BMJ Open

The iBRA-2 (immediate Breast reconstruction And Adjuvant therapy Audit) Study – Protocol for a prospective national multi-centre cohort study to evaluate the impact of immediate breast reconstruction on the delivery of adjuvant therapy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012678
Article Type:	Protocol
Date Submitted by the Author:	16-May-2016
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	immediate breast reconstruction, adjuvant therapy, trainee collaboratives, cohort study, Breast tumours < ONCOLOGY

The iBRA-2 (*i*mmediate *B*reast reconstruction *A*nd *A*djuvant therapy *A*udit) Study – Protocol for a prospective national multi-centre cohort study to evaluate the impact of immediate breast reconstruction on the delivery of adjuvant therapy

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Keywords: Immediate breast reconstruction, adjuvant therapy, breast cancer, cohort study, trainee collaboratives

Word count: 2773 (excluding tables)

ABSTRACT

Introduction

Immediate breast reconstruction (IBR) is routinely offered to improve quality of life for women with breast cancer requiring a mastectomy, but there are concerns that more complex surgery may delay the delivery of adjuvant oncological treatments and compromise long-term oncological outcomes. High-quality evidence, however, is lacking. iBRA-2 is a national prospective multicentre cohort study that aims to investigate the effect of IBR on the delivery of adjuvant therapy.

Methods and analysis

Breast and plastic surgery centres in the UK performing mastectomy with or without (+/-) IBR will be invited to participate in the study through the trainee research collaborative network. All women undergoing mastectomy+/-IBR for breast cancer between 1st July and 31st December 2016 will be included. Patient demographics, operative, oncological and complication data will be collected. Time from last definitive cancer surgery to first adjuvant treatment for patients undergoing mastectomy+/-IBR will be compared to determine the impact that IBR has on the time of delivery of adjuvant therapy. Prospective data on 3000 patients from approximately 50 centres is anticipated.

Ethics and dissemination

Research ethics approval is not required for this study. This has been confirmed using the on-line Health Research Authority (HRA) decision tool. This novel study will explore whether IBR impacts the time to delivery of adjuvant therapy. The study will provide valuable information to help patients and surgeons make more informed decisions about their surgical options. Dissemination of the study protocol will be via the Mammary Fold Academic and Research Collaborative (MFAC) and the Reconstructive Surgery Trials Network (RSTN), the Association of Breast Surgery (ABS) and the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS). Participating units will have access to their own data

and collective results will be presented at relevant surgical conferences and published in appropriate peer-reviewed journals.

STRENGTHS AND WEAKNESSES

- Large multicentre prospective study involving data collection from breast and plastic surgical units across the UK
- Will produce valuable data regarding the impact of immediate breast reconstruction on the time to delivery of adjuvant therapy which will help inform decision-making for patients and surgeons
- Will strengthen the collaborative network between breast and plastic surgical trainees and consultants to facilitate the delivery of future research
- Observational design will not address causality
- Will not collect data on non-participating units
- Short-term data collection will not allow the long-term impact of delays to adjuvant therapy to be assessed

INTRODUCTION

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

Whilst IBR may improve psychosocial outcomes for women facing mastectomy, these benefits need to be 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 10% of patients undergoing mastectomy experiencing a post-operative complication compared with 11% of patients undergoing an implant-based procedures; 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 after discharge.

Complication rates following IBR are important as they may lead to the delay or omission of adjuvant cancer therapies in the form of adjuvant chemotherapy or biological therapy and post-mastectomy 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]. Similarly, delays to radiotherapy 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 eight 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 three 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 [and] within 31 days of completion of surgery in patients with early breast cancer having these treatments'[4].

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. Therefore there is a lack of high-quality evidence to demonstrate the impact of IBR on the delivery of adjuvant therapies compared with mastectomy alone. Randomised trials (RCTs) 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 potential treatment options.

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 (implant Breast Reconstruction evAluation) study (ISRCTN37664281)[45], a national prospective cohort study to explore the feasibility, design and conduct of a pragmatic RCT in implant-based breast surgery has demonstrated the trainee collaborative 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 anticipated that this network of highly-motivated and enthusiastic breast and plastic surgical trainees and consultants can be utilised to deliver a new study exploring the impact of IBR on the timing of adjuvant therapy.

METHODS AND ANALYSIS

Primary aim

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 to:

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

Hypothesis

Immediate breast reconstruction following mastectomy for breast cancer does not increase the time to delivery of adjuvant therapy compared with mastectomy alone.

Study design

We plan to undertake a national prospective multicentre cohort study using the research collaborative model previously reported[42, 43] coordinated by the iBRA-2 Steering Group.

Setting

Any breast or plastic surgical unit in the UK performing mastectomy with or without immediate breast reconstruction will be eligible to participate to the study. Units will be invited to participate in the study through the Association of Breast Surgery (ABS), the Mammary Fold breast trainees' group (MF), the Association of Surgeons in Training (ASiT), the Reconstructive Surgery Trials Network (RSTN), the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) and the national research collaborative network (NRCN).

Participants

Inclusion criteria: All women over the age of 18 who are undergoing a mastectomy with or without immediate reconstruction for pre-invasive or invasive breast cancer with curative intent.

Exclusion criteria: Women undergoing mastectomy for risk-reduction only; however women who are undergoing a contralateral risk-reducing mastectomy at the same time as a therapeutic mastectomy for invasive or pre-invasive disease may be included. Patients undergoing partial mastectomy including lumpectomy or wide local excision with volume replacement techniques (latissimus dorsi mini flaps; lateral intercostal perforator (LICAP) or thoracodorsal artery perforator (TDAP) flaps) or therapeutic mammoplasty and patients with distant metastatic disease will be excluded.

Outcome measures

The primary outcome measure will be time in days from last definitive cancer surgery to the first adjuvant treatment. The last definitive cancer surgery will most commonly be the index mastectomy procedure, but may include completion axillary clearance or re-excision of margins as determined on review of the surgical pathology by the multidisciplinary team (MDT). Unplanned surgery such as implant explantation, debridement of skin necrosis, washout of haematoma or return to theatre for flap failure constitute complications and will

not be classified as last definitive surgery for the purposes of this study. First adjuvant therapy will be defined as the first dose of chemotherapy or the first fraction of radiotherapy. Time to endocrine therapy will not be included. This definition is based on the National Institute for Health and Care Excellence guidance for early and locally advanced breast cancer [CG80] which states that adjuvant chemotherapy or radiotherapy should be started 'as soon as clinically possible [and] within 31 days of completion of surgery in patients with early breast cancer having these treatments'[4]. In patients for whom more than one modality of adjuvant treatment is recommended, only the start date for the first adjuvant therapy will be recorded. Secondary outcomes are listed in table 1.

Table 1: Secondary outcome measures

Outcome measure	Definition
Post-operative complications	Any post-operative complication occurring before the 1st adjuvant treatment OR within 30 days of surgery for patients not requiring adjuvant chemo or radiotherapy. To be classified by the Clavien-Dindo classification of complications as applied to breast surgery[46] with specific reference to: *Mastectomy and breast reconstruction specific complications:* Seroma; haematoma; infection; mastectomy skin flap necrosis; nipple necrosis; wound dehiscence; implant loss; donor site skin necrosis; flap salvage; partial and full flap necrosis/failure. *Systemic complications:* Deep vein thrombosis, pulmonary embolism, myocardial infarction; lower respiratory tract infection; blood transfusion; unplanned admission to high dependency or intensive therapy units; urinary tract infection.
Re-admission to hospital	Any re-admission to hospital following discharge home after mastectomy+/- immediate breast reconstruction surgery directly related to the procedure with either local or systemic complications in the time prior to the delivery of the first adjuvant treatment OR within 30 days of surgery in those not requiring chemo or radiotherapy.
Unplanned re-operation/return to theatre	Any unplanned re-operation or return to the operating theatre prior to the delivery of the first adjuvant therapy OR in the 30 days following surgery to deal with any complication of the mastectomy or reconstruction. Any planned return to theatre for additional oncological surgery, such as completion axillary clearance, as decided by the multi-disciplinary team on review of surgical pathology will NOT be included in this category.
Use of adjuvant therapy	Number (proportion) of patients undergoing mastectomy +/- immediate breast reconstruction who require adjuvant i. Chemotherapy ii. Biological therapy iii. Radiotherapy
Omission, modification or delay of adjuvant therapy	Number (proportion) of patients undergoing mastectomy +/- immediate breast reconstruction whose planned adjuvant chemotherapy/biological therapy or radiotherapy is i. Omitted (not given, despite MDT recommendation) ii. Modified (dose/regimen changed from planned/standard treatment)

	iii. Delayed (not given at time scheduled following oncology appointment) as a result of a post-operative complication

Data collection

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 (MDT) 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 meeting.

For patients in whom adjuvant therapy is recommended at the post-operative MDT meeting, 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, re-admission and re-operation 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. Preliminary work suggests that, despite NICE guidelines, adjuvant therapy is unlikely to commence earlier than six weeks post-operatively. For patients not requiring or electing not to receive adjuvant therapy, therefore, data collection will continue for six weeks following their last definitive cancer surgery either by clinical or note review in those not attending for follow-up. The required data fields are shown in Table 2 and definitions and categorisation of complications summarised in Table 3.

Table 2 – Data fields for the iBRA-2 Study

Section 1 - Demographic data	
Field	**Options (definitions)**
Age	Age at diagnosis in years
Height	In metres
Weight	In kilograms
Body mass index	Actual BMI will be collected and categorised as -Underweight (<18.5 kg/m^2)/Normal weight (18.5-24.9 kg/m^2)/Overweight (25-29.9 kg/m^2)/Obese

	(30-34.9 kg/m^2)/Severely obese (35-39.9 kg/m^2) Morbid obesity (>40 kg/m^2)
Smoking status	Current smoker/Ex-smoker >6 weeks/Non-smoker
Diabetic	Yes/No
Other co-morbidities	Ischaemic heart disease (yes/no); Current steroid therapy (yes/no); Other immunosuppressive therapy (yes/no); Connective tissue disease (yes/no); Other co-morbidity (yes/no) with details
Prior and neoadjuvant treatments	
Previous radiotherapy to ipsilateral breast	Yes/No
Neoadjuvant chemotherapy within 4-6 weeks of surgery	Yes/No
Neoadjuvant endocrine therapy	Yes/No
Neoadjuvant radiotherapy	Yes/No
Previous surgery to ipsilateral breast	Wide local excision (yes/no, if yes, date MM/YY); Therapeutic mammaplasty (yes/no, if yes, date MM/YY); Breast reduction (yes/no, if yes, date MM/YY); Breast augmentation (yes/no, if yes, date MM/YY); Other (yes/no, if yes, date MM/YY): State procedure
Previous surgery to ipsilateral axilla	Sentinel node biopsy with wide local excision (yes/no, if yes, date MM/YY); Stand-alone sentinel node biopsy (yes/no, if yes, date MM/YY); Axillary sample (yes/no, if yes, date MM/YY); Axillary clearance (yes/no, if yes, date MM/YY)
Section 2 – Operative data	
Date of mastectomy +/- reconstruction	Day/month/year
ASA grade	1 – Normal healthy individual 2 – Mild systemic disease that does not limit activities 3 – Severe systemic disease that limits activities but is not incapacitating 4 – Incapacitating systemic disease which is constantly life threatening
Antibiotic use	Prophylactic (<24 hours)/1-5 days/extended course (5+days)/until drains removed/Other
Type of skin prep used at time of surgery	Iodine/Chlorhexidine/2% chlorprep/Other
Procedure details collected for RIGHT and LEFT breasts separately.	
Procedure performed	None Mastectomy only Skin-sparing (nipple sacrificing) mastectomy and immediate breast reconstruction Nipple-sparing mastectomy and immediate breast reconstruction Skin reducing (Wise pattern) mastectomy and immediate breast reconstruction Wide local excision Reduction/mastopexy Augmentation
If IBR, type of reconstruction performed	Implant-based/Pedicled flap/Free flap/Other
If patient undergoing implant reconstruction	
Implant reconstruction – planned procedure	One-stage reconstruction – insertion of permanent implant at initial surgery Two-stage reconstruction – insertion of a tissue expander to be followed by insertion of a definitive implant Immediate-delayed reconstruction – insertion of a temporary expander in patients for whom radiotherapy is anticipated with a plan to perform a definitive autologous (tissue-based) reconstruction after radiotherapy is complete.
Mode of lower pole coverage	None/Fascial or complete submuscular coverage/Dermal sling/Biological mesh (e.g. Strattice)/Synthetic mesh (e.g. TiLOOP)/Pre-pectoral implant

	with total ADM coverage e.g. BRAXON/Pre-pectoral implant with dermal sling/ADM
Details of product for lower pole coverage	Stattice/SurgiMend/Native/BioDesign/Veritas/SERI/TiLOOP/TIGR/Other
Prosthesis details	Fixed volume implant (size in ccs) Temporary expander (volume of saline inserted in mls) Combined implant e.g. Beckers (silicone component (g), size when fully expanded, volume of saline inserted in mls) Polyurethene implant (yes/no)
If patient undergoing flap based reconstruction	
Type of pedicled flap performed	Autologous LD flap (no implant)/LD with implant/Pedicled TRAM/Other
If LD with implant, prosthesis details	Fixed volume implant (size in ccs) Temporary expander (volume of saline inserted in mls) Combined implant e.g. Beckers (silicone component (g), size when fully expanded, volume of saline inserted in mls) Polyurethene implant (yes/no)
Type of free flap performed	Free TRAM/DIEP/SIEA/SGAP/IGAP/TUG/Other
Indication for surgery	Malignancy (invasive/DCIS) – first operation/Malignancy (invasive/DCIS) – following failed BCS (WLE/TM)/Risk reduction/Symmetrisation
If failed BCS (positive margins) date of initial surgery	Day/month/year
Grade of primary operating surgeon	Consultant/SAS doctor/Senior trainee (ST8+ or OPF)/ST6-7/ST5 or below
Mastectomy weight	Grams
Axillary surgery	None/Sentinel node biopsy/Axillary sample/Axillary clearance/Previous axillary staging
Section 3 – Post-operative oncology and MDT outcomes Pathology details for RIGHT and LEFT breasts will be collected separately.	
For patients having neoadjuvant chemotherapy, complete pathological response?	Yes/No
Invasive status	Invasive/DCIS
Grade of invasive disease/DCIS	1 – Low grade (DCIS) or well-differentiated (invasive) 2 – Intermediate grade (DCIS) or moderately differentiated (invasive) 3 – High grade (DCIS) or poorly differentiated (invasive)
Histological type	Ductal/Lobular/Mixed/Other
Number of tumours	Single tumour or Multifocal/centric tumours
Size of invasive tumour	Mm (largest if >1 ipsilateral tumour)
Total size of lesion including DCIS	In pathological specimen (mm) On pre-treatment diagnostic imaging (if neoadjuvant therapy) (mm)
Receptor status	ER – positive/negative/not known HER-2 – positive/negative/not known Ki67 – high/low/not known
Lymphovascular invasion	Yes/No/Not known
Lymph node involvement	Number of involved lymph nodes (macro-metastases only) Total number of lymph nodes in pathological specimen
Plan from the therapeutic (post-operative) MDT	
Date of post-operative MDT	Day/month/year
Further oncological surgery required	No/Completion axillary clearance/Re-excision of margins/Other
Surgery, planned before adjuvant therapy	Yes with date (day/month/year)
Treatments recommended	
Chemotherapy	Recommended by MDT/Not recommended by MDT/For discussion with patient/For Oncotype DX testing/Chemotherapy already received
Biological therapy (e.g Herceptin)	Recommended by MDT/Not recommended by MDT
Radiotherapy to chest wall	Recommended by MDT/Not recommended by MDT/For discussion with patient/Already received
If radiotherapy recommended	With boost (yes/no)/To supraclavicular fossa (yes/no)/To axilla (yes/no)

Endocrine therapy	Recommended by MDT/Not recommended by MDT
Section 4 – Complication data Please record any complications that occur BEFORE the start of adjuvant therapy OR in the first six weeks following surgery in patients not requiring chemo or radiotherapy.	
Post-operative complication experienced	Yes/No
If yes – details of surgical complications experienced (see table 3 for definitions)	Seroma/haematoma/infection/mastectomy skin flap necrosis/nipple necrosis/wound dehiscence/implant loss/donor site skin necrosis/impaired flap perfusion requiring return to theatre for exploration or revision of anastomosis (flap salvage)/flap necrosis/other complication
In hospital complications including systemic complications	Yes/No
If yes, complication(s) experienced (see table 3 for definitions)	Deep vein thrombosis/pulmonary embolism/myocardial infarction/lower respiratory tract infection/blood transfusion/ unplanned admission to intensive care/high dependency unit/urinary tract infection/surgical complication/other complication
Readmission to hospital	Yes/No If yes – date of readmission (day/month/year) Reason for readmission
Return to theatre/re-operation	Yes/No If yes – date of re-operation (day/month/year); Reason for re-operation
Section 5 – Adjuvant therapy data This section documents the time from **LAST CANCER SURGERY** to **FIRST ADJUVANT TREATMENT** i.e. first dose of chemotherapy or first fraction of radiotherapy.	
Date of last definitive cancer surgery	Day/month/year
Chemotherapy	
Chemotherapy – if offered	Patient accepts/Patient declines
Oncotype DX risk stratification	High risk/Intermediate risk/Low risk
Chemotherapy recommended based on Oncotype DX score	Yes/No
Actual chemotherapy start date	Day/Month/Year
Was planned treatment modified, delayed or omitted (not given) due to a post-operative complication?	Not affected/Delayed/Modified/Omitted completely/Details
Radiotherapy	
Radiotherapy - if offered	Patient accepts/Patient declines
Actual radiotherapy start date	Day/Month/Year
Was planned treatment modified, delayed or omitted (not given) due to a post-operative complication?	Not affected/Delayed/Modified/Omitted completely/Details
All adjuvant therapies	
Did any factors impact on time to delivery of adjuvant therapy?	Yes/No/Unsure
If yes, please tick any factors that apply	i. Post-operative complication (Yes/No) ii. Capacity issue – lack of medical oncology appointments (Yes/No) iii. Capacity issue – lack of clinical oncology (RT) appointments (Yes/No) iv. Capacity issue - lack of radiotherapy planning slots (Yes/No) v. Capacity issue – lack of chemotherapy delivery slots (Yes/No) vi. Capacity issue – lack of radiotherapy delivery slots (Yes/No) vii. Waiting for staging CT scan or results (Yes/No) viii. Waiting for staging bone scan or results (Yes/No) ix. Waiting for staging PET scan or results (Yes/No) x. Waiting for ECHO or results (Yes/No) xi. Awaiting Oncotype DX results (Yes/No) xii. Administrative delay – problems with booking appointments (Yes/No) xiii. Patient choice (Yes/No) xiv. Patient-related issue e.g. needing physio pre radiotherapy (Yes/No) xv. Other (Yes/No) – If yes, please give details

ADM – acellular dermal matrix; ASA – American society of Anesthesiology; BCS – breast conserving surgery; CT – computerised tomography scan; DCIS – ductal carcinoma in situ; DIEP – deep inferior epigastric perforator flap; ECHO – echocardiogram; ER – oestrogen receptor; HDU – high dependency unit; IBR – immediate breast reconstruction; IGAP – inferior gluteal artery perforator flap; LD – latissimus dorsi; ITU – intensive therapy unit; MDT – multidisciplinary team; OPF – oncoplastic fellow; PET – positron emission tomography scan; RT – radiotherapy; SAS – Staff, Associate Specialist and Speciality Doctors; SGAP – superior gluteal artery perforator flap; SIEA – superficial inferior epigastric artery perforator flap; TM – therapeutic mammaplasty; TRAM – transverse rectus abdominus myocutaneous flap; TUG – transverse upper gracilis flap; WLE – wide local excision

Table 3 – Definitions of complications

Surgical Complications Any complication occurring as a direct result of the mastectomy +/- breast reconstruction procedure		
Complication	**Definition**	**Classification/details**
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 (no GA) Major 2 – requiring surgical evacuation (under GA)
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.	Minor – requiring oral antibiotics Major 1 – requiring admission for IV antibiotics Major 2 – requiring surgical drainage or debridement (under GA)
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 surgical debridement (under GA)
Nipple necrosis	Any area of necrosis of the nipple areolar complex	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 – managed conservatively Major – requiring return to theatre for re-suturing
Implant loss	The unplanned and unexpected extirpation or loss of the implant including removal as a result of infection, seroma, haematoma or skin necrosis.	Yes/No
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 surgical debridement (under GA)
Impaired flap perfusion requiring return to theatre for exploration/revision of anastomosis	concerns regarding perfusion of the flap requiring a return to theatre for exploration +/- revision of the anastomosis	Yes/No
Flap necrosis	Any necrosis of the free/pedicled tissue flap used to reconstruct the breast	Partial flap necrosis requiring surgical debridement Total flap necrosis requiring removal of flap
Other complication	With details	Yes/No

In hospital complications Any complication occurring during the period patient is in hospital for their index mastectomy +/- reconstruction operation		
Complication	**Definition**	**Classification/details**
Deep vein thrombosis	A radiologically confirmed clot in the vessels of the lower limb treated with anticoagulation	Yes/No
Pulmonary embolism	A radiologically (CTPA or V/Q scan) confirmed clot in the lung treated with anticoagulation	Yes/No
Myocardial infarction	As confirmed by a rise in cardiac markers +/- ECG changes	Yes/No
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 (Yes/No)	Yes/No
Blood transfusion	Bleeding requiring blood transfusion following mastectomy +/- reconstructive surgery	Yes/No
Unplanned admission to intensive care/high dependency unit	Any unplanned admission to HDU/ITU following mastectomy +/- reconstructive surgery	Yes/No
Urinary tract infection	A microbiologically confirmed urinary tract infection	Yes/No
Surgical complication	As above	Yes/No
Other complication	Details	Yes/No
Readmission and re-operation		
Complication	**Definition**	**Classification/details**
Readmission	Any re-admission to hospital following discharge home prior to the delivery of the first adjuvant therapy OR in the 30 days following surgery in those not requiring chemo or radiotherapy directly related to the procedure with either local or systemic complications.	Yes/No If yes – date of readmission (day/month/year) Reason for readmission
Re-operation	Any return to the operating theatre prior to the delivery of the first adjuvant therapy OR in the 30 days following surgery to deal with any complication of the mastectomy or reconstruction.	Yes/No If yes – date of re-operation (day/month/year); Reason for re-operation

CTPA – computerised tomography pulmonary angiography; ECG – electrocardiogram; GA – general anaesthetic; HDU – high dependency unit; ITU – intensive therapy unit; IV – intravenous; V/Q-ventilation perfusion scan

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/). Advanced data logic will be used such that

only data fields relevant to the procedure and indication selected will be displayed in later data collection forms. It is anticipated this will reduce the burden of participation for collaborators and optimise the quality of data collected during the study.

The data forms will be extensively trialled in a three centre pilot prior to national roll-out of the study. This will validate the logic used; ensure the forms are complete and user-friendly and allow for any errors to be corrected prior to main study initiation.

Data validation and management

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. These cases will be selected at random. 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].

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 on a secure server 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 the University of Oxford[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.

Anticipated recruitment

The recent MASDA (MAStectomy Decisions Audit) Study (http://wmresearch.org.uk/) collected data on 1700 mastectomies +/- IBR from 68 centres 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 with implants and 90 free flaps based on figures from the NMBRA[51].

Study timelines

Data collection and analysis will be undertaken using the following time line.

- May-June 2016 – Three centre pilot study, refining of data collection forms
- March-June 2016 – Registration of interest from breast and plastic surgical units. Local audit approvals obtained. Participating centres will be required to have registered the study and obtained local approvals prior to the main study start date of 1st July 2016
- 1st July - 31st December 2016 – Main study patient recruitment – patients undergoing mastectomy +/- immediate breast reconstruction with operation dates between 1st July and 31st December 2016 are eligible for inclusion in the study.
- 28th February 2017 – deadline for data submission via REDCap
- 1st May 2017 – Data validation complete
- 30th June 2017 – Initial data analysis completed

Statistical analysis

The study report will be prepared according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for observational studies[53]. All data analysis will occur centrally 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.

All outcomes will be summarized using descriptive statistics overall and split by group (mastectomy +/- IBR). Dichotomous, categorical and short ordinal outcomes will be summarized using counts and percentages. Time to adjuvant therapy will be summarized using Kaplan-Meier curves. Continuous and long ordinal outcomes will be summarized by the mean, standard deviation, minimum and maximum (medians and interquartile ranges will be reported for skewed data).

Formal statistical testing for each outcome between groups (mastectomy +/- IBR) will be approached as follows: Rates of post-operative complications including readmission and re-operation; requirement for adjuvant therapy and delay or omission of planned adjuvant chemotherapy or radiotherapy 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. Time to the delivery of adjuvant therapy will be analysed using a log rank test. Delays to the delivery of adjuvant therapy will be analysed, controlling for risk factors of interest, using logistic regression model. 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.

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

DISCUSSION

Immediate breast reconstruction may improve psychosocial outcomes for women requiring a mastectomy for breast cancer, but more complex surgery may also result in complications that could delay the delivery of important adjuvant treatments and subsequently impact long-term oncological outcomes. As oncological safety is the central tenant of all oncoplastic surgery, the practice of IBR if adjuvant therapy is anticipated is an area of considerable controversy[54] and one for which high-quality evidence is currently lacking. The iBRA-2 study will generate much needed novel data regarding the impact of IBR on the time to delivery of adjuvant therapy compared with mastectomy alone. It will provide valuable information that may help patients and professionals make more informed decisions about the type and timing of their reconstructive surgery in the future. It will provide a large, robust prospective observational data set that will allow predictors for complications to be explored and generate hypotheses that will lead to further work in this area. The study will also generate valuable contemporaneous data relating to the practice of post-mastectomy radiotherapy (PMRT) following the emergence of data to suggest significant survival benefit in a group of women with one to three positive lymph nodes who would not traditionally have been offered treatment[55]. Finally, the study will provide a further data cycle following the National Mastectomy and Breast Reconstruction Audit[5, 78-80] to demonstrate whether surgical outcomes for women undergoing mastectomy and IBR have improved. If they have not, this will focus the attention of breast and plastic surgeons on relevant areas and highlight the need for future research.

It is anticipated that the iBRA-2 study will strengthen the collaborative network created by the iBRA (implant-breast reconstruction evaluation) study through the successful delivery of a second large-scale study in breast and reconstructive surgery. The study will reinforce the successful collaborative links between the breast and plastic surgical communities and create additional research capacity by broadening the network to include oncologists. The engagement and involvement of a wider community of trainees will lead to a new generation

of consultants who understand the importance of research and audit, who can and will participate in high-quality collaborative studies resulting in more and better research. We believe that this will ultimately improve outcomes for patients.

ETHICS AND DISSEMINATION

The proposed study will not affect clinical care and compares outcomes to published clinical standards. Research ethics approval is not required and this has been confirmed by the Health Research Authority (HRA) on-line decision tool (http://www.hra-decisiontools.org.uk/research/) and discussion with University of Bristol. A study lead will be identified at each participating centre. If the unit lead is a trainee, the named supervising consultant will act as the principal investigator for the unit for registration purposes. The study lead will be required to register the audit and obtain local audit approvals for study participation prior to commencing patient recruitment. A copy of the approval will be also forwarded to the iBRA-2 study team. Patient consent is not required as no patient identifiable data is being recorded and there is no risk to patients.

The protocol will be disseminated via the collaborative network including Mammary Fold Breast Trainees' Group, the Reconstructive Surgery Trials Network (RSTN), the Association of Surgeons in Training (ASiT) and the National Research Collaborative (NRC) as well as the professional associations the Association of Breast Surgery (ABS) and the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS). The protocol and data collection sheets will be available on line (www.ibrastudy.com). Individual centres will have access to their own data and 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 at the end of the audit. Overall audit results and results from individual centres will be fedback to ABS and BAPRAS.

Collective data will be analysed and the results of the study presented at appropriate scientific meetings and published in peer-reviewed journals. The results can then be used to inform patients and surgeons and aid decision-making for women considering breast reconstruction.

Authors' contributions

RD, ROC and TR contributed to the design and writing of the protocol, EC and PRW contributed to the study design and statistical analysis; JMB, NB, JS, AH, COB and MG contributed to study design and advised on methodology; CH and SP contributed to the conception, design, writing and editing of the protocol. All authors read and approved the final manuscript.

Ethical approval

Not required

Competing interests

The authors have no competing interests to declare.

Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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BMJ Open

The iBRA-2 (immediate Breast reconstruction And Adjuvant therapy Audit) Study – Protocol for a prospective national multi-centre cohort study to evaluate the impact of immediate breast reconstruction on the delivery of adjuvant therapy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012678.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Aug-2016
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	immediate breast reconstruction, adjuvant therapy, trainee collaboratives, cohort study, Breast tumours < ONCOLOGY

The iBRA-2 (*i*mmediate *B*reast reconstruction *A*nd *A*djuvant therapy *A*udit) Study – Protocol for a prospective national multi-centre cohort study to evaluate the impact of immediate breast reconstruction on the delivery of adjuvant therapy

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Keywords: Immediate breast reconstruction, adjuvant therapy, breast cancer, cohort study, trainee collaboratives

Word count: 2773 (excluding tables)

ABSTRACT

Introduction

Immediate breast reconstruction (IBR) is routinely offered to improve quality of life for women with breast cancer requiring a mastectomy, but there are concerns that more complex surgery may delay the delivery of adjuvant oncological treatments and compromise long-term oncological outcomes. High-quality evidence, however, is lacking. iBRA-2 is a national prospective multicentre cohort study that aims to investigate the effect of IBR on the delivery of adjuvant therapy.

Methods and analysis

Breast and plastic surgery centres in the UK performing mastectomy with or without (+/-) IBR will be invited to participate in the study through the trainee research collaborative network. All women undergoing mastectomy+/-IBR for breast cancer between 1st July and 31st December 2016 will be included. Patient demographics, operative, oncological and complication data will be collected. Time from last definitive cancer surgery to first adjuvant treatment for patients undergoing mastectomy+/-IBR will be compared to determine the impact that IBR has on the time of delivery of adjuvant therapy. Prospective data on 3000 patients from approximately 50 centres is anticipated.

Ethics and dissemination

Research ethics approval is not required for this study. This has been confirmed using the on-line Health Research Authority (HRA) decision tool. This novel study will explore whether IBR impacts the time to delivery of adjuvant therapy. The study will provide valuable information to help patients and surgeons make more informed decisions about their surgical options. Dissemination of the study protocol will be via the Mammary Fold Academic and Research Collaborative (MFAC) and the Reconstructive Surgery Trials Network (RSTN), the Association of Breast Surgery (ABS) and the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS). Participating units will have access to their own data

and collective results will be presented at relevant surgical conferences and published in appropriate peer-reviewed journals.

STRENGTHS AND WEAKNESSES

- Large multicentre prospective study involving data collection from breast and plastic surgical units across the UK
- Will produce valuable data regarding the impact of immediate breast reconstruction on the time to delivery of adjuvant therapy which will help inform decision-making for patients and surgeons
- Will strengthen the collaborative network between breast and plastic surgical trainees and consultants to facilitate the delivery of future research
- Observational design will not address causality
- Will not collect data on non-participating units
- Short-term data collection will not allow the long-term impact of delays to adjuvant therapy to be assessed

INTRODUCTION

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

Whilst IBR may improve psychosocial outcomes for women facing mastectomy, these benefits need to be 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 10% of patients undergoing mastectomy experiencing a post-operative complication compared with 11% of patients undergoing an implant-based procedures; 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 after discharge.

Complication rates following IBR are important as they may lead to the delay or omission of adjuvant cancer therapies in the form of adjuvant chemotherapy or biological therapy and post-mastectomy 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]. Similarly, delays to radiotherapy 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 eight 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 three 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 [and] within 31 days of completion of surgery in patients with early breast cancer having these treatments'[4].

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. Therefore there is a lack of high-quality evidence to demonstrate the impact of IBR on the delivery of adjuvant therapies compared with mastectomy alone. Randomised trials (RCTs) 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 potential treatment options.

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 (implant Breast Reconstruction evAluation) study (ISRCTN37664281)[45], a national prospective cohort study to explore the feasibility, design and conduct of a pragmatic RCT in implant-based breast surgery has demonstrated the trainee collaborative 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 anticipated that this network of highly-motivated and enthusiastic breast and plastic surgical trainees and consultants can be utilised to deliver a new study exploring the impact of IBR on the timing of adjuvant therapy.

METHODS AND ANALYSIS

Primary aim

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 to:

v. Identify risk factors of patients who experience a delay to or omission of their adjuvant therapy as a result of surgical complication
vi. Explore the impact of delay to adjuvant therapy on key oncological outcomes including locoregional recurrence; metastatic disease and breast cancer specific death at 5 and 10 years
vii. Generate high-quality data to inform decision-making for patients and health professionals
viii. Build and strengthen the collaborative network created by the iBRA study to include oncologists and build future research capacity

Hypothesis

Immediate breast reconstruction following mastectomy for breast cancer does not increase the time to delivery of adjuvant therapy compared with mastectomy alone.

Study design

We plan to undertake a national prospective multicentre cohort study using the research collaborative model previously reported[42, 43] coordinated by the iBRA-2 Steering Group.

Setting

Any breast or plastic surgical unit in the UK performing mastectomy with or without immediate breast reconstruction will be eligible to participate to the study. Units will be invited to participate in the study through the Association of Breast Surgery (ABS), the Mammary Fold breast trainees' group (MF), the Association of Surgeons in Training (ASiT), the Reconstructive Surgery Trials Network (RSTN), the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) and the national research collaborative network (NRCN).

Participants

Inclusion criteria: All women over the age of 18 who are undergoing a mastectomy with or without immediate reconstruction for pre-invasive or invasive breast cancer with curative intent.

Exclusion criteria: Women undergoing mastectomy for risk-reduction only; however women who are undergoing a contralateral risk-reducing mastectomy at the same time as a therapeutic mastectomy for invasive or pre-invasive disease may be included. Patients undergoing partial mastectomy including lumpectomy or wide local excision with volume replacement techniques (latissimus dorsi mini flaps; lateral intercostal perforator (LICAP) or thoracodorsal artery perforator (TDAP) flaps) or therapeutic mammoplasty and patients with distant metastatic disease will be excluded.

Outcome measures

The primary outcome measure will be time in days from last definitive cancer surgery to the first adjuvant treatment. The last definitive cancer surgery will most commonly be the index mastectomy procedure, but may include completion axillary clearance or re-excision of

margins as determined on review of the surgical pathology by the multidisciplinary team (MDT). Unplanned surgery such as implant explantation, debridement of skin necrosis, washout of haematoma or return to theatre for flap failure constitute complications and will not be classified as last definitive surgery for the purposes of this study. First adjuvant therapy will be defined as the first dose of chemotherapy or the first fraction of radiotherapy. Time to endocrine therapy will not be included. This definition is based on the National Institute for Health and Care Excellence guidance for early and locally advanced breast cancer [CG80] which states that adjuvant chemotherapy or radiotherapy should be started 'as soon as clinically possible [and] within 31 days of completion of surgery in patients with early breast cancer having these treatments'[4]. In patients for whom more than one modality of adjuvant treatment is recommended, only the start date for the first adjuvant therapy will be recorded. Secondary outcomes are listed in table 1.

Table 1: Secondary outcome measures

Outcome measure	Definition
Post-operative complications	Any post-operative complication occurring before the 1st adjuvant treatment OR within 30 days of surgery for patients not requiring adjuvant chemo or radiotherapy. To be classified by the Clavien-Dindo classification of complications as applied to breast surgery[46] with specific reference to: *Mastectomy and breast reconstruction specific complications:* Seroma; haematoma; infection; mastectomy skin flap necrosis; nipple necrosis; wound dehiscence; implant loss; donor site skin necrosis; flap salvage; partial and full flap necrosis/failure. *Systemic complications:* Deep vein thrombosis, pulmonary embolism, myocardial infarction; lower respiratory tract infection; blood transfusion; unplanned admission to high dependency or intensive therapy units; urinary tract infection.
Re-admission to hospital	Any re-admission to hospital following discharge home after mastectomy+/- immediate breast reconstruction surgery directly related to the procedure with either local or systemic complications in the time prior to the delivery of the first adjuvant treatment OR within 30 days of surgery in those not requiring chemo or radiotherapy.
Unplanned re-operation/return to theatre	Any unplanned re-operation or return to the operating theatre prior to the delivery of the first adjuvant therapy OR in the 30 days following surgery to deal with any complication of the mastectomy or reconstruction. Any planned return to theatre for additional oncological surgery, such as completion axillary clearance, as decided by the multi-disciplinary team on review of surgical pathology will NOT be included in this category.
Use of adjuvant therapy	Number (proportion) of patients undergoing mastectomy +/- immediate breast reconstruction who require adjuvant i. Chemotherapy ii. Biological therapy

	iii. Radiotherapy
Omission, modification or delay of adjuvant therapy	Number (proportion) of patients undergoing mastectomy +/- immediate breast reconstruction whose planned adjuvant chemotherapy/biological therapy or radiotherapy is i. Omitted (not given, despite MDT recommendation) ii. Modified (dose/regimen changed from planned/standard treatment) iii. Delayed (not given at time scheduled following oncology appointment) as a result of a post-operative complication
Long-term oncological outcomes	Number (proportion) of patients with and without a delay or omission of planned adjuvant chemotherapy or radiotherapy who at 5 and 10 years following their initial surgery experience i. Locoregional recurrence, defined as a histologically confirmed breast cancer recurrence within the ipsilateral breast or axilla ii. Distant metastasis, defined as radiologically or histologically confirmed distant metastatic breast cancer iii. Breast cancer specific-death, defined as death directly attributed to the disease

Data collection

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 (MDT) 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 meeting.

For patients in whom adjuvant therapy is recommended at the post-operative MDT meeting, 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, re-admission and re-operation 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. Preliminary work suggests that, despite NICE guidelines, adjuvant therapy is unlikely to commence earlier than six weeks post-operatively. For patients not requiring or electing not to receive adjuvant therapy, therefore, data collection will continue for six weeks following their last definitive cancer surgery either by clinical or note review in those not attending for follow-up. The

required data fields are shown in Table 2 and definitions and categorisation of complications summarised in Table 3.

Oncological outcomes (locoregional recurrence, distant metastasis and breast cancer specific death) will be evaluated at five and ten years following initial surgery by searching the UK Cancer Registry database. This phase of the study will be undertaken centrally by the iBRA-2 study team subject to appropriate ethical approval.

Table 2 – Data fields for the iBRA-2 Study

Section 1 - Demographic data	
Field	**Options (definitions)**
Age	Age at diagnosis in years
Height	In metres
Weight	In kilograms
Body mass index	Actual BMI will be collected and categorised as -Underweight (<18.5 kg/m^2)/Normal weight (18.5-24.9 kg/m^2)/Overweight (25-29.9 kg/m^2)/Obese (30-34.9 kg/m^2)/Severely obese (35-39.9 kg/m^2) Morbid obesity (>40 kg/m^2)
Smoking status	Current smoker/Ex-smoker >6 weeks/Non-smoker
Diabetic	Yes/No
Other co-morbidities	Ischaemic heart disease (yes/no); Current steroid therapy (yes/no); Other immunosuppressive therapy (yes/no); Connective tissue disease (yes/no); Other co-morbidity (yes/no) with details
Prior and neoadjuvant treatments	
Previous radiotherapy to ipsilateral breast	Yes/No
Neoadjuvant chemotherapy within 4-6 weeks of surgery	Yes/No
Neoadjuvant endocrine therapy	Yes/No
Neoadjuvant radiotherapy	Yes/No
Previous surgery to ipsilateral breast	Wide local excision (yes/no, if yes, date MM/YY); Therapeutic mammaplasty (yes/no, if yes, date MM/YY); Breast reduction (yes/no, if yes, date MM/YY); Breast augmentation (yes/no, if yes, date MM/YY); Other (yes/no, if yes, date MM/YY): State procedure
Previous surgery to ipsilateral axilla	Sentinel node biopsy with wide local excision (yes/no, if yes, date MM/YY); Stand-alone sentinel node biopsy (yes/no, if yes, date MM/YY); Axillary sample (yes/no, if yes, date MM/YY); Axillary clearance (yes/no, if yes, date MM/YY)
Section 2 – Operative data	
Date of mastectomy +/- reconstruction	Day/month/year
ASA grade	1 – Normal healthy individual 2 – Mild systemic disease that does not limit activities 3 – Severe systemic disease that limits activities but is not incapacitating 4 – Incapacitating systemic disease which is constantly life threatening
Antibiotic use	Prophylactic (<24 hours)/1-5 days/extended course (5+days)/until drains removed/Other
Type of skin prep used at time of surgery	Iodine/Chlorhexidine/2% chlorprep/Other

Procedure details collected for RIGHT and LEFT breasts separately.	
Procedure performed	None Mastectomy only Skin-sparing (nipple sacrificing) mastectomy and immediate breast reconstruction Nipple-sparing mastectomy and immediate breast reconstruction Skin reducing (Wise pattern) mastectomy and immediate breast reconstruction Wide local excision Reduction/mastopexy Augmentation
If IBR, type of reconstruction performed	Implant-based/Pedicled flap/Free flap/Other
If patient undergoing implant reconstruction	
Implant reconstruction – planned procedure	One-stage reconstruction – insertion of permanent implant at initial surgery Two-stage reconstruction – insertion of a tissue expander to be followed by insertion of a definitive implant Immediate-delayed reconstruction – insertion of a temporary expander in patients for whom radiotherapy is anticipated with a plan to perform a definitive autologous (tissue-based) reconstruction after radiotherapy is complete.
Mode of lower pole coverage	None/Fascial or complete submuscular coverage/Dermal sling/Biological mesh (e.g. Strattice)/Synthetic mesh (e.g. TiLOOP)/Pre-pectoral implant with total ADM coverage e.g. BRAXON/Pre-pectoral implant with dermal sling/ADM
Details of product for lower pole coverage	Stattice/SurgiMend/Native/BioDesign/Veritas/SERI/TiLOOP/TIGR/Other
Prosthesis details	Fixed volume implant (size in ccs) Temporary expander (volume of saline inserted in mls) Combined implant e.g. Beckers (silicone component (g), size when fully expanded, volume of saline inserted in mls) Polyurethene implant (yes/no)
If patient undergoing flap based reconstruction	
Type of pedicled flap performed	Autologous LD flap (no implant)/LD with implant/Pedicled TRAM/Other
If LD with implant, prosthesis details	Fixed volume implant (size in ccs) Temporary expander (volume of saline inserted in mls) Combined implant e.g. Beckers (silicone component (g), size when fully expanded, volume of saline inserted in mls) Polyurethene implant (yes/no)
Type of free flap performed	Free TRAM/DIEP/SIEA/SGAP/IGAP/TUG/Other
Indication for surgery	Malignancy (invasive/DCIS) – first operation/Malignancy (invasive/DCIS) – following failed BCS (WLE/TM)/Risk reduction/Symmetrisation
If failed BCS (positive margins) date of initial surgery	Day/month/year
Grade of primary operating surgeon	Consultant/SAS doctor/Senior trainee (ST8+ or OPF)/ST6-7/ST5 or below
Mastectomy weight	Grams
Axillary surgery	None/Sentinel node biopsy/Axillary sample/Axillary clearance/Previous axillary staging
Section 3 – Post-operative oncology and MDT outcomes Pathology details for RIGHT and LEFT breasts will be collected separately.	
For patients having neoadjuvant chemotherapy, complete pathological response?	Yes/No
Invasive status	Invasive/DCIS
Grade of invasive disease/DCIS	1 – Low grade (DCIS) or well-differentiated (invasive) 2 – Intermediate grade (DCIS) or moderately differentiated (invasive) 3 – High grade (DCIS) or poorly differentiated (invasive)
Histological type	Ductal/Lobular/Mixed/Other

Number of tumours	Single tumour or Multifocal/centric tumours
Size of invasive tumour	Mm (largest if >1 ipsilateral tumour)
Total size of lesion including DCIS	In pathological specimen (mm) On pre-treatment diagnostic imaging (if neoadjuvant therapy) (mm)
Receptor status	ER – positive/negative/not known HER-2 – positive/negative/not known Ki67 – high/low/not known
Lymphovascular invasion	Yes/No/Not known
Lymph node involvement	Number of involved lymph nodes (macro-metastases only) Total number of lymph nodes in pathological specimen
Plan from the therapeutic (post-operative) MDT	
Date of post-operative MDT	Day/month/year
Further oncological surgery required	No/Completion axillary clearance/Re-excision of margins/Other
Surgery, planned before adjuvant therapy	Yes with date (day/month/year)
Treatments recommended	
Chemotherapy	Recommended by MDT/Not recommended by MDT/For discussion with patient/For Oncotype DX testing/Chemotherapy already received
Biological therapy (e.g Herceptin)	Recommended by MDT/Not recommended by MDT
Radiotherapy to chest wall	Recommended by MDT/Not recommended by MDT/For discussion with patient/Already received
If radiotherapy recommended	With boost (yes/no)/To supraclavicular fossa (yes/no)/To axilla (yes/no)
Endocrine therapy	Recommended by MDT/Not recommended by MDT
Section 4 – Complication data Please record any complications that occur BEFORE the start of adjuvant therapy OR in the first six weeks following surgery in patients not requiring chemo or radiotherapy.	
Post-operative complication experienced	Yes/No
If yes – details of surgical complications experienced (see table 3 for definitions)	Seroma/haematoma/infection/mastectomy skin flap necrosis/nipple necrosis/wound dehiscence/implant loss/donor site skin necrosis/impaired flap perfusion requiring return to theatre for exploration or revision of anastomosis (flap salvage)/flap necrosis/other complication
In hospital complications including systemic complications	Yes/No
If yes, complication(s) experienced (see table 3 for definitions)	Deep vein thrombosis/pulmonary embolism/myocardial infarction/lower respiratory tract infection/blood transfusion/ unplanned admission to intensive care/high dependency unit/urinary tract infection/surgical complication/other complication
Readmission to hospital	Yes/No If yes – date of readmission (day/month/year) Reason for readmission
Return to theatre/re-operation	Yes/No If yes – date of re-operation (day/month/year); Reason for re-operation
Section 5 – Adjuvant therapy data This section documents the time from **LAST CANCER SURGERY** to **FIRST ADJUVANT TREATMENT** i.e. first dose of chemotherapy or first fraction of radiotherapy.	
Date of last definitive cancer surgery	Day/month/year
Chemotherapy	
Chemotherapy – if offered	Patient accepts/Patient declines
Oncotype DX risk stratification	High risk/Intermediate risk/Low risk
Chemotherapy recommended based on Oncotype DX score	Yes/No
Actual chemotherapy start date	Day/Month/Year
Was planned treatment modified, delayed or omitted (not given) due to a post-operative complication?	Not affected/Delayed/Modified/Omitted completely/Details

Radiotherapy	
Radiotherapy - if offered	Patient accepts/Patient declines
Actual radiotherapy start date	Day/Month/Year
Was planned treatment modified, delayed or omitted (not given) due to a post-operative complication?	Not affected/Delayed/Modified/Omitted completely/Details
All adjuvant therapies	
Did any factors impact on time to delivery of adjuvant therapy?	Yes/No/Unsure
If yes, please tick any factors that apply	i. Post-operative complication (Yes/No) ii. Capacity issue – lack of medical oncology appointments (Yes/No) iii. Capacity issue – lack of clinical oncology (RT) appointments (Yes/No) iv. Capacity issue - lack of radiotherapy planning slots (Yes/No) v. Capacity issue – lack of chemotherapy delivery slots (Yes/No) vi. Capacity issue – lack of radiotherapy delivery slots (Yes/No) vii. Waiting for staging CT scan or results (Yes/No) viii. Waiting for staging bone scan or results (Yes/No) ix. Waiting for staging PET scan or results (Yes/No) x. Waiting for ECHO or results (Yes/No) xi. Awaiting Oncotype DX results (Yes/No) xii. Administrative delay – problems with booking appointments (Yes/No) xiii. Patient choice (Yes/No) xiv. Patient-related issue e.g. needing physio pre radiotherapy (Yes/No) xv. Other (Yes/No) – If yes, please give details

ADM – acellular dermal matrix; ASA – American society of Anesthesiology; BCS – breast conserving surgery; CT – computerised tomography scan; DCIS – ductal carcinoma in situ; DIEP – deep inferior epigastric perforator flap; ECHO – echocardiogram; ER – oestrogen receptor; HDU – high dependency unit; IBR – immediate breast reconstruction; IGAP – inferior gluteal artery perforator flap; LD – latissimus dorsi; ITU – intensive therapy unit; MDT – multidisciplinary team; OPF – oncoplastic fellow; PET – positron emission tomography scan; RT – radiotherapy; SAS – Staff, Associate Specialist and Speciality Doctors; SGAP – superior gluteal artery perforator flap; SIEA – superficial inferior epigastric artery perforator flap; TM – therapeutic mammaplasty; TRAM – transverse rectus abdominus myocutaneous flap; TUG – transverse upper gracilis flap; WLE – wide local excision

Table 3 – Definitions of complications

Surgical Complications Any complication occurring as a direct result of the mastectomy +/- breast reconstruction procedure		
Complication	**Definition**	**Classification/details**
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 (no GA) Major 2 – requiring surgical evacuation (under GA)
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.	Minor – requiring oral antibiotics Major 1 – requiring admission for IV antibiotics Major 2 – requiring surgical drainage or debridement (under GA)
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 surgical debridement (under GA)
Nipple necrosis	Any area of necrosis of the nipple	Minor – managed conservatively with dressings

	areolar complex	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 – managed conservatively Major – requiring return to theatre for re-suturing
Implant loss	The unplanned and unexpected extirpation or loss of the implant including removal as a result of infection, seroma, haematoma or skin necrosis.	Yes/No
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 surgical debridement (under GA)
Impaired flap perfusion requiring return to theatre for exploration/revision of anastomosis	concerns regarding perfusion of the flap requiring a return to theatre for exploration +/- revision of the anastomosis	Yes/No
Flap necrosis	Any necrosis of the free/pedicled tissue flap used to reconstruct the breast	Partial flap necrosis requiring surgical debridement Total flap necrosis requiring removal of flap
Other complication	With details	Yes/No
In hospital complications Any complication occurring during the period patient is in hospital for their index mastectomy +/- reconstruction operation		
Complication	**Definition**	**Classification/details**
Deep vein thrombosis	A radiologically confirmed clot in the vessels of the lower limb treated with anticoagulation	Yes/No
Pulmonary embolism	A radiologically (CTPA or V/Q scan) confirmed clot in the lung treated with anticoagulation	Yes/No
Myocardial infarction	As confirmed by a rise in cardiac markers +/- ECG changes	Yes/No
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 (Yes/No)	Yes/No
Blood transfusion	Bleeding requiring blood transfusion following mastectomy +/- reconstructive surgery	Yes/No
Unplanned admission to intensive care/high dependency unit	Any unplanned admission to HDU/ITU following mastectomy +/- reconstructive surgery	Yes/No
Urinary tract infection	A microbiologically confirmed urinary tract infection	Yes/No
Surgical complication	As above	Yes/No
Other complication	Details	Yes/No
Readmission and re-operation		
Complication	**Definition**	**Classification/details**

Readmission	Any re-admission to hospital following discharge home prior to the delivery of the first adjuvant therapy OR in the 30 days following surgery in those not requiring chemo or radiotherapy directly related to the procedure with either local or systemic complications.	Yes/No If yes – date of readmission (day/month/year) Reason for readmission
Re-operation	Any return to the operating theatre prior to the delivery of the first adjuvant therapy OR in the 30 days following surgery to deal with any complication of the mastectomy or reconstruction.	Yes/No If yes – date of re-operation (day/month/year); Reason for re-operation

CTPA – computerised tomography pulmonary angiography; ECG – electrocardiogram; GA – general anaesthetic; HDU – high dependency unit; ITU – intensive therapy unit; IV – intravenous; V/Q-ventilation perfusion scan

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/). Advanced data logic will be used such that only data fields relevant to the procedure and indication selected will be displayed in later data collection forms. It is anticipated this will reduce the burden of participation for collaborators and optimise the quality of data collected during the study.

The data forms will be extensively trialled in a three centre pilot prior to national roll-out of the study. This will validate the logic used; ensure the forms are complete and user-friendly and allow for any errors to be corrected prior to main study initiation.

Participating centres will be required to maintain and securely store an Excel spreadsheet linking study ID numbers with patient NHS numbers to allow long-term oncological outcomes to be evaluated at five and ten years post-operatively

Data validation and management

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. These cases will be selected at random. 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].

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 on a secure server 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.

Following the completion of data collection, appropriate ethical approvals will be obtained to allow the spreadsheets linking study ID to NHS number to be collated centrally. Only centres with ethical approval will be permitted to contribute to this phase of the study. The data will be stored securely in a central location until five years following study completion. Oncological outcomes will be then be determined using a UK Cancer Registry search. This search will be repeated to determine 10 year oncological outcomes.

Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Oxford[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.

Anticipated recruitment

The recent MASDA (MAStectomy Decisions Audit) Study (http://wmresearch.org.uk/) collected data on 1700 mastectomies +/- IBR from 68 centres 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 with implants and 90 free flaps based on figures from the NMBRA[51].

Study timelines

Data collection and analysis will be undertaken using the following time line.

- May-June 2016 – Three centre pilot study, refining of data collection forms
- March-June 2016 – Registration of interest from breast and plastic surgical units. Local audit approvals obtained. Participating centres will be required to have registered the study and obtained local approvals prior to the main study start date of 1st July 2016
- 1st July - 31st December 2016 – Main study patient recruitment – patients undergoing mastectomy +/- immediate breast reconstruction with operation dates between 1st July and 31st December 2016 are eligible for inclusion in the study.
- 28th February 2017 – deadline for data submission via REDCap
- 1st May 2017 – Data validation complete
- 30th June 2017 – Initial data analysis completed
- July 2017 – Ethical approval to store patient NHS numbers to evaluate oncological outcomes
- Early 2021 – Assessment of 5 year oncological outcomes
- Early 2027 – Assessment of 10 year oncological outcomes

Statistical analysis

The study report will be prepared according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for observational studies[53]. All data analysis will occur centrally 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.

All outcomes will be summarized using descriptive statistics overall and split by group (mastectomy +/- IBR). Dichotomous, categorical and short ordinal outcomes will be summarized using counts and percentages. Time to adjuvant therapy will be summarized using Kaplan-Meier curves. Continuous and long ordinal outcomes will be summarized by the mean, standard deviation, minimum and maximum (medians and interquartile ranges will be reported for skewed data).

Formal statistical testing for each outcome between groups (mastectomy +/- IBR) will be approached as follows: Rates of post-operative complications including readmission and re-operation; requirement for adjuvant therapy and delay or omission of planned adjuvant chemotherapy or radiotherapy 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. Time to the delivery of adjuvant therapy will be analysed using a log rank test. Delays to the delivery of adjuvant therapy will be analysed, controlling for risk factors of interest, using logistic regression model. 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.

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

The statistical analysis of the five and ten year oncological outcomes will be planned following completion of the initial phase of the study.

DISCUSSION

Immediate breast reconstruction may improve psychosocial outcomes for women requiring a mastectomy for breast cancer, but more complex surgery may also result in complications that could delay the delivery of important adjuvant treatments and subsequently impact long-term oncological outcomes. As oncological safety is the central tenant of all oncoplastic surgery, the practice of IBR if adjuvant therapy is anticipated is an area of considerable controversy[54] and one for which high-quality evidence is currently lacking. The iBRA-2 study will generate much needed novel data regarding the impact of IBR on the time to delivery of adjuvant therapy compared with mastectomy alone. It will provide valuable information that may help patients and professionals make more informed decisions about the type and timing of their reconstructive surgery in the future. It will provide a large, robust prospective observational data set that will allow predictors for complications to be explored and generate hypotheses that will lead to further work in this area. The study will also generate valuable contemporaneous data relating to the practice of post-mastectomy radiotherapy (PMRT) following the emergence of data to suggest significant survival benefit in a group of women with one to three positive lymph nodes who would not traditionally have been offered treatment[55]. The proposed assessment of loco-regional recurrence, distant metastases and breast cancer specific survival at five and 10 years following surgery will provide much needed high-quality data to determine the impact of delays to adjuvant therapy on key oncological outcomes which will support decision-making and practice. Finally, the study will provide a further data cycle following the National Mastectomy and Breast Reconstruction Audit[5, 78-80] to demonstrate whether surgical outcomes for women undergoing mastectomy and IBR have improved. If they have not, this will focus the attention of breast and plastic surgeons on relevant areas and highlight the need for future research.

It is anticipated that the iBRA-2 study will strengthen the collaborative network created by the iBRA (implant-breast reconstruction evaluation) study through the successful delivery of a second large-scale study in breast and reconstructive surgery. The study will reinforce the successful collaborative links between the breast and plastic surgical communities and

create additional research capacity by broadening the network to include oncologists. The engagement and involvement of a wider community of trainees will lead to a new generation of consultants who understand the importance of research and audit, who can and will participate in high-quality collaborative studies resulting in more and better research. We believe that this will ultimately improve outcomes for patients.

The potential challenges to the success of this project require consideration. The proposed data set is complex and there is the risk of incomplete data. To address this, we will extensively pilot the data collection tools prior to study commencement. This will allow any redundant fields to be removed and any ambiguities clarified to optimize data quality. Furthermore, the REDCap data management system [47] will be used for data collection. This system has the functionality to include complex logic such that only fields relevant to the procedure or indication initially entered are displayed in subsequent forms. It is anticipated that this will minimize the burden of data collection for local participants. Defining a 'delay' to adjuvant treatment is also a potential challenge as different centres may record their 'decision to treat' at different points in the patient's post-operative recovery, especially if post-operative complications are experienced. For this reason, we will collect 'time to adjuvant therapy' in the study. This is defined as the time (in days) from the last cancer surgery to the first dose of chemotherapy or fraction of radiotherapy. It is anticipated that this will allow any potential local biases to be addressed and comparable data to be obtained so that the true impact of immediate breast reconstruction on time to adjuvant therapy can be determined.

ETHICS AND DISSEMINATION

The proposed study will not affect clinical care and compares outcomes to published clinical standards. Research ethics approval is not required and this has been confirmed by the Health Research Authority (HRA) on-line decision tool (http://www.hra-decisiontools.org.uk/research/) and discussion with University of Bristol. A study lead will be identified at each participating centre. If the unit lead is a trainee, the named supervising consultant will act as the principal investigator for the unit for registration purposes. The

study lead will be required to register the audit and obtain local audit approvals for study participation prior to commencing patient recruitment. A copy of the approval will be also forwarded to the iBRA-2 study team. Patient consent is not required as no patient identifiable data is being recorded and there is no risk to patients.

Oncological outcomes will be determined by searching the UK Cancer Registry database at five and ten years post-operatively. Following completion of the audit phase of the study, proportionate ethical approval will be sought to collect the locally maintained spreadsheets linking study ID number to patient NHS numbers from participating centres. These data will be stored securely on a University of Bristol server until five years at which point the first search will be performed. Only centres will appropriate ethical approvals will be able to contribute their data to this phase of the study.

The protocol will be disseminated via the collaborative network including Mammary Fold Breast Trainees' Group, the Reconstructive Surgery Trials Network (RSTN), the Association of Surgeons in Training (ASiT) and the National Research Collaborative (NRC) as well as the professional associations the Association of Breast Surgery (ABS) and the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS). The protocol and data collection sheets will be available on line (www.ibrastudy.com). Individual centres will have access to their own data and 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 at the end of the audit. Overall audit results and results from individual centres will be fedback to ABS and BAPRAS.

Collective data will be analysed and the results of the study presented at appropriate scientific meetings and published in peer-reviewed journals. The results can then be used to inform patients and surgeons and aid decision-making for women considering breast reconstruction.

Authors' contributions

RD, ROC and TR contributed to the design and writing of the protocol, EC and PRW contributed to the study design and statistical analysis; JMB, NB, JS, AH, COB and MG contributed to study design and advised on methodology; CH and SP contributed to the conception, design, writing and editing of the protocol. All authors read and approved the final manuscript.

Ethical approval

Not required for the main study.

Proportionate ethical approval will be sought to evaluate long-term oncological outcomes by searching the UK Cancer Registry database.

Competing interests

The authors have no competing interests to declare.

Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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