*i*BRA-2

Immediate ***B***reast ***R***econstruction and ***A***djuvant therapy ***A***udit

A national prospective multi-centre audit of the impact of immediate breast reconstruction on the delivery of adjuvant therapy

The iBRA-2 Steering Group
on behalf of the Breast Reconstruction Research Collaborative

Study Protocol V10
5th May, 2016

THE MAMMARY FOLD
ACADEMIC & RESEARCH COLLABORATIVE

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

University of BRISTOL

RSTN
Reconstructive Surgery Trials Network

CTRC
Clinical Trials Research Centre

Royal College of Surgeons
ADVANCING SURGICAL CARE

iBRA-2 Study Steering and Protocol Management Group

Contact: ibrastudy@gmail.com

Website: ibrastudy.com

Professor Jane Blazeby
Professor of Surgery
Director of the MRC ConDuct II Hub and Bristol RCS Surgical Trials Centre, University of Bristol
Methodologist and Trialist
J.M.Blazeby@bristol.ac.uk

Ms Nicola Barnes
Consultant Oncoplastic Breast Surgeon
University Hospitals South Manchester
nicolabarnes@doctors.org.uk

Miss Beth Conroy
NIHR Doctoral Research Fellow
University of Liverpool
Liverpool CTRC
Methodologist and Statistician
E.J.Conroy@liverpool.ac.uk

Mr Rajiv Dave
Specialist Registrar in Surgery
North West Deanery
docrajdave@doctors.org.uk

Mr Matthew Gardiner
Specialist Registrar in Plastic Surgery, London Deanery, Honorary Clinical Lecturer Kennedy Institute of Rheumatology, University of Oxford
RSTN Trainee Lead for Plastic Surgery
matthew.gardiner@kennedy.ox.ac.uk

Dr Adrian Harnett
Consultant Clinical Oncologist
Norfolk and Norwich Hospitals NHS Trust
adrian.harnett@nnuh.nhs.uk

Professor Chris Holcombe
Professor of Breast Surgery
Royal Liverpool and Broadgreen NHS University Trust
Chris.Holcombe@rlbuht.nhs.uk

Dr Ciara O'Brien
Specialist Registrar in Oncology
The Christie Hospital
Manchester

Miss Rachel O'Connell
Surgical Research Fellow
Royal Marsden NHS Foundation Trust
roconnell@doctors.org.uk

Miss Shelley Potter
Academic Clinical Lecturer in General Surgery
Centre for Surgical Research, University of Bristol
Shelley.Potter@bristol.ac.uk

Mr Tim Rattay
NIHR Clinical Research Fellow
Department of Cancer Studies
University of Leicester
Honorary SpR in Breast Surgery
University Hospitals of Leicester NHS Trust
tr104@le.ac.uk

Dr Sue O'Reilly
Consultant Oncologist
Clatterbridge Cancer Centre
Liverpool
Sue.O'Reilly@clatterbridgecc.nhs.uk

Miss Jo Skillman
Consultant Plastic Surgeon
University Hospitals of Coventry and Warwickshire NHS Trust
BAPRAS Representative
Joanna.skillman@uhcw.nhs.uk

Dr Zoe Tolkien
Research Associate in Health Services Research
School of Social and Community Medicine
University of Bristol
Zoe.Tolkien@bristol.ac.uk

Mr Joseph Ward
Specialist Registrar in Plastic Surgery
Pan Thames Deanery

Professor Paula Williamson
Professor of Medical Statistics
Liverpool CTRC
Methodologist and Statistician
P.R.Williamson@liverpool.ac.uk

Contents

Abbreviations

ABS – Association of Breast Surgery

ADM – acellular dermal matrix

ASA – American Association of Anesthesiologists

BAPRAS – British Association of Plastic, Reconstructive and Aesthetic Surgery

BMI – body mass index

DVT – Deep vein thrombosis

GA – general anaesthetic

IHD – ischaemic heart disease

NAC – nipple areolar complex

NMBRA – National Mastectomy and Breast Reconstruction Audit

PE – pulmonary embolus

QC – Quality criteria (as specified in the Oncoplastic Breast Reconstruction Guidelines for Best Practice)

RCT – randomised clinical trial

SNB – sentinel node biopsy

SSM – skin sparing mastectomy

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

TBC – To be confirmed

UK – United Kingdom

1. Background

1.1. Immediate Breast Reconstruction

Approximately 51,000 women each year will be diagnosed with breast cancer[1], and of these, up to 40% may require a mastectomy as the primary surgical treatment for their disease[2]. The loss of breast can profoundly impact women's quality of life and body image[3] and, immediate breast reconstruction (IBR) is routinely offered in the UK to improve outcomes[4].

While breast reconstruction may improve psychosocial outcomes for women facing mastectomy, these benefits need to weighed against the increased risk of complications associated with more complex procedures. The National Mastectomy and Breast Reconstruction Audit (NMBRA) reported a step-wise increase in complication rates with procedure complexity with 11% of patients undergoing an implant-based procedures experiencing an in-patient complication compared with 16% of patients undergoing a pedicled flap and 18% of those undergoing immediate free-flap reconstruction[5]. These complication rates are likely to represent an underestimation of the burden of post-operative morbidity as significant number of complications, in particular wound infections and seromas, continue to occur following discharge.

1.2 Impact of delays in adjuvant therapies to oncological outcomes

Complication rates following immediate breast reconstruction are important as they may lead to the delay or omission of important adjuvant cancer therapies such as chemo and/or radiotherapy. The clinical significance of short delays is unclear, but delays of between seven[6] and 12 weeks[7] have been shown to adversely impact on key oncological outcomes including recurrence free and overall survival. Furthermore, a recent meta-analysis suggests a 15% decrease in overall survival for every four week delay in the delivery of adjuvant chemotherapy[8]. Delays to radiotherapy similarly adversely impact oncological outcomes although the time-frames are less well-established. An early meta-analysis suggested an increased risk of loco-regional recurrence if radiotherapy was delayed by more than 8 weeks following surgery[9]. More recent studies, however suggest there to be no adverse effect on disease-free or overall survival if radiotherapy is commenced within 3 months of surgery[10-13] with one large UK cohort study showing no deleterious effects with delays of up to 20 weeks[10]. To ensure timely delivery of adjuvant therapies, the National Institute of Health and Care Excellence (NICE) recommends that adjuvant chemotherapy or radiotherapy should be commenced 'as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments.'[4]

1.3 Impact of immediate breast reconstruction on delivery of adjuvant therapies

Evidence regarding the impact of IBR on the delivery of adjuvant therapy, however is inconsistent. Observational studies have generated conflicting results[14-39] and a recent systematic review[40] of 14 studies failed to demonstrate any convincing adverse impact of IBR on the time to adjuvant treatments. This review, however, was based on small, poorly-designed single-centre often retrospective case-series the results of which cannot be relied upon. There is therefore a lack of high-quality evidence to demonstrate the impact of IBR on the delivery of adjuvant therapies compared with mastectomy alone. Randomised trials provide the best evidence of treatment effect, but in this context are largely inappropriate. A large-scale prospective cohort study is therefore required to provide high-quality evidence regarding the impact of IBR on the delivery of adjuvant therapy to allow patients and surgeons to make more informed decisions about their treatment options.

1.4 Trainee research collaboratives

The challenges to the design and conduct of large-scale cohort studies are well-documented, but the trainee collaborative model has emerged as a time and cost-effective means of delivering high-quality prospective research and audit[41-44]. The on-going iBRA study[45], a national audit of the practice and outcomes of implant-based breast surgery has demonstrated the model is transferable to breast and plastic surgery and has established a network of centres willing and able to participate in future projects. It is hypothesised that this network of highly-motivated and enthusiastic breast and plastic surgical trainees and consultants can be utilised to deliver further high-quality audits in breast and reconstructive surgery.

2. Aims and Objectives

The aim of iBRA-2 is to work with the Breast Reconstruction Research Collaborative network to evaluate the impact of immediate breast reconstruction (IBR) on the time to delivery of adjuvant therapy. The group undergoing mastectomy without IBR and the group undergoing mastectomy with IBR will be compared with respect to:

i. The rate of post-operative complications
ii. The requirement for adjuvant chemo and/or radiotherapy
iii. The experience of a delay to or omission of their adjuvant therapy as a result of a surgical complication
iv. The time to adjuvant therapy

Other non-comparative objectives are:

v. Identify risk factors of patients who experience a delay to or omission of their adjuvant therapy as a result of surgical complication
vi. Generating high-quality data to inform decision-making for patients and health professionals
vii. Build on the network created by the iBRA study to include oncologists and build capacity for future research studies

3. Definitions

The following definitions will be used for this audit.

3.1 Oncological definitions

Adjuvant therapy – Chemotherapy, biological or radiotherapy delivered after mastectomy +/- IBR. Endocrine therapy is NOT included

Time to adjuvant treatment – time in days from last definitive surgery to 1st adjuvant treatment (chemotherapy or radiotherapy). Last definitive surgery is likely to be mastectomy +/- reconstruction or completion axillary clearance (ANC) in some cases (i.e cancer-related surgery). Unplanned surgery such as implant explanantation, debridement of skin necrosis, washout haematoma, flap return to theatre should be considered to be complications and not as last definitive surgery.

3.2 Clinical definitions

Seroma - A symptomatic collection of fluid in the mastectomy or donor site or around the reconstructed breast following surgery requiring aspiration.

- Requiring 1-2 aspirations
- Requiring 3 or more aspirations

Haematoma - A collection of blood in the mastectomy site/reconstructed breast/donor site

- **Minor** – managed conservatively
- **Major 1** – requiring aspiration in clinic, freehand or under USS guidance (No GA)
- **Major 2** – requiring surgical evacuation

Infection - A hot, red swollen wound/reconstructed breast/donor site associated with one of the following; a temperature, pus at the wound site, a raised white cell count; a positive wound culture 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

Mastectomy skin flap necrosis - Any area of skin loss on the mastectomy flaps

- **Minor** – managed conservatively with dressings
- **Major 1** – requiring debridement in clinic (no GA)
- **Major 2** – requiring debridement in theatre (GA)

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

- **Minor** – managed conservatively with dressings;
- **Major 1** – requiring surgical debridement
- **Major 2** – complete nipple loss

Wound dehiscence – separation of the skin edges at the wound site (breast or donor site).

- **Minor** – treated conservatively;
- **Major** – requiring return to theatre for re-suturing under GA

Implant loss - Unplanned and unexpected extirpation or loss of the implant including removal as a result of infection, seroma or skin necrosis.

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

Donor site skin necrosis – any area of skin loss at the donor site (abdomen, back, buttock or thigh)

- **Minor** – managed conservatively with dressings
- **Major 1** – requiring debridement in clinic (no GA)
- **Major 2** – requiring debridement in theatre (GA)

Impaired flap perfusion requiring re-exploration or revision of the anastomosis – concerns regarding perfusion of the flap requiring a return to theatre for exploration +/- revision of the anastomosis

Partial flap necrosis/failure – Partial flap necrosis requiring surgical debridement

Total flap necrosis/failure – total flap necrosis or failure requiring surgical removal

Other complication – any complication that occurs in the first 30 days following the patient's mastectomy +/- IBR. These include

- *Deep vein thrombosis* – a radiologically confirmed clot in the vessels of the lower limb treated with anticoagulation
- *Pulmonary embolism* – a radiologically (CTPA or V/Q scan) confirmed clot in the lung treated with anticoagulation
- *Myocardial infarction* – as confirmed by a rise in cardiac markers +/- ECG changes
- *Lower respiratory tract infection* – a lower respiratory tract infection diagnosed clinically by the presence of clinical signs or radiologically and treated with oral or intravenous antibiotics
- *Blood transfusion* – bleeding requiring blood transfusion following reconstructive surgery
- *Unplanned admission to intensive care/high dependency unit* following mastectomy +/- reconstructive surgery
- *Urinary tract infection* – microbiologically confirmed urinary tract infection
- Other

Readmission to hospital – any re-admission to hospital prior to the delivery of the first adjuvant therapy OR in the six weeks following surgery in those not requiring chemo or radiotherapy directly related to the procedure with either local or systemic complications.

Return to theatre – Return to the operating theatre prior to the delivery of the first adjuvant therapy OR in the first six weeks following surgery to deal with any complication of the mastectomy or reconstruction.

4. Audit standards

For the purposes of this audit, standards from the NICE CG80[4] and 'Oncoplastic Surgery – A guide to good practice'[46] will be used as follows:

4.1 Oncological audit standards

NICE guidelines (2009): Early and locally advanced breast cancer: Diagnosis and treatment [CG80]:

- 1.6.8 *Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments.*

4.2 Clinical audit standards

'Oncoplastic Breast Surgery – A guide to good practice'

- <5% of patients return to theatre for local complication (wound infection, skin flap necrosis requiring debridement or haematoma requiring evacuation)(QC16)[46]

5. Methods

This is a national research collaborative led audit project that will be co-ordinated by the iBRA-2 Steering group.

Any centre performing mastectomy with or without reconstruction will be eligible to participate to the audit. Units will be invited to participate in the study through the Association of Breast Surgery, the Mammary Fold, the Association of Surgeons in Training (ASiT), the Reconstructive Surgery Trials Network (RSTN), the British Association of Plastic Reconstructive and Aesthetic Surgeons and the national research collaborative network.

A local study lead will be identified at each centre. This is a trainee collaborative project, but if the unit does not have a trainee, the unit lead can be a Consultant surgeon or oncologist, a Speciality or Associate Specialist (SAS) doctor, a clinical nurse specialist or a research co-ordinator depending on local arrangements. If the lead is a trainee, they will be required to identify a supervising consultant to act as principle investigator for the study. Unit leads will responsible for obtaining the support of other members of the department and the oncology team.

Support will also be sought from the professional associations – the Association of Breast Surgery (ABS), the British Association of Plastic and Reconstructive Surgery (BAPRAS), the Royal College of Radiologists (RCR) and Oncologists. We will ask that they encourage all Consultant members who treat breast cancer to support their units in this audit and to enter all their patients undergoing mastectomy with or without immediate reconstruction in to the study.

5.1. Logistical and clinical governance issues

This project is a clinical audit and outcomes will be compared with published standards of care.

The unit lead will be responsible for registering their unit with the iBRA-2 team (via www.ibrastudy@gmail.com); obtaining local audit approvals for study participation and forwarding a copy of the approvals to the iBRA-2 team ***prior to the study start date (1st July 2016).***

If the unit lead is a trainee, the named supervising consultant will act as the principal investigator for the unit for registration purposes.

Patient recruitment and data collection will be completed by the unit lead. It is anticipated that each unit lead will identify a small team of 2-3 people to help conduct the audit and will liaise with the wider team including oncologists and breast care and reconstructive nurses.

The study will be piloted in two to three centres prior to national roll-out of the audit to test the acceptability of data collection pro-formas and evaluate feasibility of collecting adjuvant treatment data.

5.2. Patient inclusion and exclusion criteria

5.2.1. Inclusion criteria

Any patient undergoing a mastectomy with or without immediate reconstruction for pre-invasive or invasive disease with curative intent is eligible for inclusion in the study.

5.2.2. Exclusion criteria

- Patients without pre-invasive or invasive disease (i.e. those undergoing risk-reducing surgery ONLY – those women having a mastectomy for invasive disease or DCIS on one side and a contralateral risk reducing mastectomy ARE eligible for inclusion)
- Patients undergoing partial mastectomy including lumpectomy, wide local excision or therapeutic mammaplasty ONLY
- Patients with metastatic disease

5.3. Participation identification and recruitment

It is expected that participating centres will recruit consecutive patients into the audit.

Patients undergoing mastectomy with or without immediate reconstruction will be identified prospectively from clinics, multidisciplinary team meetings and theatre lists.

Simple demographic, co-morbidity, operative and oncology data will be collected on all patients. Decisions regarding the recommendation for adjuvant treatment will be identified from the post-operative MDT.

For patients in whom adjuvant therapy is recommended at the post-operative MDT, data will be collected on whether or not the offer was accepted. In those patients electing to receive adjuvant therapy, date of the first treatment will be collected.

Data regarding complications and re-admissions will be collected prospectively until the patient commences adjuvant therapy or a decision is made that they will not undergo adjuvant therapy due

to the complications they have experienced. Pilot work suggests that adjuvant therapy is unlikely to commence earlier than six weeks following surgery. For patients not requiring or electing not to receive adjuvant therapy, data collection will therefore cease at **six weeks** following their initial surgery either by clinical or note review in those not attending for follow up.

Data will be recorded in an anonymised format using a unique alphanumeric study identification number on a secure web-based database (REDCap) designed by Vanderbilt University[47-49] (http://www.projectredcap.org/).

6. Data Collection

Section 1 – Demographic data

1.1 Age at diagnosis
1.2 Height (m)
1.3 Weight (kg)
1.4 BMI
1.5 Smoking status (current smoker/ex-smoker >6 weeks/non smoker)
1.6 Diabetic (yes/no)
1.7 Other comorbidities (yes/no)
Ischaemic heart disease/Current steroid therapy/other immunosuppressive therapy/ Connective tissue disease/other co-morbidities
1.8 Previous radiotherapy to ipsilateral breast (yes/No)
1.9 Neoadjuvant chemotherapy within 4-6 weeks of surgery (yes/no)
1.10 Neoadjuvant endocrine therapy (yes/no)
1.11 Neoadjuvant radiotherapy (yes/no)
1.12 Previous surgery to ipsilateral breast
(wide local excision/therapeutic mammaplasty/reduction/augmentation/other) (yes/no)
if yes, date
1.13 Previous surgery to ipsilateral axilla
Sentinel node biopsy as part of cancer operation; Stand-alone sentinel node biopsy (to plan whether or not to offer IBR); axillary sample; axillary clearance
If yes, date

Section 2 – Operative data

2.1 Date of mastectomy +/- reconstruction
2.2 ASA grade

2.3 Antibiotic use (single dose/1-5 days/extended course > 5 days/until drains out)

2.4 Type of skin prep used at time of surgery (iodine/chlorhexidine/2% chlorprep/other)

Right breast

2.5 Procedure performed to **right breast**
(none/mastectomy only/skin-sparing mastectomy and IBR/nipple sparing mastectomy and IBR/skin reducing mastectomy and IBR/wide local excision/reduction or mastopexy/augmentation)

2.6 If immediate reconstruction (IBR), type of reconstruction performed to right breast (implant-based/pedicled flap/free flap/other)

If patient undergoing **implant-based reconstruction** to right breast

2.7 Right breast – implant reconstruction – planned procedure
(one stage/two stage/immediate delayed)

2.8 Right breast – implant reconstruction – mode of lower pole coverage
(none/complete fascial or submuscular/dermal sling/biological mesh/synthetic mesh/pre-pectoral implant with complete ADM coverage/prepectoral implant with dermal sling/ADM coverage

2.9 Right breast - Details of product used
(Strattice/SurgiMend/Native/BioDesign/Veritas/Seri/TiLOOP/TiGR Mesh/Other with (details)

2.10 Right breast – breast prosthesis details
(fixed volume – size(ccs)/temporary expander – volume of saline inserted(mls)/combined implant (Beckers) – silicone component (g), size when fully inflated, volume of saline inserted)

If patient undergoing **flap-based reconstruction** to right breast

2.11 Right breast – type of flap used
Pedicled flap
(autologous LD (no implant)/LD with implant/pedicled TRAM/other)
2.11.1 If LD with implant – prosthesis details
(fixed volume – size(ccs)/temporary expander – volume of saline inserted(mls)/combined implant (Beckers) – silicone component (g), size when fully inflated, volume of saline inserted)
Free flap
(free TRAM/DIEP/SIEA/TUG/SGAP/IGAP/Other)

All patients

2.12 Indication for surgery to right breast

(malignancy – DCIS/invasive – first operation/malignancy – failed BCS (WLE/TM)/risk reduction/symmetrisation)

If failed WLE/TM (ie mastectomy for positive margins) date of initial surgery (DD/MM/YY)

2.13 Grade of operating surgeon – right breast

Consultant/senior trainee(OPF/ST8)/(ST7-6)/Speciality or Staff grade/other)

2.14 Mastectomy weight – right breast (g)

2.15 Axillary surgery

(none/sentinel node biopsy/axillary sample/axillary clearance/previous axillary staging)

Left breast

2.16 Procedure performed to **left breast**

(none/mastectomy only/skin-sparing mastectomy and IBR/nipple sparing mastectomy and IBR/skin reducing mastectomy and IBR/wide local excision/reduction or mastopexy/augmentation)

2.17 If immediate reconstruction (IBR), type of reconstruction performed to left breast (implant-based/pedicled flap/free flap/other)

If patient undergoing **implant-based reconstruction** to left breast

2.18 Left breast – implant reconstruction – planned procedure

(one stage/two stage/immediate delayed)

2.19 Left breast – implant reconstruction – mode of lower pole coverage

(none/complete fascial or submuscular/dermal sling/biological mesh/synthetic mesh/pre-pectoral implant with complete ADM coverage/prepectoral implant with dermal sling/ADM coverage

2.20 Left breast - Details of product used

(Strattice/SurgiMend/Native/BioDesign/Veritas/Seri/TiLOOP/TiGR Mesh/Other with (details)

2.21 Left breast – breast prosthesis details

(fixed volume – size(ccs)/temporary expander – volume of saline inserted(mls)/combined implant (Beckers) – silicone component (g), size when fully inflated, volume of saline inserted)

If patient undergoing **flap-based reconstruction** to left breast

2.22 Left breast – type of flap used

Pedicled flap

(autologous LD (no implant)/LD with implant/pedicled TRAM/other)

2.11.1 If LD with implant – prosthesis details

(fixed volume – size(ccs)/temporary expander – volume of saline inserted(mls)/combined implant (Beckers) – silicone component (g), size when fully inflated, volume of saline inserted)

Free flap

(free TRAM/DIEP/SIEA/TUG/SGAP/IGAP/Other)

All patients

2.23 Indication for surgery to left breast

(malignancy – DCIS/invasive – first operation/malignancy – failed BCS (WLE/TM)/risk reduction/symmetrisation)

If failed WLE/TM (ie mastectomy for positive margins) date of initial surgery (DD/MM/YY)

2.24 Grade of operating surgeon – left breast

Consultant/senior trainee(OPF/ST8)/(ST7-6)/Speciality or Staff grade/other)

2.25 Mastectomy weight – left breast (g)

2.26 Axillary surgery

(none/sentinel node biopsy/axillary sample/axillary clearance/previous axillary staging)

Section 3 – Post-operative oncological and MDT outcomes

To be collected for each side from which surgery is performed for malignancy (invasive/DCIS)

Right breast

3.1 Invasive/DCIS

3.2 Grade

3.3 Type (IDC/ILC/mixed/other)

3.4 One tumour (unifocal)/ multifocal

3.5 Size of invasive tumour (mm) (largest if >1)

3.6 Total size of lesion including DCIS (mm) in pathological specimen and on diagnostic imaging (if neoadjuvant chemo/endocrine therapy)

3.7 Receptor status

3.7.1 ER (positive/negative/not known)

3.7.2 HER-2 (positive/negative/not known)

3.7.3 Ki67 (high/low/not known)

3.8 Lymphovascular invasion (yes/no/not known)

3.9 Lymph node involvement

3.9.1 Number of LN involved (macromets only)

3.9.2 Total of LN in the pathological specimen

Left breast

3.10 Invasive/DCIS

3.11 Grade

3.12 Type (IDC/ILC/mixed/other)

3.13 One tumour (unifocal)/ multifocal

3.14 Size of invasive tumour (mm) (largest if >1)

3.15 Total size of lesion including DCIS (mm) in pathological specimen and on diagnostic imaging (if neoadjuvant chemo/endocrine therapy)

3.16 Receptor status

3.17.1 ER (positive/negative/not known)

3.17.2 HER-2 (positive/negative/not known)

3.17.3 Ki67 (high/low/not known)

3.17 Lymphovascular invasion (yes/no/not known)

3.18 Lymph node involvement

3.18.1 Number of LN involved (macromets only)

3.18.2 Total of LN in the pathological specimen

Plan from the post-operative MDT

3.19 Date of post-operative MDT (DD/MM/YY)

3.20 Further oncological surgery required

(no/completion axillary clearance/further margins/other)

3.20.1 Surgery planned before adjuvant therapy (yes/no)

3.20.2 If yes, planned date of surgery (DD/MM/YY)

3.21 Treatments recommended

3.21.1 Chemotherapy

(recommended by MDT/not recommended by MDT/for discussion with patient/for Oncotype DX/already received)

3.21.2 Radiotherapy

(recommended by MDT/not recommended by MDT/discuss with patient/already received)

3.21.3 Biological therapy (e.g Herceptin)

(recommended by MDT/not recommended by MDT)

3.21.4 Endocrine therapy

(recommended by MDT/not recommended by MDT)

Section 4 - Complication data (data for left and left breasts to be collected separately)

4.1 Post-operative complication experienced (yes/no)

If yes

Side Right/left/

Tick if complication experienced (breast or donor site)

Right breast

4.2 Seroma (breast/donor site)

4.2.1 Requiring aspiration 1-2 times

4.2.2 Requiring aspiration 3 or more times

4.3 Haematoma (breast/donor site)

4.3.1 Minor (conservative management)

4.3.2 Major 1 requiring evacuation in clinic +/- USS guidance (no GA)

4.3.3 Major 2 requiring surgical evacuation (GA)

4.4 Wound infection

4.4.1 Minor (oral Abx) (breast/donor site)

4.4.2 Major 1 (IV Abx) (breast/donor site)

4.4.3 Major 2 (surgical drainage +/- debridement) (breast/donor site)

4.5 Mastectomy skin flap necrosis

4.5.1 Minor (conservative management)

4.5.2 Major 1 requiring surgical debridement in clinic (no GA)

4.5.3 Major 2 requiring surgical debridement in theatre (GA)

4.6 Nipple necrosis

4.6.1 Minor (conservative management)

4.6.2 Major I (requiring debridement)

4.6.3 Major II (complete NAC loss) (left/left/no)

4.7 Wound dehiscence

4.7.1 Minor – managed conservatively (breast/donor site)

4.7.2 Major – requiring return to theatre (breast/donor site)

4.8 Implant loss

4.9 Donor site skin necrosis

4.9.1 Minor (conservative management)

4.9.2 Major 1 requiring surgical debridement in clinic (no GA)

4.9.3 Major 2 requiring surgical debridement in theatre (GA)

4.10 Impaired flap perfusion requiring return to theatre for exploration/revision of anastomosis (flap salvage)

4.11 Flap necrosis

4.11.1 Partial flap necrosis requiring return to theatre for debridement

4.11.2 Total flap necrosis requiring removal of flap

Left breast

4.12 Seroma (breast/donor site)

4.12.1 Requiring aspiration 1-2 times

4.12.2 Requiring aspiration 3 or more times

4.13 Haematoma (breast/donor site)

4.13.1 Minor (conservative management)

4.13.2 Major 1 requiring evacuation in clinic +/- USS guidance (no GA)

4.13.3 Major 2 requiring surgical evacuation (GA)

4.14 Wound infection

4.14.1 Minor (oral Abx) (breast/donor site)

4.14.2 Major 1 (IV Abx) (breast/donor site)

4.14.3 Major 2 (surgical drainage +/- debridement) (breast/donor site)

4.15 Mastectomy skin flap necrosis

4.15.1 Minor (conservative management)

4.15.2 Major 1 requiring surgical debridement in clinic (no GA)

4.15.3 Major 2 requiring surgical debridement in theatre (GA)

4.16 Nipple necrosis

4.16.1 Minor (conservative management)

4.16.2 Major I (requiring debridement)

4.16.3 Major II (complete NAC loss) (left/left/no)

4.17 Wound dehiscence

4.17.1 Minor – managed conservatively (breast/donor site)

4.17.2 Major – requiring return to theatre (breast/donor site)

4.18 Implant loss

4.19 Donor site skin necrosis

4.19.1 Minor (conservative management)

4.19.2 Major 1 requiring surgical debridement in clinic (no GA)

4.19.3 Major 2 requiring surgical debridement in theatre (GA)

4.20 Impaired flap perfusion requiring return to theatre for exploration/revision of anastomosis (flap salvage)

4.21 Flap necrosis

4.21.1 Partial flap necrosis requiring return to theatre for debridement

4.21.2 Total flap necrosis requiring removal of flap

4.22 In-hospital complication including systemic complications e.g. DVT/PE at time of initial surgery (yes/no with drop list – DVT/PE/MI/LRTI/UTI/transfusion/unplanned admission to HDU/ITU)

4.23 Readmission to hospital within 30 days (yes/no with reason)

4.24 Re-operation for complication within 30 days (yes/no with reason)

Clavien-Dindo classification of surgical complications will also be determined by the study team (http://www.surgicalcomplication.info/index-2.html)

Grade; I (conservative) □ II (antibiotics) □ III (surgery) □ IIIa □ IIIB □ IV □ IVa □ IVb □ V □

Section 5 – Adjuvant therapy data

This section documents time from LAST surgery to FIRST adjuvant treatment i.e 1st dose of chemotherapy OR 1st dose of radiotherapy. DO NOT INCLUDE ENDOCRINE

If patient is planned to receive chemotherapy and radiotherapy, only data on the first adjuvant therapy i.e. chemotherapy needs to be collected

To be auto filled by MDT outcome proforma depending on recommendations

5.1 Date of last definitive cancer surgery (if not mastectomy procedure) DD/MM/YY

5.2 Chemotherapy

5.2.1 If offered – patient accepts/patient declined

5.2.2 If Oncotype DX – high/intermediate/low risk

- Chemotherapy yes/no based on Oncotype-DX score

5.2.3 Actual chemotherapy start date (DD/MM/YY)

5.2.4 Was planned treatment modified, delayed or omitted (not given) due to as post-operative complication?
(not affected/delayed/modified/omitted completely)
Details

5.3 Radiotherapy

5.3.1 If offered – patient accepts/patient declines

5.3.2 Actual radiotherapy start date (DD/MM/YY)

5.3.3 Was planned treatment modified, delayed or omitted (not given) due to as post-operative complication?

(not affected/delayed/modified/omitted completely)

Details

5.4 Did any factors impact on the delivery of adjuvant therapy? (yes/no/unsure)

If yes – please tick any factors that apply (multiple tick boxes) (yes/no)

Post-operative complication

Capacity issue – lack of medical oncology (chemotherapy) appointments

Capacity issue – lack of clinical oncology (RT) appointments

Capacity issue – lack of chemotherapy delivery slots

Capacity issue – lack of radiotherapy delivery slots

Waiting for staging CT scan or results

Waiting for staging bone scan or results

Waiting for staging PET scan or results

Waiting for ECHO or results

Awaiting Oncotype DX results

Administrative delay – problems with booking appointments

Patient choice

Patient-related issue e.g. needing physio to receive RT

Other – please give details

7. Data validation and quality assurance

It is anticipated that participating centres will recruit consecutive patients undergoing mastectomy into the study.

Following data collection, only data sets with >95% data completeness will be included in the analysis[50]. For quality assurance purposes, the Consultant principal investigator at selected sites will be asked to identify an independent person to validate a proportion of the submitted data. Overall, approximately 5% of the datasets will be independently validated. The independent assessors will also be asked to examine theatre logbooks, operating diaries and Trust computer systems to check case ascertainment. If concordance between the number of cases submitted on REDcap and those identified independently is <90%, the Unit's data will be excluded from the analysis. This is consistent with the quality assurance procedure used in other large collaborative audit projects[50].

8. Data Management and Storage

This project is an audit. Data collection will occur in accordance with Caldicott II principles (http://systems.hscic.gov.uk/infogov/caldicott/caldresources). Data for each patient will be anonymised using a unique alphanumeric study identification number. Collaborators will be ask to store an Excel spreadsheet linking study ID to NHS number locally to ensure patients are appropriately followed up during the study. No patient identifiable data will be recorded centrally for the purpose of the audit.

Study data will be collected and managed using REDCap electronic data capture tools hosted at University of Bristol[47]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

During the pilot phase of the study, the feasibility of using real-time data collection using electronic data collection systems with central data storage will be explored and data collection forms refined based on user feedback.

9. Data analysis

All data analysis will occur centrally and will be led by the iBRA-2 study team with support from statisticians and methodologists in the RCS Surgical Trials Centre and the University of Liverpool Clinical Trials Research Centre.

The recent MASDA (MAStectomy Decisions Audit) collected data on 1700 mastectomies +/- IBR over a three month period. It is therefore anticipated that given its increased complexity, the iBRA-2 study will recruit approximately 3000 patients over a six month period. Assuming an IBR rate of 21%[51, 52], this should include approximately 630 reconstructions comprising approximately 220 implant-only reconstructions; 170 autologous pedicled flaps; 130 pedicled flaps+ implants and 90 free flaps based on figures from the NMBRA[51].

Descriptive statistics

All outcomes will be summarized using descriptive statistics overall and split by group (mastectomy +/- IBR) as follows:

- *Dichotomous, categorical and short ordinal outcomes* (objectives i, ii, iii and v) will be summarized using counts and percentages.

- *Time to event outcomes* (objective iv) will be summarized using Kaplan Meier curves.

Formal statistical testing

- *Continuous and long ordinal outcomes* (objective v) will be summarized by the mean, standard deviation, minimum and maximum (medians and interquartile ranges will be reported for skewed data).

A p-value of 0.05 or less will be used to declare statistical significance for all analyses. Rather than adjust for multiplicity relevant results from other studies already reported in the literature will be taken into account in the interpretation of results.

Formal statistical testing for each outcome between groups (mastectomy +/- IBR) will be approached as follows:

- *Objectives i, ii and iii* will be analysed using a chi-squared test and the effect estimate will be reported in terms of the relative risk and 95% confidence interval.
- *Objective iv* will be analysed using a log rank test.
- *Objective v* will be analysed, controlling for risk factors of interest, using logistic regression model.

Results for each participating Trust will be summarised and fed back to individual units to allow comparison with national averages and ranges.

10. Publication and Authorship Policy

The iBRA-2 Study Steering Group which will be responsible for drafting manuscripts and preparing them for publication.

All presentations and publications from this project will be made on behalf of the 'Breast Reconstruction Research Collaborative'.

The International Committee of Medical Journal Editors (ICMJE) criteria (www.icmje.org) for authorship is based on the following four criteria:

1. Substantial contribution to the conception or design of the work; or the acquisition, analysis or interpretation of the data for the work and
2. Drafting the work or revising it critically for important intellectual content and
3. Final approval of the version to be published and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The ICMJE states '*when submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript and MEDLINE lists authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators*.'

All citable collaborators will therefore be listed at the end of the paper and their roles identified.

10.1 Criteria for citable collaborators status

Citable collaborators will have been required to make considerable contribution to the study. These will include Unit leads and ANY other team members (including consultant surgeons, clinical nurse specialists, trainees, oncologists, research nurses or students) who have recruited at least ten patients to the study. Recruitment in this context includes the submission of ***at least ten completed data sets***. Judgement may be used to determine participation according to local centre practice. Unit leads will be asked to provide details of their local team and whether individuals fulfil the criteria for citable or acknowledged collaborator status.

10.2 Acknowledged collaborators

Acknowledged collaborators will include consultant surgeons and oncologists who contributed patients to the audit, but did not personally collect data and individuals who have made a lesser contribution to patient recruitment and data collection than that required for citable collaborator status. Individuals who are acknowledged contributors will also receive a certificate of participation for inclusion in their portfolios.

Local collaboratives and hospital Trusts will have ownership of their own data and will be able to present it locally if they wish.

The final reports will be prepared in accordance with the STROBE[53] (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

11. Research Governance

The main aim of the audit is to determine the impact of immediate breast reconstruction on the delivery of adjuvant therapy and explore factors that may influence this.

The length of time from mastectomy to start of adjuvant therapy for each individual centre will be calculated and compared with the national average and quality standards determined by NICE. Data will be fedback to centres in the form of St Elsewhere reports at the end of the audit.

Overall audit results and results from individual centres will be fedback to ABS and BAPRAS.

12. Study Management

Oversight of the audit will be by the iBRA-2 Steering Group which will have wide representation from reconstructing surgeons, trainees, oncologists, the professional societies, patient representative and those with experience of study management and statistics. This group is expected to meet twice per year, but may also meet more frequently if necessary.

There will in addition be a smaller executive group for day to day audit management. It is expected that most of this work will be done as a 'virtual group' by e mail.

A writing and data analysis group will also be convened.

13. Study timeline

The following study time line is proposed

- Draft protocol paper for publication (BMJ Open)
  - Feb – May 2016
- 3 centre pilot study
  - March 2016 onwards
- Registration of interest from breast units
  - Feb –June 2016
- Local audit approvals in participating units
  - Feb-June 2016

****** All units must have registered, obtained local audit approvals for study participation and sent a copy of the form/email confirming audit approvals to the iBRA-2 Study Team by the study start date 1st JULY 2016******

- Patient recruitment
  - Patients undergoing mastectomy +/- BR with operation dates between 1st July 2016 and 31st December 2016 inclusive
- Data collection period
  - 5th September 2016- 31st January 2017 (allowing for 30 day FU)

- Closing date for data submission
  - 14th February 2017
- Data analysis
  - March-May 2017
- Write up and dissemination
  - June/July 2017
- Design of prospective cohort study and grant submission
  - Sept-Dec 2017