the existing surgical practices (retractors versus fingers-based).

This prospective case-control study represents an opportunity to compare tissue perfusion during breast mastectomy when using metal retractors versus fingers to lift the tissue. This study does not propose a new surgical technique or use a new instrument.

Differences in tissue perfusion between the two sides in the same patient (so there are no patient confounding factors) will help demonstrate the perceived problem objectively. The outcome of this study will establish the difference in trauma caused to the breast tissues due to current surgical practices, consequently, help improve intra-operative dissection techniques and reduce post-surgery infection and in addition, help to build an evidence-based case for the possible innovation of a new device to aid surgeons during this type of surgery.

In immediate breast reconstruction, the skin envelope with or without nipple must be preserved/spared (skin/nipple sparing mastectomy) after the removal of underlying breast tissue. However, mastectomy removes the dominant blood supply through the breast tissue, so the spared skin needs to survive on smaller blood vessels (capillary network) travelling along the skin's surface.

Tissue perfusion is the blood flow and oxygen supply to tissues, including the skin. Even brief periods of compromised perfusion to the tissue can lead to irreversible harm and complications. Currently tissue flap perfusion for mastectomies (simple, skin and nipple sparing), localised perforator flaps and larger pedicled (LD flap) or anastomotic (DIEP) flaps are assessed by reviewing capillary refill, warmth, and serial patient reviews. There are no additional methods for actual real-time visualisation of the tissue's vasculature.

This study will use Stryker’s SPY-PHI handheld imager device to measure tissue perfusion. This device allows the surgical team to measure tissue perfusion in real-time during surgery. Following the intravenous injection of a licensed fluorescent Indocyanine Green (ICG) dye, the Stryker SPY-PHI device detects the circulating fluorescent dye. The equipment and dye are widely used in surgery already. Stryker’s SPY-PHI has a SPY-QP mode assessment software that detects percentage perfusion allowing for quantifiable and objective comparison between the breasts as per the SPY-PHI technology brochure.

A study by Harless et al. (16) and per the SPY-PHI technology brochure, this device enables the surgeon to objectively evaluate tissue perfusion of mastectomy flaps and make real-time adjustments to breast reconstruction.

8 STUDY DESIGN AND METHODS

8.1 Statement of Design

Patients (n=30) undergoing bilateral mastectomy with immediate breast construction (n=60 breasts) will be invited to take part in this prospective case-control, multi-centre study.

Consenting patients will complete a pre-operative questionnaire and then undergo surgery. In the same patient during the same operative episode, sequential tissue perfusion measurements will be taken as follows:

- **First, in the right breast – use the finger dissection non-retractor technique for as long as possible before reverting to metal retractors**
- **Secondly, in the left breast – using retractors only throughout the entire procedure**

The sequential measurements taken in each breast will allow for the comparison of tissue perfusion between the two different skin lift techniques.

Patients will be blinded to the technique used in each breast.

Following surgery, patients will be followed in order to observe the patient's 30-day post-operative recovery period.

8.2 Number of Centres

This trial will be conducted at Cambridge University Hospitals NHS Foundation Trust.

8.3 Number of Subjects

A total of 30 evaluable patients are required.

Evaluable patients are those with all three tissue perfusion measurements collected by the surgeon at each of the three time points on both breasts during surgery.

8.4 Patient Study Duration

The study duration consists of up to 28 days eligibility requirement check period for patients, and if eligible, they will be registered. Registered patients will undergo surgery. The time between registration and surgery will vary between patients, and surgery will be scheduled in accordance with local procedures. Patients will be followed up post-surgery to observe their 30-day post-operative recovery period. As the study will follow the patient's standard of care visit schedule and the timing of these post-operative visits may differ between patients, it is expected that patients may be on study for up to 42 days post-surgery in order to capture

clinical information for the 30-day post-surgery period. Study completion will be defined as when the last patient registered has completed their last post-operative visit.

9 STUDY OBJECTIVES

9.1 Primary Objective

To determine if there is a difference in blood perfusion (Relative Value %) in the breast where the non-retractor technique is used during surgery versus the breast where the retractor technique is used in the same patient.

9.2 Secondary Objectives

To assess whether there are differences in the post-surgical complications, post-surgical recovery and post-surgical pain levels associated with the breast where the non-retractor technique is used during surgery versus the breast where the retractor technique is used in the same patient.

9.3 Exploratory Objectives

1. To evaluate the surgeon's experience of each different operative technique, retractors, and non-retractors.
2. To assess the differences in overall operative times between the breast where the non-retractor technique is used during surgery, versus the breast where the retractor technique is used.

10 TRIAL ENDPOINTS

10.1 Primary Endpoint

The relative difference (%) in blood perfusion between each breast in the same patient. Blood perfusion will be measured at 3 time-points (T1: baseline, T2: mid-point, T3: end) during the mastectomy procedure. The relative difference is defined as the difference, D, of Blood perfusion at T2-T1. The t-test will be applied on the between-breast difference on D.

10.2 Secondary Endpoints

To compare the following post-surgical outcomes, as associated with the breast where the retractor technique is used during surgery versus the breast where the non-retractor technique is used, within the first 30 days post-surgery:

- Patient hospital re-admission, where applicable

- Patient hospital stay duration, where applicable
- Patient re-operation required, where applicable
- Patient-reported post-surgery pain scores assessed at the following time points: 18 hours, follow-up week 1, week 2 and week 4-6
- Incidence, type and severity of surgery-related adverse events, where applicable

Comparison of patient's pre- and post-surgery outcomes as measured by Modules 7, 8, 9 and 14 of the BREAST-Q Recon version 2.0 questionnaire.

10.3 Exploratory Endpoints

1. Comparison of surgeon's self-reported scores of the following between retractor and non-retractor techniques:
    - Operative comfort
    - Operative difficulty/complexity
    - Operative visibility
    - Safety of technique
    - Physical demand of technique
2. Comparison of:
    - Overall operative time in breast where the non-retractor technique is used, versus the breast where the retractor technique is used, in the same patient.
    - Proportion of time before the retractor is used in the breast where non-retractor technique is employed.

11 STUDY PARTICIPANTS SELECTION

11.1 Inclusion Criteria

To be included in the study, the patient must meet all the following criteria:

- Signed informed consent form
- Female aged 18 years old or above
- Bilateral breast cancer
- Needing bilateral mastectomy for breast cancer or for risk reduction (due to pathological gene mutation or high-risk family history or previous mantle radiotherapy for lymphoma)

- Undergoing bilateral mastectomy concurrently with immediate breast reconstruction
- Undergoing the same type of breast reconstruction on both sides
- Adequate liver function where bilirubin is ≤1.5 x ULN
- Adequate renal function with a serum creatinine ≤ 1.5 x ULN
- Willing and able to comply with scheduled visits and study procedures for the duration of the study.

11.2 Exclusion Criteria

The presence of any of the following will exclude patients:

- Unilateral breast cancer
- Undergoing unilateral mastectomy
- Not undergoing immediate breast reconstruction
- Locally advanced breast cancer with skin involvement
- Previous unilateral breast radiotherapy (if mastectomy is for local recurrence)
- Previous significant unilateral breast surgery (such as reduction) judged by the recruiting/operating surgeon to have adversely affected breast supply on that side
- Known allergies or hypersensitivity to indocyanine green (ICG) dye, sodium iodide or iodine or having experienced previous side-effects of ICG dye or its components
- Patients with an overactive thyroid or benign tumours of the thyroid gland
- Patients with severe renal insufficiency
- Women who are pregnant, plan to become pregnant, or are lactating during the study period.

11.3 Co-enrolment Guidance

Enrolment into other ethically approved clinical trial(s) or studies is allowed, where co-enrolment is permitted as part of the corresponding trial or study protocol provided there is no conflict of interest to PerfACT. It is the responsibility of the participating clinical trial/study Investigator to ensure oversight of co-enrolment throughout the PerfACT study. Questions regarding co-enrolment should be directed to a member of the PerfACT Study Management Group.

11.4 Patient Identification and Recruitment

Women that are due to undergo a double mastectomy with immediate reconstruction as part of breast cancer treatment will be identified during MDTs and will be approached and given a brief description of the clinical study by their treating clinician and asked if they would like to discuss the study further with a member of the research team. This will be recorded by the

treating clinician in the medical notes. Patients who are referred by the genetics or family history team to the breast unit for consideration of risk reduction mastectomy will be identified at the point of receipt of referral by the breast surgeon or the breast care nursing team within participating units and flagged up to the research team.

The process for trial recruitment in this study is as follows:

- The investigating breast team will identify potentially suitable breast cancer patients at the specialist Breast multidisciplinary team (MDT) meeting.
- Risk reduction patients will be identified by the Clinical Genetics Team and highlighted to the PI or another member of the research team.
- Patients will attend an initial outpatient appointment at the surgical Breast clinic.
- At this appointment, the patient will be seen jointly by a surgeon and a research team member.
- Standard treatment options will be explained to the patient first.
- If the clinical team feel that the patient is suitable for the trial, the trial option will also be explained to the patient.
- If the patient expresses an interest in participation, they will be given a copy of the patient information sheet (PIS) to take away and review.
- The study research team will phone the patient later (minimum 24 hours) to ascertain whether she wishes to participate.
- If the patient agrees to participate, written informed consent will be obtained before commencing study specific procedures.

11.5 Patient Informed Consent

The Patient Informed Consent Form will be approved by a Research Ethics Committee (REC) and must follow GCP, local regulatory requirements and legal requirements. The Investigator or designee must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with their participation.

The Investigator or designee will obtain written informed consent from each patient before any study-specific activity is performed. The Investigator will retain the original of each patient's signed informed consent form in the Investigator Site File (ISF).

As this is a low-risk, non-interventional study, patients may consent to take part on the same day as being offered the opportunity to participate. However, they must be given sufficient time

to read the PIS, consider taking part in the study and ask any questions before consenting. The Principal Investigator may delegate responsibility for consenting patients to appropriately trained healthcare professionals (including research nurses and practitioners) who may not be medical staff if this is accepted local practice. In order to limit risks to patients, including face-to-face contact or to negate additional hospital visits, consent can be obtained remotely. Several options will be considered acceptable:

- Verbal consent witnessed on speakerphone by two members of the research team. The consent form will be signed and dated by the two research team members and subsequently also signed by the patient at the next available opportunity.
- Consent form to be sent to the patient by mail or electronically, signed and dated by the patient and returned by mail or electronically, to be countersigned by a member of the research team.
- Email confirmation of consent sent from the patient's personal email address; the consent form will be signed and dated by a research team member and subsequently signed by the patient at the next available opportunity. The patient's email will be filed with a copy of the consent form.

In all remote consenting scenarios, the investigator is requested to document the rationale for remote consenting and the method planned/undertaken. In the case of remote consent, it is recognised that the date of the research team's signature may not always match that of the patient's signature.

Should a patient require written or a verbal translation of the trial documentation, it is the responsibility of the individual Investigator to use locally approved translators. Copies of translated documents must be provided to the central coordination team for filing in the Trial Master File (TMF).

Any new information that becomes available which might affect the patient's willingness to continue participating in the study will be communicated to the patient as soon as possible.

Study-specific procedures will only be performed after patients have consented to participation and signed the informed consent form.

11.6 Patient Eligibility Requirements

After patient informed consent has been obtained, the research team will confirm the eligibility of the patient by reviewing the following:

- Concomitant medications

- Medical history
- Review of most recent SoC pre-operative blood results as evidence of adequate liver and renal function
- Review of SoC pre-operative pregnancy test for women of childbearing potential

Within 28 days prior to registration, it must be verified that the patient satisfies all protocol eligibility criteria.

11.7 Patient Registration

Eligibility requirements documented in sections 11.1 and 11.2 must be met before registering a patient in this study. Only consenting patients who meet the eligibility requirements of the study at screening will be registered.

The following data will be required in order to enrol the patient:

- Confirmation that the patient satisfies all the eligibility criteria
- Year of birth
- Date of signed informed consent

Once it has been confirmed by the Investigator or suitably trained and delegated medically qualified member of the trial team that a patient meets the eligibility criteria, the investigator or designee must complete the registration electronic CRF in the REDCap™ database (see the eCRF completion guidelines for instructions).

A unique study ID will be assigned to the patient, and this should be used in all future correspondence and on all patient-related documents.

12 PROCEDURES AND ASSESSMENTS

Refer to Section 26.1: Appendix 1 for Schedule of Assessments.

Patients will be clinically assessed throughout the study as per local practice.

Clinical assessments may be done remotely by telephone or videoconferencing, as appropriate and as per local practice.

Surgery-related adverse events will be recorded at each clinic visit from the point of surgery until the end of the 30-day follow-up period.

12.1 Pre-Surgery

Those patients who meet all eligibility criteria as per sections 11.1 and 11.2 and have been registered into the study will be asked to complete the BREAST-Q Version 2.0© Reconstruction Pre-operative Scales questionnaire, modules 8 and 7, prior to their surgery visit.

12.2 Surgery Visit

Registered patients will undergo surgery in accordance with local NHS timelines.

12.2.1 Surgery Procedure

The mastectomy with immediate reconstruction will be undertaken as per usual local procedures. Consented patients will undergo surgery and have sequential intra-operative fluorescence imaging assessments on each breast, whereby a fluorescent Indocyanine Green (ICG) dye will be injected intravenously and then detected using the Stryker's SPY-PHI handheld imager device to provide tissue perfusion measurements. The ICG dye will be administered intravenously as a bolus injection at the recommended dose of 0.1-0.3mg/kg body weight as per the manufacturer's guidelines for tissue perfusion diagnostics detailed in the ICG dye SmPC.

Right breast (Non-Retractor Technique)

The operating surgeon will first conduct the mastectomy procedure in the right breast using the non-retractor (finger dissection) technique to lift the breast tissue.

At the beginning of the mastectomy procedure, (defined as pre-incision on table and referred to as time TR1), and once confirmed that the fluorescent imager is ready to use, working and in hand, the surgeon will request that the ICG dye injection be administered to the patient. Once the dye is visualised, two tissue perfusion relative values (%) and the time in HH: MM (24hr format) will be taken and recorded. The first value will be the worst tissue perfusion relative value (%) observed in the 10x10cm area surrounding the incision, and the second value will be the best tissue perfusion relative value (%) observed anywhere in the breast.

The surgeon will then commence the mastectomy procedure and continue with the non-retractor (finger dissection) technique for as long as is comfortably possible and until finger fatigue prevents using this technique any longer. At this time point (referred to as TR2), the process of the ICG dye injection and two tissue perfusion measurements will be repeated as described for TR1.

After time point TR2 the surgeon will complete the mastectomy procedure using retractors to lift the breast tissue and the final ICG dye injection and two tissue perfusion measurements

will be completed at the end of the mastectomy procedure (defined as post-mastectomy before wound closure and referred to as time TR3).

In summary, the surgeon will request that the ICG dye be administered to the patient, after confirming the fluorescent imager is ready to use, working and in hand at the following three time points:

- **TR1**- beginning of mastectomy procedure, defined as pre-incision on table
- **TR2**- when the surgeon switches from finger dissection technique to metal retractors
- **TR3**- end of mastectomy, defined as post-mastectomy before wound closure

At each time point (TR1, TR2 & TR3), two tissue perfusion relative values (%) and the time in HH: MM (24hr format) will be taken and recorded. The first value will be the worst tissue perfusion relative value (%) observed in the 10x10cm area surrounding the incision, and the second value will be the best tissue perfusion relative value (%) observed anywhere in the breast.

Left Breast (Retractor Technique)

The operating surgeon will then conduct the mastectomy procedure in the left breast using metal retractors **only** from the beginning until the end of the procedure.

The surgeon will request that the ICG dye be administered to the patient, after confirming the fluorescent imager is ready to use, working and in hand at the following three time points:

- **TL1**- beginning of mastectomy procedure, defined as pre-incision on table
- **TL2**- at the same time point that the surgeon switched from using fingers to metal retractors in the right breast (Time in mins = Right breast TR2 –Right breastTR1)

For example: If surgeon switched from the non-surgical (finger dissection) technique to retractors after 30 minutes in the right breast, then the tissue perfusion measurements in the left breast at time point TL2 will be taken 30 minutes after the beginning of the mastectomy procedure TL1 in the left breast.

- **TL3**- end of mastectomy, defined as post-mastectomy before wound closure

At each time point (TL1, TL2 & TL3), two tissue perfusion relative values (%) and the time in HH: MM (24hr format) will be taken and recorded. The first value will be the worst tissue perfusion relative value (%) observed in the 10x10cm area surrounding the incision. The second value will be the best tissue perfusion relative value (%) observed anywhere in the breast.

12.2.2 Post-Surgery

Following the conclusion of the surgery procedure, the surgeon will complete a short paper questionnaire for each breast surgery technique, refer to section 26.2, appendix 2: Surgeon Questionnaire.

The study team will record the patient-reported pain scores in both breasts at 18 hours (+/- 2 hours) post-surgery.

Patient will be asked to complete Modules 7, 9 and 14 of the BREAST-Q Version 2.0© Reconstruction questionnaire at their last follow up visit.

12.3 Adverse Event Monitoring and Management

Patients experiencing adverse events while in the study will be managed according to local guidelines. Any adverse reactions to the fluorescent Indocyanine Green (ICG) dye will be reported according to local procedures.

This study is a non-interventional study. No routine adverse event reporting will be undertaken as part of this protocol.

12.3.1 Surgery-related Adverse Events

All adverse events considered by the Investigator to be surgery related will be recorded in the eCRF and classified using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5 criteria for preferred term and severity grading.

13 COLLECTION OF CLINICAL DATA

No additional clinic visits or consultations are required for this study. Cancer patients will be followed up during their routine clinic visits/consultations, with study data collection time points approximating 1 week, 2 weeks, and 4-6 weeks post-surgery. Additional clinic assessments may be required per local practice, but study data collection will only occur at the approximate aforementioned time points.

The following clinical information will be collected at approximately week 1, week 2 and week 4-6 post-surgery:

- Re-admissions, where applicable (30-day Hospital re-admission rates, in line with HES)
- Patient hospital stay duration, where applicable
- Patient re-operation required, where applicable
- Patient-reported post-surgery pain scores for each breast

- Surgery-related adverse events, where applicable

14 PATIENT WITHDRAWAL

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioural, or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document relevant patient outcomes. The Investigator will enquire about the reason for withdrawal. If the patient explicitly states they no longer wish to contribute further data to the trial, the Investigator should inform the co-ordinating centre in writing and the withdrawal of consent should be documented in the patient's medical records and in the electronic Case Report Form (eCRF). However, data collected up to the time of consent withdrawal will be included in the data reported for the trial unless the individual explicitly requests that these not be used or deleted.

In the event of a discontinuation or withdrawal of consent, if needed the research team may look to find a suitable replacement patient to ensure the study meets the planned sample size.

15 FORMS AND PROCEDURES FOR COLLECTING DATA

All data collected during the study, including patient and surgeon questionnaire responses, will be transferred into an eCRF by participating sites. This study will use the password protected, web based REDCap™ electronic data capture system and is being designed, built and administered by the CCTU-CT. The data will be held on servers managed by CUH NHS Foundation Trust's IT service partner. Data on the eCRF will be linked to the patient's data using their trial identifier and date of birth. All trial data in the eCRF must be extracted from and be consistent with the relevant source documents. The eCRFs will be completed and held in a secure electronic data capture system. It remains the investigator's responsibility for the timing, completeness and accuracy of the eCRF. The eCRF will be accessible to trial coordinators, data managers, investigators, Clinical Trial Monitors, Auditors and Inspectors as required. Paper CRFs will only be used in the unlikely event of the data capture system failure, as a backup. For further information, please refer to the Case Report Form Guidelines document.

The investigators must ensure that the eCRFs and other study-related documentation sent to the study co-ordination centre contain no patient-identifiable data.

15.1 Source Data

To enable monitoring, audit and/or inspection, the investigator must agree to keep the records of all patients (sufficient information to link records, e.g., eCRFs, hospital records), all original signed informed consent forms and original completed questionnaires.

Source data include, but are not limited to:

- Patient Medical Records
- Online Medical Records (e.g. medical records, results/reports from clinical investigations such as blood tests)
- Signed and dated informed consent forms
- Completed BREAST-Q and surgeon questionnaires

16 DATA PROTECTION AND PATIENT CONFIDENTIALITY

All investigators and trial site staff involved in this trial must comply with the requirements of the EU General Data Protection Regulations (GDPR) and the Data Protection Act 2018 and Trust Policy with regard to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

In particular, the Investigator and site staff must ensure that no patient-identifiable information (including name, address, and hospital number) is transmitted to the Study Team or Sponsor. Every patient will be allocated a unique Study ID that will link all of the clinical information held about them on the trial database. It will also be used in all correspondence with participating clinical trial sites. At no point in presentations or publications of trial data will individual patients be identified.

The Investigator will be provided with an Investigator Site File prior to opening to recruitment. This file contains all essential documentation pertaining to the study and must be kept up to date during the course of the study.

All essential sources and study documentation must be securely archived after the Sponsor has confirmed in writing that the study has ended. Archiving should be for a period of at least 5 years, or the length of time specified by current, applicable legislation, whichever is longer.

The Investigator must not destroy any documents or records associated with the study without written approval from the Sponsor.

17 STATISTICS

17.1 The Number of Participants

A likely hypothesis relates to the possibly worse performance of the retractors. Hence, we will use a t-test in order to test the null hypothesis of no difference in perfusion between the two breasts (retractor and non-retractor sides) against the alternative of a 10% difference. With power=80%, a one-sided significance level of 10% and assuming an SD of 25%, the required sample size is n=30 evaluable patients.

17.2 Analysis of Endpoints

- *Primary Outcome* – The relative difference (%) in blood perfusion between each breast in the same patient. Blood perfusion will be measured at 3 time-points (T1: baseline, T2: mid-point, T3: end). The relative difference is defined as the difference, D, of Blood perfusion at T2-T1. The t-test will be applied on the between-breast difference on D.

- Secondary Outcomes -

To compare the following post-surgical outcomes, as associated with the breast where the retractor technique is used during surgery, versus the breast where the non-retractor technique is used, within the first 30 days post-surgery:

- Patient hospital re-admission, where applicable
- Patient hospital stay duration, where applicable
- Patient re-operation required, where applicable
- Patient-reported post-surgery pain scores assessed at the following time points: 18hrs, follow-up week 1, week 2 and week 4-6
- Incidence, type and severity of surgery related adverse events, where applicable

Comparison of patients' pre- and post-surgery outcomes as measured by Modules 7, 8, 9 and 14 of the BREAST-Q Recon version 2.0 questionnaire.

- Exploratory Outcomes -

1. Comparison of surgeons self-reported scores of the following between retractor and non-retractor technique:
   - Operative comfort
   - Operative difficulty/complexity
   - Operative visibility
   - Safety of technique
   - Physical demand of technique

2. Comparison of:

- Overall operative time in breast where the non-retractor technique is used, versus the breast where the retractor technique is used, in the same patient.
- Proportion of time before the retractor is used in the breast where non-retractor technique is employed.

The primary endpoint will be measured through sequential intra-operative fluorescence imaging assessments on each breast during the surgery, whereby a fluorescent Indocyanine Green (ICG) dye will be injected intravenously into the patient at three different time points: at the beginning of the surgery, halfway through the surgery, and at the end of the mastectomy procedure. The dye will be detected using the handheld Stryker's SPY-PHI imager device to provide tissue perfusion measurements.

18 DEFINITION OF THE END OF THE STUDY

The end of the study will be declared 6 months after the last patient's last visit, which will allow sufficient time for the data to be cleaned for primary analyses and reports.

19 OVERSIGHT COMMITTEE

The Study Management Group will meet monthly to review the progress of this study.

20 ETHICAL AND REGULATORY COMPLIANCE

20.1 Ethical Committee Review

Before the start of the study or implementation of any amendment we will obtain approval of the study protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

20.2 Regulatory Compliance

The protocol and study conduct will comply with all national regulatory research requirements. It is the Chief Investigator's responsibility to produce any annual reports as required.

20.3 Protocol Amendments

Protocol amendments will be reviewed, and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA and REC.

20.4 Declaration of Helsinki and Good Clinical Practice

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

20.5 GCP Training

All research staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with local Trust's policy.

21 SPONSORSHIP, FINANCIAL AND INSURANCE

The study is sponsored by Cambridge University Hospitals NHS Foundation Trust and funded by Addenbrookes Charitable Trust and Innovate UK.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical study caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the study, but no-one has acted negligently.

22 MONITORING, AUDIT & INSPECTION

Should a monitoring visit or audit be requested, the investigator must make the study documentation, source data and related records available to the Sponsor's representative. All patient data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the study. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the study. Throughout the course of the study, the risk assessment will be reviewed, and the monitoring frequency adjusted as necessary.

23 PROTOCOL COMPLIANCE AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action.

24 PUBLICATIONS POLICY

Ownership of the data arising from this study resides with the study management group (SMG). On completion of the study, the data will be analysed and tabulated, and a Final Report prepared.

The main study results may be presented at national and international conferences and published in a peer-reviewed journal, on behalf of all collaborators. All presentations and publications relating to the study must be authorised by the SMG.

The manuscript will be prepared by a writing group appointed from amongst the SMG and high-accruing investigators. The CCTU-CT, ACT and Innovate UK and all Investigators will be acknowledged in publications and presentations. Senior authorship shall be shared between members of the SMG according to their leadership role in the trial. Priority will be given to the lead scientific and clinical teams co-ordinating the trial.

In addition, participants who have consented to receive updates on study progress and results, will be provided with appropriate updates and a summary of the results in lay terms.

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26 APPENDICES

26.1 Appendix 1: Schedule of Assessments

	Eligible to Register	Pre surgery	Surgery			Post surgery		Follow-Up Approx. Week 1, Week 2 & Week 4-6
			T1	T2	T3	1hr	18hrs (+/- 2hr)	
Informed consent	x							
Eligibility criteria assessment[1]	x							
BREAST-Q Version 2.0© Reconstruction Module questionnaire		x						x[2]
Demographics	x							
Worst Tissue perfusion relative value (%) in specified area for each breast			x	x	x			
Highest Tissue perfusion relative value (%) anywhere in the breast for each breast			x	x	x			
Surgeon questionnaire						x		
Patient reported pain scores (for each breast)							x	x
Surgery related adverse events								x
Patient re-admission, if applicable								x

Patient hospital stay duration, if applicable								**x**
Patient re-operation, if applicable								**x**

[1] To include review of the following: medical history, concomitant medication, most recent SoC pre-operative check blood results and pregnancy test results (where applicable)

[2] BREAST-Q post-operative questionnaire given at last follow up visit only (approximately 4-6 weeks post-surgery).

26.2 Appendix 2: Surgeon Questionnaire

Question	**Score for the right breast** (Non-retractor technique)	**Score for the left breast** (Retractor technique)
1. How physically fatiguing was the procedure? **(0–10 scale; 0—not at all demanding; 10—extremely demanding)** (17)		
2. How complex was the procedure**? (0–10 scale; 0—not at all complex; 10—extremely complex)** (18)		
3. What was the degree of difficulty of the operation? **(0–10 scale; 0—not at all difficult; 10—extremely difficult)**(18)		
4. Compared to other mastectomies of this type, how difficult was this operation? **(0–10 scale; 0—not at all difficult; 10—extremely difficult)** (19)		
5. How difficult was visualization during the operation? **(0–10 scale; 0—not at all difficult; 10—extremely difficult)** (19)		
6. How fatigued were you at the end of the operation? **(0–10 scale; 0—not at all fatigued; 10—extremely fatigued)** (18)		
7. What is your degree of satisfaction with the technique used to complete the surgery? **(0–10 scale; 0—not at all satisfied; 10—extremely satisfied)** (Original to this study)		

8 . Rate your perception of the safety of each soft tissue lift technique to the soft tissue around the incision **(0–10 scale; 0—not at all safe; 10—extremely safe)** (Original to this study)		