The iBRA-2 (immediate breast reconstruction and adjuvant therapy audit) study: protocol for a prospective national multicentre cohort study to evaluate the impact of immediate breast reconstruction on the delivery of adjuvant therapy

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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 1 July and 31 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 ∼50 centres are anticipated.

Ethics and dissemination: Research ethics approval is not required for this study. This has been confirmed using the online Health Research Authority 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.

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

Strengths and limitations of this study

- 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.
- Short-term data collection will not allow the long-term impact of delays to adjuvant therapy to be assessed.

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of breast can profoundly impact a woman’s quality of life and body image. Immediate breast reconstruction (IBR) is routinely offered in the UK to improve outcomes.

While 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 stepwise increase in complication rates with procedure complexity: 10% of patients undergoing mastectomy experiencing a postoperative 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. These complication rates are likely to represent an underestimation of the burden of postoperative 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 therapies in the form of adjuvant chemotherapy or biological therapy and postmastectomy radiotherapy. The clinical significance of short delays is unclear, but delays of between 7 and 12 weeks 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 4-week delay in the delivery of adjuvant chemotherapy. Similarly, delays to radiotherapy adversely impact oncological outcomes, although the timeframes are less well established. An early meta-analysis suggested an increased risk of locoregional recurrence if radiotherapy was delayed by more than 8 weeks following surgery. More recent studies, however, suggest there to be no adverse effect on disease-free or overall survival if radiotherapy is started within 3 months of surgery, with one large UK cohort study showing no deleterious effects with delays of up to 20 weeks. To ensure timely delivery of adjuvant therapies, the National Institute of Health and Care Excellence (NICE) recommends 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.

Evidence regarding the impact of IBR on the delivery of adjuvant therapy, however, is inconsistent. Observational studies have generated conflicting results, and a recent systematic review 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 on. 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 controlled 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-effective and cost-effective means of delivering high-quality prospective research and audit. The ongoing iBRA (implant Breast Reconstruction eValuation) study (ISRCTN37664281), 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 used 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 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:

1. the rate of postoperative complications,
2. the requirement for adjuvant chemotherapy and/or radiotherapy,
3. the experience of a delay to or omission of their adjuvant therapy as a result of a surgical complication,
4. the time to adjuvant therapy.

Other non-comparative objectives are to:

5. identify risk factors of patients who experience a delay to or omission of their adjuvant therapy as a result of surgical complication,
6. 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,
7. generate high-quality data to inform decision-making for patients and health professionals,
8. build and strengthen the collaborative network created by the iBRA study to include oncologists and build future research capacity.

Hypothesis

IBR 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 by the iBRA-2 Steering Group.

Setting
Any breast or plastic surgical unit in the UK performing mastectomy with or without IBR 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 preinvasive 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 or thoraco-dorsal artery perforator 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 the start date for the first adjuvant therapy will be recorded. Secondary outcomes are listed in Table 1.

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, MDT meetings and theatre lists.

Simple demographic, comorbidity, operative and oncology data will be collected on all patients. Decisions regarding the recommendation for adjuvant treatment will be identified from the postoperative MDT meeting.

For patients in whom adjuvant therapy is recommended at the postoperative 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 begins 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 start earlier than 6 weeks postoperatively. For patients not requiring or electing not to receive adjuvant therapy, therefore, data collection will continue for 6 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 5 and 10 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.

Data will be recorded in an anonymised format using a unique alphanumerical study identification number on a secure web-based database (REDCap) designed by Vanderbilt University (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 rollout 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 5 and 10 years postoperatively.
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, ~5% of the data sets 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 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.

Table 1 Secondary outcome measures

| Outcome measure | Definition |
|-----------------|------------|
| Postoperative complications | Any postoperative complication occurring before the first adjuvant treatment or within 30 days of surgery for patients not requiring adjuvant chemotherapy or radiotherapy. To be classified by the Clavien-Dindo classification of complications as applied to breast surgery46 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. |
| Readmission to hospital | Any readmission 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 reoperation/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 multidisciplinary 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 therapy. Chemotherapy, Biological therapy, 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 omitted (not given, despite MDT recommendation), modified (dose/regimen changed from planned/standard treatment), delayed (not given at time scheduled following oncology appointment) as a result of a postoperative 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: Locoregional recurrence, defined as a histologically confirmed breast cancer recurrence within the ipsilateral breast or axilla. Distant metastasis, defined as radiologically or histologically confirmed distant metastatic breast cancer. Breast cancer specific-death, defined as death directly attributed to the disease. |
Table 2  Data fields for the iBRA-2 study

| Field | Options (definitions) |
|-------|-----------------------|
| **Section 1: demographic data** | |
| 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/m²)/normal weight (18.5–24.9 kg/m²)/overweight (25–29.9 kg/m²)/obese (30–34.9 kg/m²)/severely obese (35–39.9 kg/m²)/morbid obesity (>40 kg/m²) |
| Smoking status | Current smoker/ex-smoker >6 weeks/non-smoker |
| Diabetic | Yes/no |
| Other comorbidities | Ischaemic heart disease (yes/no); current steroid therapy (yes/no); other immunosuppressive therapy (yes/no); connective tissue disease (yes/no); other comorbidity (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 the 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 | 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 |
### Section 2: operative data

**Date of mastectomy±reconstruction** Day/month/year

| Mode of lower pole coverage | None/fascial or complete submuscular coverage/dermal sling/biological mesh (eg, Strattice)/synthetic mesh (eg, TiLOOP)/prepectoral implant with total ADM coverage, for example, BRAXON/prepectoral 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 ml) Combined implant, for example, Beckers (silicone component (g), size when fully expanded, volume of saline inserted in ml) 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 ml) Combined implant, for example, Beckers (silicone component (g), size when fully expanded, volume of saline inserted in ml) 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: postoperative 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 pretreatment 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 (postoperative) MDT**

| Date of postoperative 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 (eg, Herceptin) | Recommended by MDT/not recommended by MDT/for discussion with patient/already received |
| Radiotherapy to chest wall | Recommended by MDT/not recommended by MDT/for discussion with patient/already received |

Continued
Table 2  Continued

**Section 3: postoperative oncology and MDT outcomes**

| Clinical Details | Yes/no |
|------------------|--------|
| Pathology details for RIGHT and LEFT breasts will be collected separately |        |
| For patients having neoadjuvant chemotherapy, complete pathological response? | Yes/no |
| 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 6 weeks following surgery in patients not requiring chemotherapy or radiotherapy

| Complication | Yes/no |
|--------------|--------|
| Postoperative complication experienced |        |
| 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 |
| Inhospital 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 |
| Return to theatre/reoperation | If yes—date of readmission (day/month/year); reason for readmission |

**Section 5: adjuvant therapy data**

This section documents the time from LAST CANCER surgery to FIRST ADJUVANT treatment, that is, first dose of chemotherapy or first fraction of radiotherapy

| Clinical Details | Day/month/year |
|------------------|----------------|
| Date of last definitive cancer surgery | Patient accepts/patient declines |
| Chemotherapy—if offered | High risk/intermediate risk/low risk |
| Oncotype DX risk stratification | Yes/no |
| Chemotherapy recommended based on Oncotype DX score | Day/month/year |
| Actual chemotherapy start date | Not affected/delayed/modified/omitted completely/details |
| Was planned treatment modified, delayed or omitted (not given) due to a postoperative complication? |        |
| Radiotherapy | Patient accepts/patient declines |
| Radiotherapy—if offered | Day/month/year |
| Actual radiotherapy start date | Not affected/delayed/modified/omitted completely/details |
| Was planned treatment modified, delayed or omitted (not given) due to a postoperative complication? |        |
| All adjuvant therapies | Yes/no/unsure |
| Did any factors impact on time to delivery of adjuvant therapy? |        |
| If yes, please tick any factors that apply | 1. Postoperative complication (yes/no) |
| | 2. Capacity issue—lack of medical oncology appointments (yes/no) |
| | 3. Capacity issue—lack of clinical oncology (RT) appointments (yes/no) |
| | 4. Capacity issue—lack of radiotherapy planning slots (yes/no) |
| | 5. Capacity issue—lack of chemotherapy delivery slots (yes/no) |
| | 6. Capacity issue—lack of radiotherapy delivery slots (yes/no) |
| | 7. Waiting for staging CT scan or results (yes/no) |
| | 8. Waiting for staging bone scan or results (yes/no) |
| | 9. Waiting for staging PET scan or results (yes/no) |
Table 2  Continued

| Section 5: adjuvant therapy data | Day/month/year |
|---------------------------------|----------------|
| This section documents the time from LAST CANCER surgery to FIRST ADJUVANT treatment, that is, first dose of chemotherapy or first fraction of radiotherapy | |
| Date of last definitive cancer surgery | |

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; ITU, intensive therapy unit; LD, latissimus dorsi; MDT, multidisciplinary team; OPF, oncoplastic fellow; PET, positron emission tomography scan; RT, radiotherapy; SAS, Staff, Associate Specialist and Specialty Doctors; SGAP, superior gluteal artery perforator flap; SIEA, superficial inferior epigastric artery perforator flap; TM, therapeutic mammoplasty; TRAM, transverse rectus abdominus myocutaneous flap; TUG, transverse upper gracilis flap; WLE, wide-local excision.

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. 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 3-month period. It is therefore anticipated that given its increased complexity, the iBRA-2 study will recruit ~3000 patients over a 6-month period. Assuming an IBR rate of 21%, this should include ~630 reconstructions comprising ~220 implant-only reconstructions; 170 autologous pedicled flaps; 130 pedicled flaps with implants and 90 free flaps based on figures from the NMBRA.

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 1 July 2016.
- 1 July—31 December 2016—Main study patient recruitment—patients undergoing mastectomy ± IBR with operation dates between 1 July and 31 December 2016 are eligible for inclusion in the study.
- 28 February 2017—deadline for data submission via REDCap.
- 1 May 2017—Data validation complete.
- 30 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. 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 summarised using descriptive statistics overall and split by group (mastectomy ± IBR). Dichotomous, categorical and short ordinal outcomes will be summarised using counts and percentages. Time to adjuvant therapy will be summarised using the Kaplan-Meier curves. Continuous and long ordinal outcomes will be summarised by the mean, SD, minimum and maximum (medians and IQRs will be reported for skewed data).
### Table 3  Definitions of complications

| Complication | Definition | Classification/details |
|--------------|------------|------------------------|
| **Surgical complications** | | |
| Seroma | A symptomatic collection of fluid in the mastectomy or donor site or around the reconstructed breast following surgery requiring aspiration | Minor—requiring 1–2 aspirations  
Major—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 intravenous 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 |
| **Wound dehiscence** | Separation of the skin edges at the wound site (breast or donor site) | Minor—managed conservatively  
Major—requiring return to theatre for resuturing |
| **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 | | |
Formal statistical testing for each outcome between groups (mastectomy ± IBR) will be approached as follows: Rates of postoperative complications, including readmission and reoperation; requirement for adjuvant therapy and delay or omission of planned adjuvant chemotherapy or radiotherapy will be analysed using a $\chi^2$ test and the effect estimate will be reported in terms of the relative risk and 95% CI. 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 5-year and 10-year oncological outcomes will be planned following completion of the initial phase of the study.

**DISCUSSION**

IBR 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 tenet of all oncoplastic surgery, the practice of IBR if adjuvant therapy is anticipated is an area of considerable controversy 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 postmastectomy radiotherapy 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. The proposed assessment of locoregional recurrence, distant metastases and breast cancer-specific survival at 5 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 NMBRA to

**Table 3** Continued

| Inhospital complications | Details |
|--------------------------|---------|
| **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 (Yes/no) |
| **Blood transfusion** | Bleeding requiring blood transfusion following mastectomy ± reconstructive surgery |
| **Unplanned admission to intensive care/ high-dependency unit** | Any unplanned admission to HDU/ITU following mastectomy ± reconstructive surgery |
| **Urinary tract infection** | A microbiologically confirmed urinary tract infection |
| **Surgical complication** | As above |
| **Other complication** | Details |

| Readmission and reoperation | Details |
|----------------------------|---------|
| **Readmission** | Any readmission 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 chemotherapy or radiotherapy directly related to the procedure with either local or systemic complications |
| **Reoperation** | 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 |

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

10 Dave R, et al. BMJ Open 2016;6:e012678. doi:10.1136/bmjopen-2016-012678

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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 initiation. This will allow any redundant fields to be removed and any ambiguities clarified to optimise data quality. Furthermore, the REDCap data management system 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 minimise 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 postoperative recovery, especially if postoperative 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 IBR 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) online 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 starting 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 are being recorded and there is no risk to patients.

Following completion of the audit phase of the study, proportionate ethical approval will be sought centrally by the iBRA-2 study team 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 5 years and 10 years, respectively, at which point a search of the UK Cancer Registry database 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, RSTN, ASiT and the National Research Collaborative (NRC) as well as the professional associations the ABS and BAPRAS. The protocol and data collection sheets will be available online (http://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 fed back to centres at the end of the audit. Overall audit results and results from individual centres will be fed back 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.

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