BMJ Open

Prepectoral versus subpectoral implant-based breast reconstruction after skin-sparing mastectomy or nipple-sparing mastectomy (OPBC-02/ PREPEC): a pragmatic, multicentre, randomised, superiority trial

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To cite: Kappos EA, Schulz A, Regan MM, *et al*. Prepectoral versus subpectoral implant-based breast reconstruction after skin-sparing mastectomy or nipple-sparing mastectomy (OPBC-02/ PREPEC): a pragmatic, multicentre, randomised, superiority trial. *BMJ Open* 2021;**11**:e045239. doi:10.1136/bmjopen-2020-045239

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-045239).

EAK and AS are joint first authors.
MarH and WPW are joint senior authors.

Received 28 September 2020
Accepted 20 July 2021

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ABSTRACT

Introduction The emphasis on aesthetic outcomes and quality of life (QoL) has motivated surgeons to develop skin-sparing or nipple-sparing mastectomy (SSM/ NSM) for breast cancer treatment or prevention. During the same operation, a so-called immediate breast reconstruction is performed. The breast can be reconstructed by positioning of a breast implant above (prepectoral) or below (subpectoral) the pectoralis major muscle or by using the patients' own tissue (autologous reconstruction). The optimal positioning of the implant prepectoral or subpectoral is currently not clear. Subpectoral implant-based breast reconstruction (IBBR) is still standard care in many countries, but prepectoral IBBR is increasingly performed. This heterogeneity in breast reconstruction practice is calling for randomised clinical trials (RCTs) to guide treatment decisions.

Methods and analysis International, pragmatic, multicentre, randomised, superiority trial. The primary objective of this trial is to test whether prepectoral IBBR provides better QoL with respect to long-term (24 months) physical well-being (chest) compared with subpectoral IBBR for patients undergoing SSM or NSM for prevention or treatment of breast cancer. Secondary objectives will compare prepectoral versus subpectoral IBBR in terms of safety, QoL and patient satisfaction, aesthetic outcomes and burden on patients. Total number of patients to be included: 372 (186 per arm).

Ethics and dissemination This study will be conducted in compliance with the Declaration of Helsinki. Ethical approval has been obtained for the lead investigator's site by the Ethics Committee 'Ethikkommission Nordwest- und Zentralschweiz' (2020–00256, 26 March 2020). The results of this study will be published in a peer-reviewed medical journal, independent of the results, following the Consolidated Standards of Reporting Trials standards for RCTs and good publication practice. Metadata describing the type, size and content of the datasets will be shared along with the study protocol and case report forms on public repositories adhering to the FAIR (Findability, Accessibility, Interoperability, and Reuse) principles.

Strengths and limitations of this study

- International, multicentre, randomised superiority trial, which has the potential to impact clinical practice in implant-based breast reconstruction (IBBR).
- The pragmatic design of this trial, developed using PRECIS tools, will reflect the variation of clinical practice thereby providing generalisable results.
- Patient advocates were intensely involved throughout the trial design, which is reflected in the primary endpoint focusing on patient-reported outcome measures.
- Subpectoral IBBR is still standard care in many countries, but prepectoral IBBR is increasingly performed, resulting in heterogeneity in breast reconstruction practice that callis for randomised clinical trials to guide treatment decisions.

Trial registration number NCT04293146.

INTRODUCTION

Breast cancer affects 2.1 million women each year.[1] Overtreatment, distress and morbidity of patients with breast cancer are serious global challenges, and quality of life (QoL) of breast cancer patients can be optimised without jeopardising safety.[2 3]

The emphasis on aesthetic outcomes and QoL has motivated surgeons to develop skin-sparing or nipple-sparing mastectomy (SSM/NSM). During the same operation, immediate breast reconstruction is performed to minimise deformity and optimise QoL. The breast can be reconstructed by positioning a breast implant either above (prepectoral) or below (subpectoral) the pectoralis major muscle or by using autologous tissue reconstruction.[4 5]

Following broad introduction of immediate implant-based breast reconstruction (IBBR) in clinical practice in the late 1970s, the implants were originally positioned above the pectoralis major muscle after NSM and SSM to reconstruct the breast in its natural pocket (prepectoral positioning). Initially, however, this technique was associated with unacceptably high rates of complications, including implant loss due to skin necrosis or infection, implant exposure and capsular contracture.[6] To decrease the risk of complications, the procedure has been modified to position the implant below the pectoralis major muscle. While two-staged IBBR (initial tissue expander placement later exchanged to implant) has been the traditional approach, one-stage direct implant placement has recently become standard care in many European countries.[7–11]

Compared with the subpectoral technique, the prepectoral positioning has been suggested to reduce discomfort with no differences in overall complication rates.[12 13] Indeed, since the prepectoral positioning of the implant respects the anatomic position of the breast and avoids surgical alterations to the pectoralis major muscle, it offers a variety of potential advantages including improved physical well-being, easier recovery and aesthetically, no animation deformity.

To date, major heterogeneity in breast reconstruction practice exists, as identified during the first Oncoplastic Breast Consortium (OPBC) consensus conference of specialised oncological, oncoplastic and reconstructive breast surgeons.[2] The OPBC panel concluded that the heterogeneity in breast reconstruction practice calls for randomised clinical trials (RCTs) to evaluate the safest and most effective reconstruction techniques.

METHODS AND ANALYSIS

Aims

The main purpose of this trial is to evaluate whether prepectoral IBBR provides better QoL with respect to long-term (24 months) physical well-being of the chest compared with subpectoral IBBR for patients undergoing SSM or NSM (also including skin reducing techniques) for prevention or treatment of breast cancer. The primary endpoint is the patient-reported assessment of the QoL (BREAST-Q) scale 'physical well-being: chest' assessed 24 months after mastectomy.[14] The study is designed to prove superiority by four points between prepectoral and subpectoral IBBR, with an expected common standard deviation (SD) of 13 points.

Design

This pragmatic, multicentre, randomised, international superiority trial will compare two surgical strategies for IBBR in parallel with a 1:1 random allocation to prepectoral or subpectoral breast reconstruction (figure 1). A total of 372 patients will be recruited in over 20 sites in Europe, China and the USA. Following a pragmatic approach, randomly assigned IBBR will be performed according to the surgeons' usual standard care by use of a one-stage or two-stage approach with or without adjunctive mesh. The study duration is planned for thirteen years: approximately 2 years of recruitment, end of the main study and analysis of the primary objective after 24 months of follow-up (FU) of the last patient, end of the extended oncological FU 10 years after inclusion of the last patient and end of the final analysis 1 year after that.

Participants

Participants are women from the age of 18 years undergoing therapeutic or risk-reducing NSM or SSM and IBBR with the ability to complete QoL questionnaires. Patients must be able to comprehend the character and personal implications of the study and give written informed consent before any protocol-specific procedure and trial preregistration. Both unilateral and bilateral surgery cases are included in the therapeutic, as well as the prophylactic setting. Randomisation will take place at the patient and not at the breast level, so that bilateral cases will have the same implant position for both breasts. Patients with no indication for IBBR according to clinical judgement of the treating surgeon, patients with use of an implant as place holder only for immediate delayed autologous reconstruction, as well as patients with intraoperatively inadequate skin flaps for prepectoral IBBR will be excluded before randomisation. Each patient will be informed that the participation in the study is voluntary and that she may withdraw from the study at any time and that withdrawal of consent will not affect her subsequent medical assistance and treatment.

Intervention and procedures

After written informed consent has been obtained by the local principal investigator and the inclusion and exclusion criteria have been confirmed patients will be preregistered. Patient information will be assessed in the screening visit as well as in FU visits. Prior to surgery, patients' demographics, personal and medical history, breast aesthetics, previous treatment, previous surgery

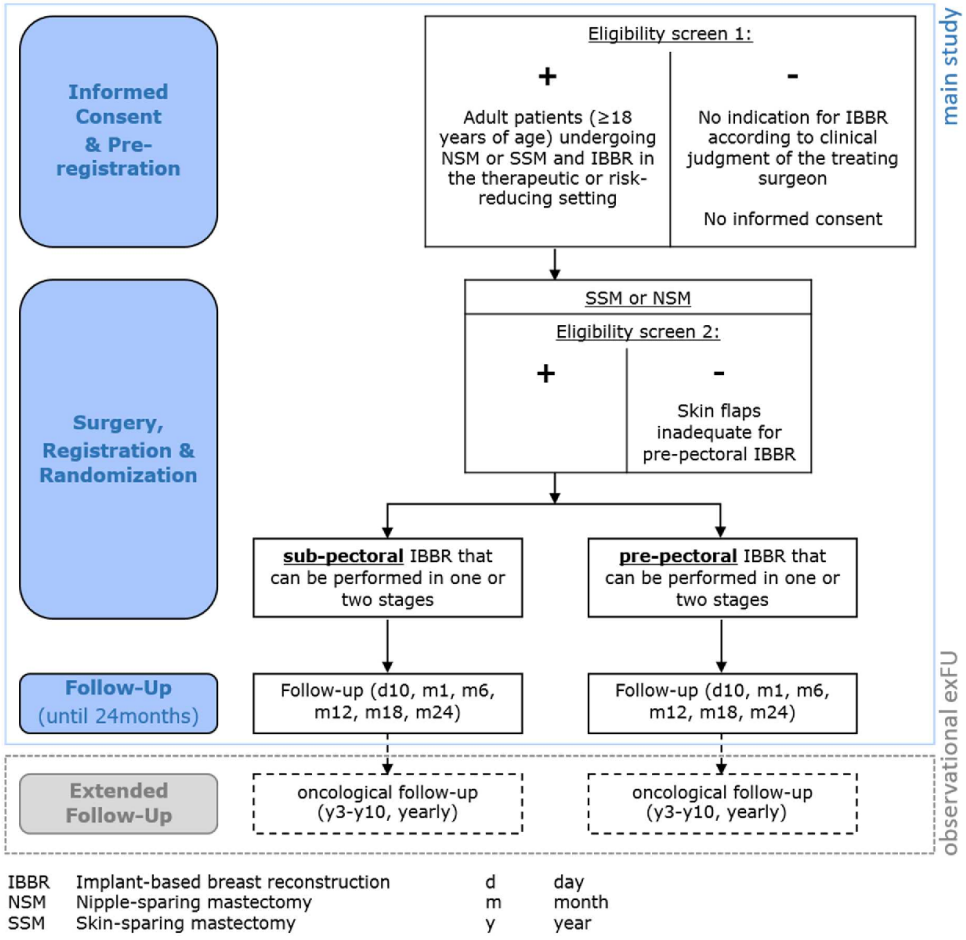

Figure 1 Flow chart of study design. FU, follow-up.

of the breast/axilla, previous oncological history and therapy, tumour characteristics (if applicable) will be recorded, and the BREAST-Q and baseline breast aesthetics evaluation (including photographs) will be conducted.

During the surgery (visit 1), after completion of NSM or SSM and before IBBR, the surgeon will determine the adequacy of the mastectomy skin flaps with regard to perfusion and viability for both surgical strategies. In the case this is adequate, patients will be randomised via the Clinical Data Management System (CDMS) secuTrial. Neither surgeons nor patients will be blinded to the trial allocation, but the central outcome assessment team will be blinded.

According to the pragmatic study design, the intervention will not be standardised to assure flexibility for surgeons to perform IBBR that reflects the variability in usual care.[15–17] However, the key aspects of the intervention will be documented including the types of meshes, matrices, expanders and implants used to perform IBBR, as well as practical details on the handling of devices and technology such as type, number and location of sutures, drains and use of antibiotics.

The FU schedule of this trial is in line with the usual care FU visits of patients after IBBR in accordance with the pragmatic trial design and should therefore promote participant retention. Patients will be seen 10 days as well as 1, 6, 12, 18 and 24 months after the mastectomy and IBBR, examined according to local standards and asked to fill out the QoL-questionnaires. If patients would not routinely perform the follow-up at the site, these visits can also be performed remotely by mail/phone. Only the 24 months visit will be required to be done at the sites for all patients. The use of optimising procedures and supporting measures, such as supportive bra or breast band, are at the full discretion of the treating physician and will be recorded. All additional procedures are allowed to improve breast aesthetics, both during primary and secondary surgery, including autologous fat grafting, mastopexy, as well as symmetrising procedures of the contralateral breast (eg, reduction mammoplasty) and will be documented in detail.

All treatments for complications are at the full discretion of the treating physicians to prevent implant loss in case of wound healing disorders, skin necrosis or surgical site infection.

Further concomitant care including radiotherapy and systemic therapies is at the discretion of the treating physicians and will be documented. The primary endpoint of the study will be assessed 24 months after mastectomy. Additional to the regular FU procedures, this visit will include a photographic documentation of the breast for

central analysis of aesthetics by a blinded outcome assessment team.

This pragmatic trial will mostly follow local standards, therefore the study specific procedures are limited to the randomisation and the assessment of:

1. Randomisation of the patient during the surgery.
2. Patient QoL and satisfaction using BREAST-Q (primary endpoint: Long-term physical well-being (chest), secondary endpoints: early physical well-being (chest), psychosocial well-being, sexual well-being, adverse effects of radiation, breast animation deformity, satisfaction with breasts and satisfaction with implants) and EQ-5D-5L assessment of health status (Swiss sites only for economic evaluation) at each study visit in the first 2 years after mastectomy and IBBR.
3. Surgical complications and thromboembolic events (details described under 'adverse events').
4. Breast aesthetics (evaluated by the patient, study physicians and a central blinded outcome assessment team) at screening and 24 months after the surgery.
5. Burden on patients within 24 months after mastectomy with assessment of foreign body sensation, cold feeling, pain as well as the number of breast-related operative procedures, length of hospital stay and the number of outpatient visits.

After 24 months, patients move to an extended FU in the years 3–10, in order to be able to determine oncological outcomes and long-term complications. Patients will be followed up by their oncological surgeon, oncologist or gynaecologist. The yearly extended FU will mostly be done by using routinely collected data (patient chart review). If patients do not visit the site regularly and the data can therefore not be obtained by chart review, aftercare physicians (performing the oncological FU) will be contacted by phone or patients can be contacted by phone to obtain the information for the following endpoints: Recurrence-free survival (RFS), burden on patients and long-term complications.

Adverse events

The main safety endpoint of the trial is 'loss of expander or implant,' at 24 months of follow up defined as an unplanned surgical removal of expander/implant with or without immediate replacement. It will be assessed within the first month particularly for safety monitoring and beyond that as 'surgical complication' as described below.

Adverse events of interest that will be documented include surgical complications and thromboembolic events. They will be assessed at each study visit within 24 months of mastectomy and IBBR, covering both surgical stages in case of two-staged IBBR. Surgical complications (wound dehiscence, haematoma, seroma, infection, mastectomy skin flap/ nipple necrosis, implant/ expander exposure/extrusion, implant/ expander rotation/ malpositioning, rippling, capsular contraction) will be evaluated according to the modified classification of Clavien-Dindo.[18] Additionally animation deformity will be assessed as a surgical complication according to Spear *et al*.[19] Thromboembolic events will be assessed according to Common Terminology Criteria for Adverse Events v5.04.[20]

Long-term complications will also be assessed during the extended FU in the years 3–10 as far as possible from chart review (including, seroma, implant/expander rotation/malpositioning, infection, capsular contraction, rippling, animation deformity, loss of expander or implant).

An annual safety report is submitted according to the national regulations once a year to the local ethics committees (EC) by the Sponsor-Investigator.

Reporting of serious adverse events

Trial intervention related serious adverse events (SAEs) are documented and reported immediately (within a maximum of 24 hours) to the sponsor–investigator of the study. SAEs related to (adjuvant) systemic therapy or planned hospitalisations for example, for the seconds-stage surgery or procedures to improve breast aesthetics are exempted from expedited reporting. If it cannot be excluded that the SAE is attributable to the intervention under investigation, the sponsor–investigator reports it to the respective EC according to national regulations.

Follow-up of (serious) adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, FU may require additional tests or medical procedures as indicated, and/or referral to a general physician or a medical specialist.

Outcomes and measurements

Primary endpoint of this study is long-term physical well-being of the chest, assessed by the respective BREAST-Q scale 24 months after mastectomy and IBBR.

Secondary safety endpoints are loss of expander or implant, surgical complications, thromboembolic events and RFS. Patient reported secondary endpoints are other QoL domains: early physical well-being (chest), psychosocial well-being, sexual well-being, adverse effects of radiation, animation deformity using the BREAST-Q, patient satisfaction with breasts and implants. Other endpoints are central assessment of breast animation deformity, capsular contracture and breast aesthetics as well as the burden on patients and health economics (for the Swiss sites). Interference of different dose distributions of radiation therapy and its consequences on the distribution of local tumour recurrences will be assessed.

Present accrual and target accrual

By July 2021, twenty study sites have been initiated and over 140 patients have been randomised. During a 21-month recruitment period, we plan to include 372 patients at over 20 sites in Switzerland, USA, China, Austria, Germany, Hungary and Sweden. Two back-up strategies have been pre-specified in case of under-recruitment. First, estimated versus actual accrual is continuously monitored for each study site with an early first evaluation of recruitment

already 6 months after opening the first site. If the trial is under-recruiting, the second back-up strategy includes an international site escalation. Further OPBC study centres will be prepared between months 6 and 12 for back-up opening during the second year of trial recruitment. A total of 14 additional international OPBC study sites have committed to participate in this case.

Statistical considerations

Methods of minimising bias

Randomisation will be performed using the method of minimisation to ensure a balance between patients to receive one of the two surgical strategies (prepectoral vs subpectoral IBBR) with a 1:1 allocation of a total of 186 patients per treatment arm. Randomisation will be stratified by study site, SSM versus NSM and unilateral versus bilateral surgery. All other potential confounding factors including one-staged versus two-staged procedures, performance of axillary surgery and use of biological versus synthetic vs no mesh will be addressed at the analysis level. The randomisation procedure will be implemented by the Clinical Trial Unit of the University Hospital Basel into the CDMS secuTrial. The minimisation method which will ensure that allocation to one of the two treatment groups is balanced with respect to the three stratification factors. To avoid predictable alternation of treatment allocation, patients will be allocated with a probability of 80% to the treatment group that would minimise the imbalance between the two treatment groups within each study site.

Selection bias at inclusion will be minimised by use of the well-defined criterion for inclusion 'adult patients (≥18 years of age) undergoing NSM or SSM and IBBR in the therapeutic or risk-reducing setting'. Furthermore, only patients will be fully registered and randomised who qualify for both surgical strategies.

For the primary endpoint and other QoL assessments, validated questionnaires only will be used.

Blinding would not be successful in patients, who report the primary endpoint. Due to the nature of the surgical procedure, the surgical team cannot be blinded to the allocated surgical strategy either. The surgical team will follow all patients according to clinical standards including diagnosis and treatment of complications. A central and blinded outcome assessment team will determine the following secondary endpoints using pictures from before and 24 months after the mastectomy: Animation deformity, capsular contraction (≥grade 3) and breast aesthetics (BCCT.core). This team will be profoundly trained by education, guidance and experience to assess all endpoints in a uniform and reproducible manner.

Unblinding of the secondary outcomes assessment team will not be necessary since it is the (not blinded) surgical team and aftercare physicians who are responsible for diagnosis and treatment of complications.

Sample size

The sample size was determined for the primary endpoint 'physical well-being (chest)' at 24 months. Based on observations from the BRIOS trial and observational studies,[21–23] the observation of mean scores of 76 and 80 points respectively are expected for subpectoral and prepectoral implants (score ranges 0–100, with higher indicating better QoL). The clinically relevant difference in BREAST-Q 'physical well-being: chest' score that should be detected in a superiority design is four points between prepectoral and subpectoral IBBR,[24 25] with an expected common SD of 13 points. Based on these assumptions, a sample size of 334 patients provides a 80% power for a two-sided t-test at level α=0.05. In order to compensate for a potential drop-out rate of 10%, the total sample size was calculated to include n=372 patients. Due to the primary analysis planning to include covariates of prognostic importance in a regression model, an increase of the power with respect to the t-test may be expected.

Primary analysis

The main study analysis of the primary and most secondary objectives will occur after 24 months of follow-up of the last patient enrolled. The primary analysis will be performed on the full analysis set composed of all randomised patients following the intention-to-treat (ITT) principle. To compare the two treatment arms and test the primary hypothesis, a linear mixed model will be fitted with the BREAST-Q physical well-being (chest) score at 24 months as response variable, with treatment assignment as independent variable, and adjusted for the baseline BREAST-Q physical well-being (chest) score, stratification factors (ie, unilateral vs bilateral surgery and NSM vs SSM) and other factors potentially associated with the endpoint (eg, expected use of one-stage vs two-stage procedure, expected type of surgical mesh. Additionally a random intercept to account for the centre effect will be included. As a sensitivity analysis an unadjusted t-test will be performed on the BREAST-Q physical well-being (chest) score change from baseline to compare the two treatment arms.

Following the recommendations in Jakobsen *et al*, the following strategies for missing data will be adopted, under the missing at random assumption[26]:

1. Complete-case analyses will be performed if the proportion of missing data is below 5% or if data are only missing in the outcome variable. In this case, also best-worst and worst-best case sensitivity analyses will be performed.
2. In the unlikely event that missingness exceeds 40% only a complete-case analysis will be reported, which cannot however be considered confirmative due to the extent of missingness.
3. Multiple imputation will be otherwise implemented.

To explore whether estimated treatment effects for the primary endpoint vary significantly between subcategories of the trial population, subgroup analyses will be performed

of the BREAST-Q physical well-being (chest) score for each of the following baseline (presurgery) variables:

Unilateral versus bilateral surgery, NSM versus SSM procedure, expected use of postoperative radiation therapy, expected use of a one-staged versus two-staged procedure, expected type of mesh.

In addition, exploratory subgroup analyses will be considered for the following postrandomisation variables capturing actual treatment, interpreted with caution as they may be on the causal pathway between the intervention and the endpoint: Use of postoperative radiation therapy, one-staged versus two-staged procedure, biological matrix versus synthetic mesh versus neither matrix nor mesh.

Secondary analyses

The safety evaluation will be mainly based on the rate of loss of expander or implant for any reason or duration within 24 months. The expected rate of expander or implant loss is 10% for subpectoral and prepectoral IBBR, with an expected non-inferiority margin of 5%. Under these assumptions and with the planned sample size of 167 patients per arm after potential drop-out, the power to show non-inferiority is very low (around 44%).[27] Nevertheless the rate of loss of expander or implant will be estimated with its 95% CI according to treatment assignment, as well as for their difference with 95% CI. With the low expected frequency of an event, an exact binomial CI methodology will be implemented.

Similarly as described for the primary endpoint, a model based analysis will be conducted to adjust for relevant baseline covariates (eg, unilateral vs bilateral surgery, NSM vs SSM), using a logit link function for the regression model, as reasonable in consideration of the observed event frequency. At a minimum, the loss rates according to treatment assignment (and difference) will be estimated by stratum with 95% CIs; hypothesis testing of treatment-by-factor interaction is not anticipated.

Surgical complications and thromboembolic events, as well as animation deformity, capsular contracture and breast aesthetics, will be analysed similarly.

To test whether prepectoral IBBR leads to better QoL with respect to additional QoL outcomes and better patient satisfaction in the short-term and long-term as compared with subpectoral IBBR over 24 months, the analysis will implement mixed linear modelling of the serial time points.

The oncological safety of prepectoral IBBR will be assessed primarily on the basis of RFS. A 5-year RFS event rate is expected to be approximately 7.5% (ie, 5-year RFS of 92.5%) in both treatment groups. At the time of the main analysis, the 2-year rates will be estimated by Kaplan-Meier method with 95% CIs. With extended follow-up, 5- and 10-year rates will be estimated. After 10 years, approximately 58 events are expected (assuming exponential distribution of RFS), to allow estimation of 10-year RFS and treatment effect HR estimation using Cox regression according to subgroups, for example, stratification factors.

Additional analyses: translational research

A number of subprojects have been proposed, spanning a range of oncologic, therapeutic, surgical and economic questions. Additional questions to be investigated include:

1. Impact of prepectoral versus subpectoral IBBR on oncological safety (RFS).
2. Impact of NSM versus SSM on the local recurrence rate (LRR).
3. Impact of postoperative complications on LRR.
4. Impact of IBBR on dose distribution in target volumes and organs at risk (mainly ipsilateral lung and heart) in patients with postmastectomy radiation therapy.
5. Impact of mastectomy flap thickness on reconstructive complications related to breast reconstruction and oncological safety.
6. Impact of implant size and shape on risk of complications and QoL.
7. Impact of preoperative breast cup size and ptosis on risk of complications, QoL and oncological safety.
8. Impact of surgical one-team versus two-team approach on risk of complications and oncological safety.
9. Impact of prepectoral versus subpectoral IBBR on risk of early complications.
10. Health economics analysis of the Swiss sites to compare burden on patients and assess the incremental costs and the incremental cost effectiveness ratio of the respective surgical strategies.
11. Impact of prepectoral versus subpectoral IBBR on breast animation deformity assessed by the new BREAST-Q scale versus objective photographical assessment.

Monitoring and data safety monitoring board

The trial is following a risk-adapted monitoring approach, which is described in detail in the study monitoring plan. The safety of the trial will be evaluated twice-yearly by the independent data safety monitoring board of the International Breast Cancer Study Group, consisting of a study-independent statistician, three independent breast cancer oncologist experts, a patient advocate and a surgeon with expertise in IBBR.

Patient and public involvement

Patient advocates were involved in the whole process of developing this protocol and two of them are coauthors of this manuscript as well. Patients prioritised and decided the primary outcome of this study. The results of this study will be made available to study participants after publication in form of the scientific manuscript. The burden of the intervention was also be assessed by our patient advocates.

DISCUSSION

All published studies on prepectoral IBBR are small and observational.[12 13 22 28–32] They predominantly suggest that prepectoral IBBR is safe and effective. Baker *et al* published a prospective cohort study of 40 patients. The

authors compared prepectoral versus subpectoral IBBR performed preferably in one stage and found no relevant differences in mean short-term pain scores (1.5 vs 1.5; p=0.45) and mean mid-term BREAST-Q scores (72 and 71; p=0.81).[22] Sbitany *et al* emphasised in a retrospective study that the main benefit of prepectoral IBBR is the elimination of pectoralis major muscle alteration and animation deformity.[29] They showed data suggesting the lack of a difference between the prepectoral and the subpectoral approach in terms of overall complication rate (17.9% vs 18.8%; p=0.49). Bettinger *et al* retrospectively investigated 213 patients undergoing prepectoral IBBR versus subpectoral IBBR with acellular dermal matrix (ADM) versus subpectoral IBBR without ADM and found numerically lower rates of complications, although not significant, in the prepectoral compared with the subpectoral ADM-based group (adjusted risk ratio: 0.25; 95% CI 0.06 to 1.00).[28] However they did not evaluate PROs in this single-centre trial. Jafferbhoy *et al* reported an implant loss rate of 10.2% and a mean length of stay of 1.48 days in a series of 78 NSM procedures with one-staged prepectoral positioning of implants by using a newer ADM called Braxon.[30] They concluded that the advantages of prepectoral IBBR are quicker postoperative recovery and short post-operative hospital stay, and that long-term studies are required to assess rippling, postoperative animation, capsular contracture and impact of radiotherapy. Sigalove *et al* reported low rates of complications in a series of 353 prepectoral predominantly two-staged reconstructions including infection, seroma and skin flap necrosis, each occurring at an incidence of less than 5%.[12] They discussed that the advantage of prepectoral reconstruction is the absence of muscle elevation which may decrease animation deformity caused by muscle contraction, chest tightness, pain and muscle spasm and the avoidance of an unnatural state by subpectoral placement. Woo *et al* reported a series of 135 prepectoral predominantly two-staged IBBR with 87% of patients having an uneventful recovery without complications.[13] They discussed that the primary benefit of prepectoral IBBR using ADM is the precise control of the breast pocket, simultaneously avoiding any animation deformity.

Given this lack of clear scientific evidence, clinical decision making in IBBR is very heterogeneous. Subpectoral IBBR is still standard care in many countries, but prepectoral IBBR is increasingly performed. This heterogeneity in breast reconstruction practice is calling for RCTs like this one to guide treatment decisions.

This trial compares prepectoral to subpectoral IBBR with the hypothesis that prepectoral approach is superior in terms of physical well-being of the chest at 24 months. The aim is to adhere to standard of care as much as possible to follow the pragmatic trial design to generate data that are applicable to today's practice. Its randomised study design and pragmatic nature will make this current study unique in its applicability and feasibility for different centres across the world. The study findings will make a significant impact in clinical decision making and surgical standards worldwide in the field of evolving IBBR.

ETHICS AND DISSEMINATION

Risks and benefits of study participants are described above. This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

Before the start of the trial, the trial protocol, informed consent document and any other appropriate documents were submitted to the respective independent ECs. Ethical approval has been obtained for the lead investigator's site by the EC 'Ethikkommission Nordwest-und Zentralschweiz' (2020–00256, 26 March 2020). Substantial changes to the study setup and study organisation, the protocol and relevant study documents are submitted to the EC for approval before implementation.

Before being admitted to the clinical trial, all subjects must consent in writing to participate after the nature, scope and possible consequences of the clinical trial have been explained in a form understandable to her. The further use of the trial data is requested from trial participants in a separate consent form.

The results of this study will be published in a peer-reviewed medical journal, independent of the results, following the Consolidated Standards of Reporting Trials standards for RCTs and good publication practice. Metadata describing the type, size and content of the datasets will be shared along with the study protocol and case report forms on public repositories adhering to the FAIR principles (Findability, Accessibility, Interoperability, and Reuse).

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Funding The main funding of this study is provided by the Swiss National Science Foundation (SNSF) Investigator initiated clinical trials (IICT) call 2018 (33IC30_185613/1). Additional funding for has been received by both, the Swiss and the Basel Cancer League. The Study protocol has undergone extensive peer-review by the funding body.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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