BMJ Open

Protocol for a multicenter, prospective, cohort study to investigate patient satisfaction and quality of life after immediate breast reconstruction in Japan: the SAQLA study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042099
Article Type:	Protocol
Date Submitted by the Author:	25-Jun-2020

Complete List of Authors:	Saiga, Miho; Okayama University Hospital, Department of Plastic and Reconstructive Surgery Hosoya, Yuko; Iwate Medical University, Department of Plastic and Reconstructive Surgery Utsunomiya, Hiroki; Showa University Koto Toyosu Hospital, Department of Surgery・Plastic Surgery Kuramoto, Yukiko; Cancer Institute Hospital of Japanese Foundation for Cancer Research, Department of Plastic and Reconstructive Surgery Watanabe, Satoko; Okayama University Hospital, Department of Plastic and Reconstructive Surgery Tomita, Koichi; Osaka University, Department of Plastic and Reconstructive Surgery, Graduate School of Medicine Aihara, Yukiko; University of Tsukuba, Department of Plastic and Reconstructive Surgery, Faculty of Medicine Muto, Mayu; Yokohama City University Medical Center, Department of Plastic and Reconstructive Surgery Hikosaka, Makoto; National Center for Child Health and Development, Department of Plastic and Reconstructive Surgery Kawaguchi, Takashi; Tokyo University of Pharmacy and Life Sciences, Department of Practical Pharmacy Miyaji, Tempei; The University of Tokyo, Department of Clinical Trial Data Management, Graduate School of Medicine Yamaguchi, Takuhiro; Tohoku University Graduate School of Medicine, Division of Biostatistics Zenda, Sadamoto; National Cancer Center-Hospital East, Division of Radiation Oncology Goto, Aya; Iwate Medical University, Department of Plastic and Reconstructive Surgery Sakuraba, Minoru; Iwate Medical University, Department of Plastic and Reconstructive Surgery Kusano, Taro; Kusano Taro Clinic Miyabe, Kenta; Showa University, Department of Plastic Surgery Kuroki, Tomoaki; Showa University, Department of Plastic Surgery Yano, Tomoyuki; Cancer Institute Hospital of Japanese Foundation for Cancer Research, Department of Plastic and Reconstructive Surgery Taminato, Mifue; Osaka University, Department of Plastic and Reconstructive Surgery, Graduate School of Medicine Sekido, Mitsuru; University of Tsukuba, Department of Plastic and Reconstructive Surgery, Faculty of Medicine

	Tsunoda, Yui; Yokohama City University Medical Center, Department of Plastic and Reconstructive Surgery Satake, Toshihiko ; Toyama University Hospital, Department of Plastic and Reconstructive Surgery Doihara, Hiroyoshi ; Okayama University Hospital, Department of Breast and Endocrine surgery Kimata, Yoshihiro; Okayama University Hospital, Department of Plastic and Reconstructive Surgery
Keywords:	PLASTIC & RECONSTRUCTIVE SURGERY, Breast surgery < SURGERY, Breast tumours < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Protocol for a multicenter, prospective, cohort study to investigate patient satisfaction and quality of life after immediate breast reconstruction in Japan: the SAQLA study

Authors:

Miho Saiga[1], Yuko Hosoya[2], Hiroki Utsunomiya[3], Yukiko Kuramoto[4], Satoko Watanabe[1], Koichi Tomita[5], Yukiko Aihara[6], Mayu Muto[7], Makoto Hikosaka[8], Takashi Kawaguchi[9], Tempei Miyaji[10], Takuhiro Yamaguchi[11], Sadamoto Zenda[12], Aya Goto[2], Minoru Sakuraba[2], Taro Kusano[13], Kenta Miyabe[14], Tomoaki Kuroki[14], Tomoyuki Yano[4], Mifue Taminato[5], Mitsuru Sekido[6], Yui Tsunoda[7], Toshihiko Satake[15], Hiroyoshi Doihara[16], Yoshihiro Kimata[1]

Affiliations:

1. Department of Plastic and Reconstructive Surgery, Okayama University Hospital, Okayama, Japan
2. Department of Plastic and Reconstructive Surgery, Iwate Medical University, Morioka, Japan
3. Department of Surgery・Plastic Surgery, Showa University Koto Toyosu Hospital, Tokyo, Japan
4. Department of Plastic and Reconstructive Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan
5. Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan
6. Department of Plastic and Reconstructive Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.
7. Department of Plastic and Reconstructive Surgery, Yokohama City University Medical Center, Yokohama, Japan
8. Department of Plastic and Reconstructive Surgery, National Center for Child Health and Development, Tokyo, Japan
9. Department of Practical Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan
10. Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
11. Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan
12. Division of Radiation Oncology, National Cancer Center Hospital East, Chiba, Japan
13. Kusano Taro Clinic, Tokyo, Japan
14. Department of Plastic Surgery, Showa University, Tokyo, Japan
15. Department of Plastic and Reconstructive Surgery, Toyama University Hospital, Toyama, Japan
16. Department of Breast and Endocrine surgery, Okayama University Hospital, Okayama, Japan

Corresponding Author: Miho Saiga

Mailing Address: Department of Plastic Surgery, Okayama University Hospital, 2-5-1, Shikata-cho,

Okayama-city, Okayama 700-8558, Japan

Telephone: +86-235-7214

Fax: +86-235-7210

E-mail: gmd20076@s.okayama-u.ac.jp

Key Words: Breast reconstruction, PRO, Health-related quality of life, Breast Cancer

ABSTRACT

Introduction: The aim of breast reconstruction (BR) is to improve patients' health-related quality of life (HRQOL). Therefore, measuring patient-reported outcomes (PROs) would clarify the value and impact of BR on a patient's life and thus provide evidence-based information to help decision-making. As there is very little evidence regarding PROs after BR in Japan, the SAQLA study (**Sa**tisfaction and **q**uality of **l**ife **a**fter immediate breast reconstruction) aims to investigate satisfaction and HRQOL in Japanese patients with breast cancer who undergo mastectomy and immediate breast reconstruction (IBR).

Methods and analysis: This prospective, observational multicenter study will assess 406 patients who had unilateral breast cancer and underwent mastectomy and IBR from April 2018 to July 2019. The patients will be followed up for 36 months postoperatively. The primary end point of this study will be the time-dependent changes in BREAST-Q satisfaction with breasts subscale score for 12 months after reconstructive surgery, which will be collected via an electronic PRO system.

Ethics and dissemination: This study will be performed in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects published by Japan's Ministry of Education, Science and Technology and the Ministry of Health, Labour and Welfare, and the modified Act on the Protection of Personal Information, as well as the Declaration of Helsinki. This study protocol was approved by the institutional ethics committee at the Okayama University Graduate School of Medicine, Dentistry on 2nd February, 2018 (1801-039), and all other participating sites. The findings of this trial will be submitted to an international peer-reviewed journal.

Registration: This trial is registered in the UMIN Clinical Trials Registry: UMIN000032177.

Protocol version: 1.2. 1st, January, 2020.

Strengths and limitations of this study

- The SAQLA will be the first prospective, multicenter study in Japan to investigate satisfaction and HRQOL after immediate breast reconstruction.
- Our data will provide time-dependent changes in BREAST-Q scores after reconstructive surgery following mastectomy and IBR among Japanese breast cancer patients. This data will be informative and aid patients in decision-making.

- The Decision Regret Scale has been added to better understand the impact of breast implant recall.

INTRODUCTION

Background and rationale

Breast cancer is the most common type of cancer in Japanese women. One in 11 Japanese women will develop breast cancer over the course of her lifetime.[1] The number of newly diagnosed cases was over 76,000 in 2014,[1] and the incidence rate is increasing. In terms of age, the incidence begins to increase from the age of 30 and peaks in the forties to the sixties.[1] As the survival rate of breast cancer increases,[2] the health-related quality of life (HRQOL) of survivors has become more important in deciding the course of treatment.

Breast reconstruction (BR) after mastectomy is a surgical option to restore the breast shape. It has been recognized as a part of comprehensive breast cancer surgery to improve patients' HRQOL and satisfaction.[3-9] In Japan, autologous BR has been covered by the national healthcare insurance (NHI) since 2006, and implant-based reconstruction since 2013. The number of immediate BR (IBR) cases has rapidly increased since that time and reached 4700 in 2018, with 70% being implant-based procedures.[10-12]

Despite this, some problems remain for patients making BR decisions. BR has potential risks and additional burdens compared to mastectomy without BR. Insertion of a silicone breast implant involves risks of infection, rupture, and deformation caused by capsule contracture,[13-15] and autologous reconstruction involves the sacrifice of donor sites and the risk of flap necrosis.[16-18] Evidence-based information about the available reconstruction options is needed, including the possible complications, HRQOL prognosis, and patients' perception of cosmetic results to help patients know what to expect after BR.[19-21]

In the past decade, patient-reported outcomes (PROs) have been utilized to understand how BR impacts on a patient's life and to measure the value of BR.[7, 22-26] Among these PROs, the BREAST-Q,[24] the first BR-specific instrument, has been most commonly used worldwide because of its high validity. It enables evaluation of the outcome of BR in terms of various aspects such as aesthetic satisfaction, physical well-being, psychosocial well-being, and satisfaction with care. Research conducted using the BREAST-Q has provided much important information about BR.[7, 8, 9] A recent large prospective cohort study in North America, the Mastectomy Reconstruction Outcome Consortium, enrolled over 4,400 women, and demonstrated that HRQOL and satisfaction after autologous reconstruction were higher than after implant-based reconstruction, and that post-mastectomy radiation therapy was better tolerated.[9, 27] They also investigated the recovery phase and reported that many participants may not be fully recovered at 3 months postoperatively, regardless of the reconstruction procedure, and patients who underwent abdominally-based autologous reconstruction had less chest and upper extremity morbidities.[21]

Evidence regarding BR is being developed in Western countries, although there is very little evidence from Japan. Since there are physical, psychological, and cultural differences between Western and Japanese women, investigations in Japanese cohorts are essential to improve medical care.[4, 28, 29] The health care environment also differs between countries, and there are some limitations in terms of BR performed under medical insurance in Japan. The acellular dermal matrix that supports the lower pole of the breast in implant-based reconstruction,[30] which is more commonly used in other developed countries, is not available in Japan; therefore, most implant cases require a staged procedure. Risk-reducing mastectomy (RRM) for HBOC has been covered by the NHI since April 2020 and is limited to women who have already developed breast or ovarian cancer; therefore, currently, fewer women in Japan undergo RRM and bilateral BR.[31] Types of implants covered under the NHI have been limited to Allergan products; therefore, Allergan's July 2019 recall of Biocell textured breast implants due to the risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)[32-35] had a significant impact on women who had undergone implant-based reconstruction in Japan, as well as those who were undergoing the reconstruction.

Objective

The aim of this study, the **Sa**tisfaction and **q**uality of **l**ife **a**fter immediate breast reconstruction (SAQLA) study, is to investigate the satisfaction and HRQOL in Japanese patients with breast cancer following mastectomy and IBR to further understand their experience. We will focus on the differences due to reconstructive procedure so as to provide useful information for decision-making in BR. This will be the first prospective, multi-center study in Japan to investigate the time-dependent change in BREAST-Q scores, which will contribute toward fundamental data for future clinical research leading to new hypotheses and evidence for Japanese breast cancer patients.

In addition, since Allergan's recall occurred during the study period, just before recruitment was closed, we will also explore how it affected our participants by watching for trends in participants opting out of reconstruction surgery or changing their chosen reconstruction procedure, and evaluating their regret about their decision.

METHODS AND ANALYSIS

Patient and public involvement statement

This study protocol was derived without patient involvement. Patients were not invited to comment on the study design.

Design and setting

This study was designed as a multi-center, longitudinal, observational study. All participants were recruited from seven major BR hospitals; Okayama University Hospital, Iwate Medical University

Hospital, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Showa University Hospital, University of Tsukuba Hospital, Osaka University Hospital, and Yokohama City University Medical Center. The study is currently on-going. Recruitment began in April 2018 and closed in July 2019. A total of 406 patients are enrolled in the study and they will be followed up for 36 months postoperatively.

Patients and recruitment

The eligible subjects are patients diagnosed with initial unilateral breast cancer who underwent mastectomy and IBR. All participants receive regular treatment at their participating sites. The breast reconstructive procedures included implant-based reconstruction, latissimus dorsi flap and abdominal flaps including deep inferior epigastric artery perforator flap, transverse rectus abdominus myocutaneous (TRAM) flap, and superficial inferior epigastric artery perforator flap, which are all commonly practiced in Japan. Potential participants were recruited at each site before surgery if they fulfilled all the eligibility criteria and did not come under any of the exclusion criteria (Table 1). Consenting participants were then registered on the electric data capture (EDC) system and study IDs were given.

Table 1. Eligibility criteria

Inclusion criteria
1. Pathological diagnosis of breast cancer.
2. Planned total mastectomy (including Bt, SSM, and NSM).
3. Breast surgeon determined an indication for breast reconstruction and immediate breast reconstruction is planned.
4. Aged between 20 and 75 years.
5. ECOG PS of 0 or 1.
6. Written informed consent provided.
Exclusion criteria
1. Reconstruction for breast conserving surgery.
2. History of breast conserving surgery.
3. History of ipsilateral breast reconstruction (re-reconstruction).
4. Heterochronic and simultaneous bilateral breast cancer.
5. Breast shape has been remarkably changed by previous surgery, such as augmentation.
6. Difficulty participating in the study due to a mental condition.
7. Doctor indicates unsuitability for the study.
8. No device such as a smart phone, tablet, or PC, and inability to respond to the ePRO at home.

Bt, mastectomy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ePRO,

electronic version of the patient-reported outcomes questionnaire; NSM, nipple-sparing mastectomy; PC, personal computer; SSM; skin-sparing mastectomy.

Outcomes

Primary and secondary outcomes

The primary endpoint of this study is to evaluate the time-dependent changes in BREAST-Q satisfaction with breasts scores over the 12 months after surgery. BREAST-Q evaluations will be performed at baseline, and 1, 3, 6, and 12 postoperative months, and summary statistics will be calculated each time according to BR procedure. The secondary endpoints include: (1) the time-dependent changes in BREAST-Q subscale scores including psychosocial wellbeing, physical well-being, and sexual well-being for 12 months after surgery, (2) the time-dependent changes in SF-8 (Medical Outcome Survey 8-item Short-Form Health Survey) summary score and physical and mental component summary score for 12 months after surgery,[36] (3) long-term patient satisfaction and HRQOL after IBR evaluated by BREAST-Q and SF-8 for up to 36 months, (4) the burden of IBR, (5) the complication rate, and (6) bilateral symmetry measured by the 4-point Harris scale[37] and Mamma Balance®.[38]

Patient-reported outcomes

We set questionnaire items of satisfaction and HRQOL based on a core outcome set proposed by Potter et al.[39] BREAST-Q will be used for measurement of satisfaction and HRQOL related to BR. The satisfaction with general health, which cannot be evaluated with BREAST-Q, will be measured using SF-8.[36] Ad-hoc questionnaires to investigate the patient burden associated with IBR and motivation for further reconstructive procedures such as revision surgery or nipple reconstruction will also be used. Since depression and anxiety of preoperative patients may affect the level of postoperative satisfaction,[40] screening for depression / anxiety will be performed with HADS (Hospital Anxiety and Depression Scale)[41, 42] at baseline. The baseline questionnaire also includes the participants' social background data such as education level, employment, income, and marital status.

Following the Allergan implant recall, the distress with regard to the decision of BR will be assessed using the Decision Regret Scale (DRS)[43, 44] 1 year after completing BR.

BREAST-Q

BREAST-Q is a self-administrated rating scale consisting of 15 subscales and 121 items that measures the effect of breast surgery on patient satisfaction and HRQOL. The recall period is the past week. There is a score for each subscale, and a higher score indicates a higher satisfaction level and QOL. The following subscales are used in this study: satisfaction with breasts, satisfaction with implant, psychosocial well-being, sexual well-being, adverse effects of radiation, physical well-being of chest

and upper extremity, satisfaction with abdomen, physical well-being of abdomen, satisfaction with back appearance, and physical well-being of shoulder and back. A formal Japanese version was developed,[45] and the validation of the reconstruction module has been completed (Cronbach $\alpha > 0.7$, inter-rater reliability [ICC] > 0.8).

SF-8

This tool is a self-administered questionnaire consisting of eight items to evaluate HRQOL: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Based on the eight subscales, SF-8 can calculate two summary scores, a physical and a mental component summary.[36]

HADS

HADS is a 14-item questionnaire that evaluates depression and anxiety. There are seven depression items and seven anxiety items which are scored separately. Each item is scored from 0 to 3 points, with a maximum subscale score of 21. A subscale score of more than eight indicates anxiety or depression.[42]

DRS

DRS is a self-administered questionnaire consisting of five items that measures distress or remorse after health care decisions. Possible score is 0–100, where higher scores indicate stronger regret. A formal Japanese version has been developed.[44] In this study, an item will be added to determine whether or not implant recall has affected the response.

Medical history and physical examination

Medical history and physical examination data will be collected from medical records by researchers, and this will include age, breast cancer clinical stage, adjuvant therapy, body mass index, smoking habits, HbA1c, American Society of Anesthesiologists classification, regular administration of steroids, and breast ptosis. Surgery-related factors to be collected on the day of surgery include reconstruction procedure, mastectomy procedure (nipple-sparing or skin-sparing mastectomy), axillary dissection or sentinel node biopsy, and weight of resected specimen. The factors that influence whether participants undergo additional reconstructive procedures such as nipple reconstruction, fat injection, revision of reconstructed breast, or mastopexy of the contralateral breast will be collected at 12 and 36 months after reconstruction.

Complications of surgery

Complications related to BR procedures will be divided into four categories as follows: (1)

complications of the breast area common to all procedures; postoperative hemorrhage, hematoma, seroma, wound dehiscence, wound infection, and skin and nipple-areola necrosis, (2) systemic complications common to all procedures, (3) complications related to the tissue expansion (TE)/implant; infection or implant explantation, and (4) autologous reconstruction-related complications; emergent additional surgery for blood flow insufficiency, flap necrosis, or donor-site complications. Complications will be graded according to Japan Clinical Oncology Group postoperative complications criteria (Clavien-Dindo classification) version 2.0. Complications will be reviewed at 1, 12, and 36 months after surgery.

Cosmetic outcomes

Objective cosmetic outcomes of the breast will be evaluated by medical staff using photographs taken at 12 and 36 months after reconstruction. The following two methods will be used for evaluation: (1) Harris scale (4-point scale):[37] classification of the global cosmetic outcomes into four categories (excellent, good, fair, or poor), (2) Mamma Balance®[38] software that digitizes the position difference between the left and right nipples and objectively evaluates bilateral symmetry. The ICC of this method is 0.78.

Sample size determination

The sample size was not calculated based on a statistical perspective. The number of target participants was determined as 400 patients based on the annual number of IBR cases in the participating seven sites and consideration of the eligibility criteria.

Data collection and timelines

This study will collect data using electronic data capture (EDC) systems, Viedoc 4 and ePRO, Viedoc me (PCG Solutions, Sweden). Data entry to the electronic case report form will be performed by researchers using the EDC at each hospital. The PRO questionnaire will be administered to patients using ePRO at nine study time points: baseline and 1, 3, 6, 12, 18, 24, 30, and 36 postoperative months through the patient's own device. Data regarding participants' medical history, physical examination, complications of surgery, and cosmetic outcomes will be gathered by medical staff and entered into the EDC system on the Web at each site and linked to the PRO data. The study timeline is shown in Tables 2 and 3.

Table 2. Study timeline: patient-reported outcomes

	Baseline	Time after breast cancer surgery							
		1	3	6	12	18	24	30	36

		month	months	months	months	months	months	months	months
HADS	●								
BREAST-Q	●	●	●	●	●	●	●	●	●
SF-8	●	●	●	●	●	●	●	●	●
Burden of BR		●	●	●	●	●	●	●	●
Motivation for further revision									●
DRS					●*				

*12 months after second operation for staged reconstruction patients

HADS: Hospital Anxiety and Depression Scale; SF-8, Medical Outcome Survey 8-item Short Form Health Survey; BR, breast reconstruction; DRS: Decision Regret Scale

Table 3. Study timeline: clinician-reported outcomes

	Before breast cancer surgery	Day of surgery	After breast cancer surgery		After breast reconstruction*		
	Upon enrollment		1 month	12 months	1 month	12 months	36 months
Medical history and physical examination	●						
Surgery-related factors		●					
Review of complications			●		●	●	●
Review of adjuvant therapy				●			
Review of additional reconstructive procedure						●	●
Cosmetic outcome (photograph)						●	●

*Second operation for staged-reconstruction

Data management, data monitoring, and auditing

The data center is located in the Department of Clinical Trial Data Management, Tokyo University Graduate School of Medicine, Tokyo, Japan. No personally identifiable information will be entered into the EDC to protect participants' privacy. Data management and central data monitoring will be

performed using the EDC. There will be no data monitoring committee. Similarly, auditing is also not planned for this study. Following completion of the study, the fixed data will be exported, and then deleted from the EDC. The data will be stored in a public data repository.

Harms

No serious harm is expected in this observational study. Some patients might feel psychological distress when asked about sexual well-being.[45] The estimated time to complete a survey is about 10 minutes, and this may be a burden.

Statistical analysis

The primary analysis of this study will describe the time-dependent changes in satisfaction with breasts score of the BREAST-Q during the postoperative 12 months. BREAST-Q evaluation will be performed at baseline, and at 1, 3, 6, and 12 months after surgery, and summary statistics at each time point will be calculated for each surgical procedure.

ETHICS AND DISSEMINATION

Research ethical approval

All investigators involved in the current research will conduct this study in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare, 2015).

Consent

Before enrolling a patient in this study, the researcher will give the patient an informed consent form, and the detail about this study will be explained according to the Ethical Guidelines for Medical and Health Research involving Human Subjects. All the participants will be informed that they have the right to withdraw consent without any disadvantages.

Trial registration

This study protocol and the informed consent form have been approved by the Institutional Review Boards at all the participating sites. The study was registered with UMIN Clinical Trial Registry (UMIN000032177).

Access to data

Only clinical data managers at the central data center will have access to reported case data through the EDC system during the study. Site investigators will have access to case data within all their

sites. The data manager will transfer the final dataset to the principal investigator and the data will be stored in electronic format.

Dissemination policy

The results will be analyzed and reported in a form in which individuals cannot be identified. The findings of the study will be presented at conferences and published in peer-reviewed medical journals domestically and internationally.

DISCUSSION

Although the number of cases of BR is increasing in Japan, the outcomes of BR have not been adequately evaluated due to the lack of established outcome measures. Considering the purpose of BR is to improve patients' satisfaction and HRQOL, PROs are very useful and essential. SAQLA is the first multicenter study in Japan to evaluate BR from this perspective. Our data will provide time-dependent changes in BREAST-Q and SF-8 scores following mastectomy and IBR. Information on the recovery process is helpful for patients who are to make BR decisions, and can facilitate patient engagement in decision-making. It can also serve as fundamental data for future clinical research and contribute to improving healthcare surrounding BR.

Implant recall has had a significant impact on the field of BR in Japan. We cannot rule out the possibility that the fear of developing BIA-ALCL might decrease satisfaction and HRQOL of our participants, and therefore, the study results will be skewed. To account for that, DRS has been added to help us understand the psychological impact of implant recall while paying attention to discontinued reconstruction cases caused by the recall. We also considered making a comparison between outcomes of patients with recalled implants and those with other types of implant.

There are some limitations to this study protocol. First, this is a hypothesis-generating observational study. The number of target participants has not been set statistically, but is based on the actual number of cases in the participating seven sites. Therefore, although we will describe the time-dependent changes on PROs following reconstruction procedures, this study will not determine the difference between the procedures. Second, it was discussed whether the time-dependent changes in staged reconstruction should start from the primary operation (TE insertion) or the second operation (exchange to permanent implant or autologous tissue). The latter can be better to evaluate the recovery period of second operation. However, regarding the period of TE as downtime of the staged reconstruction, the impact on physical and psychosocial well-being should be evaluated at the same timepoint from the primary operation. Third, subjects with reconstruction failure will be excluded from the primary endpoint analysis since from an ethical point of view, it is not appropriate to ask them questionnaires about aesthetic satisfaction, and this may lead to bias. Finally, our participant group includes only women who choose BR. It would be more informative to include women who

undergo other breast cancer surgery such as mastectomy without BR and breast conserving surgery. This will be investigated in a future study.

Authors' contributions

All authors listed will participate in the study, and will revise and approve the final manuscript. MS, YH, TK, TM, TY, and YK contributed to the conception and design of this study protocol. TK, TM, and YK will contribute to data management, planned data analysis.

Funding statement

This research is supported by the AMED (Japan Agency for Medical Research and Development) under Grant Number JP19ck0106325.

Competing interests: None declared.

Acknowledgments: We are grateful to Sawaizumi M. for our long-term collaboration and his advice. We would like to thank Editage (www.editage.com) for their writing support on the Abstract.

Data availability: Data sharing not applicable as no datasets generated and/or analysed for this study

Patient and Public involvement: Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

REFERENCES

1 Cancer Statistics in Japan; Table download. Cancer Information Service. http://ganjoho.jp/reg_stat/statistics/dl/index.html. Date accessed: 29 Mar 2020.

2 Center for Cancer Control and Information Services, National Cancer Center. Monitoring of Cancer Incidence in Japan - Survival 2006-2008 Report.

3 Wellisch DK, DiMatteo R, Silverstein M, et al. Psychosocial outcomes of breast cancer therapies: lumpectomy versus mastectomy. *Psychosomatics* 1989;30:365–73.

4 Fobair P, Stewart SL, Chang S, et al. Body image and sexual problems in young women with breast cancer. *Psychooncology* 2006;15:579–94.

5 Elder EE, Brandberg Y, Björklund T, et al. Quality of life and patient satisfaction in breast cancer patients after immediate breast reconstruction: a prospective study. *Breast* 2005;14:201–8.

6 Dauplat J, Kwiatkowski F, Rouanet P, et al. Quality of life after mastectomy with or without immediate breast reconstruction. *Br J Surg* 2017;104:1197–206.

7 Winters ZE, Benson JR, Pusic AL. A systematic review of the clinical evidence to guide

treatment recommendations in breast reconstruction based on patient- reported outcome measures and health-related quality of life. *Ann Surg* 2010;252:929–42.

8 Jeevan R, Browne JP, Gulliver-Clarke C, et al. Surgical determinants of patient-reported outcomes following postmastectomy reconstruction in women with breast cancer. *Plast Reconstr Surg* 2017;139:1036e–45e.

9 Pusic AL, Matros E, Fine N, et al. Patient-reported outcomes 1 year after immediate breast reconstruction: results of the mastectomy reconstruction outcomes consortium study. *J Clin Oncol* 2017;35:2499–506.

10 Oda A, Kuwabara H, Fushimi K. Disparities associated with breast reconstruction in Japan. *Plast Reconstr Surg* 2013;132:1392–9.

11 Tanakura K, Sawaizumi M, Miyashita H, et al. The impact in an institute of social insurance coverage for breast reconstruction using silicone breast implants. *Oncoplastic Breast Surgery* 2017;2:40–5.

12 Annual report of the Japan Society of Plastic and Reconstructive Surgery Database. https://jsprs.or.jp Date accessed: 1 May 2020.

13 Sbitany H, Wang F, Peled AW, et al. Immediate implant-based breast reconstruction following total skin-sparing mastectomy: defining the risk of preoperative and postoperative radiation therapy for surgical outcomes. *Plast Reconstr Surg* 2014;134:396–404.

14 Spear SL, Murphy DK; Allergan silicone breast implant U.S. core clinical study group. Natrelle round silicone breast implants: core study results at 10 years. *Plast Reconstr Surg* 2014;133:1354–61.

15 Fischer JP, Wes AM, Tuggle CT 3rd, et al. Risk analysis of early implant loss after immediate breast reconstruction: a review of 14,585 patients. *J Am Coll Surg* 2013;217:983–90.

16 Sailon AM, Schachar JS, Levine JP. Free transverse rectus abdominis myocutaneous and deep inferior epigastric perforator flaps for breast reconstruction: a systematic review of flap complication rates and donor-site morbidity. *Ann Plast Surg* 2009;62:560–3.

17 Gill PS, Hunt JP, Guerra AB, et al. A 10-year retrospective review of 758 DIEP flaps for breast reconstruction. *Plast Reconstr Surg* 2004;113:1153–60.

18 Selber JC, Kurichi JE, Vega SJ, et al. Risk factors and complications in free TRAM flap breast reconstruction. *Ann Plast Surg* 2006;56:492–7.

19 Hoffman AS, Cantor SB, Fingeret MC, et al. Considering breast reconstruction after mastectomy: a patient decision aid video and workbook. *Plast Reconstr Surg Glob Open* 2019;7:e2500.

20 Flitcroft K, Brennan M, Spillane A. Making decisions about breast reconstruction: a systematic review of patient-reported factors influencing choice. *Qual Life Res* 2017;26:2287–319.

21 Weichman KE, Hamill JB, Kim HM, et al. Understanding the recovery phase of breast

reconstructions: Patient-reported outcomes correlated to the type and timing of reconstruction. *J Plast Reconstr Aesthet Surg* 2015;68:1370–8.

22 Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. *J Clin Oncol* 1997;15:974–86.

23 Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;14:2756–68.

24 Pusic AL, Klassen AF, Scott AM, et al. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg* 2009;124:345–53.

25 Kanatas A, Velikova G, Roe B, et al. Patient-reported outcomes in breast oncology: a review of validated outcome instruments. *Tumori* 2012;98:678–88.

26 Cohen WA, Mundy LR, Ballard TN, et al. The BREAST-Q in surgical research: a review of the literature 2009-2015. *J Plast Reconstr Aesthet Surg* 2016;69:149–62.

27 Jagsi R, Momoh AO, Qi J, et al. Impact of radiotherapy on complications and patient-reported outcomes after breast reconstruction. *J Natl Cancer Inst* 2018;110:157–65.

28 Albornoz CR, Bach PB, Mehrara BJ, et al. A paradigm shift in U.S. breast reconstruction: increasing implant rates. *Plast Reconstr Surg* 2013;131:15–23.

29 Zelken J, Cheng MH. Asian breast augmentation: a systematic review. *Plast Reconstr Surg Glob Open* 2015;3:e555.

30 Sheflan M, Brown I. Immediate implant-based breast reconstruction using variable lower pole support. In: Urban C, Rietjens M, eds. Oncoplastic and reconstructive breast surgery. Milan: Springer 2013:235-52

31 Yoshimura A, Okumura S, Sawaki M, et al. Feasibility study of contralateral risk-reducing mastectomy with breast reconstruction for breast cancer patients with BRCA mutations in Japan. *Breast Cancer* 2018;25:539–46.

32 Calobrace MB, Schwartz MR, Zeidler KR, et al. Long-term safety of textured and smooth breast implants. *Aesthet Surg J* 2017;38:38–48.

33 Collett DJ, Rakhorst H, Lennox P, et al. Current risk estimate of breast implant–associated anaplastic large cell lymphoma in textured breast implants. *Plast Reconstr Surg* 2019;143:30S–40S.

34 McCarthy CM, Loyo-Berrios N, Qureshi AA, et al. Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE): initial report of findings, 2012–2018. *Plast Reconstr Surg* 2019;143:65S–73S.

35 Marra A, Viale G, Pileri SA, et al. Breast implant-associated anaplastic large cell lymphoma: a comprehensive review. *Cancer Treat Rev* 2020;84:101963.

36 Ware JE, Kosinski M, Dewey JE, et al. How to Score and Interpret Single-item Health Status

Measures: A Manual for Users of the SF-8™ Health Survey. Lincoln, RI: Quality-Metric Incorporated 2001.

37 Harris JR, Levene MB, Svensson G, et al. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1979;5:257–61.

38 Mukai Y, Watanabe S, Matsumoto M, et al. Reliability and validity of Mamma Balance®: novel software to assess the symmetry of the nipple-areola-complex position. *J Plast Reconstr Aesthet Surg* 2017;70:1147–9.

39 Potter S, Holcombe C, Ward JA, et al. Development of a core outcome set for research and audit studies in reconstructive breast surgery. *Br J Surg* 2015;102:1360–71.

40 Unukovych D, Johansson H, Brandberg Y. Preoperative psychosocial characteristics may predict body image and sexuality two years after risk-reducing mastectomy: a prospective study. *Gland Surg* 2017;6:64–72.

41 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.

42 Kugaya A, Akechi T, Okuyama T, et al. Screening for psychological distress in Japanese cancer patients. *Jpn J Clin Oncol* 1998;28:333–8.

43 Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003:23:281–92.

44 Tanno K, Bito S, Isobe Y, et al. Validation of a Japanese version of the Decision Regret Scale. *J Nurs Meas* 2016;24:E44–54.

45 Saiga M, Taira N, Kimata Y, et al. Development of a Japanese version of the BREAST-Q and the traditional psychometric test of the mastectomy module for the assessment of HRQOL and patient satisfaction following breast surgery. *Breast Cancer* 2017;24:288–98.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	?
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a multicenter, prospective, cohort study to investigate patient satisfaction and quality of life after immediate breast reconstruction in Japan: the SAQLA study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042099.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2020

Complete List of Authors:	Saiga, Miho; Okayama University Hospital, Department of Plastic and Reconstructive Surgery Hosoya, Yuko; Iwate Medical University, Department of Plastic and Reconstructive Surgery Utsunomiya, Hiroki; Showa University Koto Toyosu Hospital, Department of Surgery・Plastic Surgery Kuramoto, Yukiko; Cancer Institute Hospital of Japanese Foundation for Cancer Research, Department of Plastic and Reconstructive Surgery Watanabe, Satoko; Okayama University Hospital, Department of Plastic and Reconstructive Surgery Tomita, Koichi; Osaka University, Department of Plastic and Reconstructive Surgery, Graduate School of Medicine Aihara, Yukiko; University of Tsukuba, Department of Plastic and Reconstructive Surgery, Faculty of Medicine Muto, Mayu; Yokohama City University Medical Center, Department of Plastic and Reconstructive Surgery Hikosaka, Makoto; National Center for Child Health and Development, Department of Plastic and Reconstructive Surgery Kawaguchi, Takashi; Tokyo University of Pharmacy and Life Sciences, Department of Practical Pharmacy Miyaji, Tempei; The University of Tokyo, Department of Clinical Trial Data Management, Graduate School of Medicine Yamaguchi, Takuhiro; Tohoku University Graduate School of Medicine, Division of Biostatistics Zenda, Sadamoto; National Cancer Center-Hospital East, Division of Radiation Oncology Goto, Aya; Iwate Medical University, Department of Plastic and Reconstructive Surgery Sakuraba, Minoru; Iwate Medical University, Department of Plastic and Reconstructive Surgery Kusano, Taro; Kusano Taro Clinic Miyabe, Kenta; Showa University, Department of Plastic Surgery Kuroki, Tomoaki; Showa University, Department of Plastic Surgery Yano, Tomoyuki; Cancer Institute Hospital of Japanese Foundation for Cancer Research, Department of Plastic and Reconstructive Surgery Taminato, Mifue; Osaka University, Department of Plastic and Reconstructive Surgery, Graduate School of Medicine Sekido, Mitsuru; University of Tsukuba, Department of Plastic and Reconstructive Surgery, Faculty of Medicine

	Tsunoda, Yui; Yokohama City University Medical Center, Department of Plastic and Reconstructive Surgery Satake, Toshihiko ; Toyama University Hospital, Department of Plastic and Reconstructive Surgery Doihara, Hiroyoshi ; Okayama University Hospital, Department of Breast and Endocrine surgery Kimata, Yoshihiro; Okayama University Hospital, Department of Plastic and Reconstructive Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	PLASTIC & RECONSTRUCTIVE SURGERY, Breast surgery < SURGERY, Breast tumours < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Protocol for a multicenter, prospective, cohort study to investigate patient satisfaction and quality of life after immediate breast reconstruction in Japan: the SAQLA study

Authors:

Miho Saiga[1], Yuko Hosoya[2], Hiroki Utsunomiya[3], Yukiko Kuramoto[4], Satoko Watanabe[1], Koichi Tomita[5], Yukiko Aihara[6], Mayu Muto[7], Makoto Hikosaka[8], Takashi Kawaguchi[9], Tempei Miyaji[10], Takuhiro Yamaguchi[11], Sadamoto Zenda[12], Aya Goto[2], Minoru Sakuraba[2], Taro Kusano[13], Kenta Miyabe[14], Tomoaki Kuroki[14], Tomoyuki Yano[4], Mifue Taminato[5], Mitsuru Sekido[6], Yui Tsunoda[7], Toshihiko Satake[15], Hiroyoshi Doihara[16], Yoshihiro Kimata[1]

Affiliations:

1. Department of Plastic and Reconstructive Surgery, Okayama University Hospital, Okayama, Japan
2. Department of Plastic and Reconstructive Surgery, Iwate Medical University, Morioka, Japan
3. Department of Surgery and Plastic Surgery, Showa University Koto Toyosu Hospital, Tokyo, Japan
4. Department of Plastic and Reconstructive Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan
5. Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan
6. Department of Plastic and Reconstructive Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
7. Department of Plastic and Reconstructive Surgery, Yokohama City University Medical Center, Yokohama, Japan
8. Department of Plastic and Reconstructive Surgery, National Center for Child Health and Development, Tokyo, Japan
9. Department of Practical Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan
10. Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
11. Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan
12. Division of Radiation Oncology, National Cancer Center Hospital East, Chiba, Japan
13. Kusano Taro Clinic, Tokyo, Japan
14. Department of Plastic Surgery, Showa University, Tokyo, Japan
15. Department of Plastic and Reconstructive Surgery, Toyama University Hospital, Toyama, Japan
16. Department of Breast and Endocrine surgery, Okayama University Hospital, Okayama, Japan

Corresponding Author: Miho Saiga

Mailing Address: Department of Plastic Surgery, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama-city, Okayama 700-8558, Japan

Telephone: +86-235-7214

Fax: +86-235-7210

E-mail: gmd20076@s.okayama-u.ac.jp

Key Words: Breast reconstruction, Patient-reported outcomes, Health-related quality of life, Breast Cancer

ABSTRACT

Introduction: The aim of breast reconstruction (BR) is to improve patients' health-related quality of life (HRQOL). Therefore, measuring patient-reported outcomes (PROs) would clarify the value and impact of BR on a patient's life and thus provide evidence-based information to help decision-making. The SAQLA study (**Sa**tisfaction and **q**uality of **l**ife **a**fter immediate breast reconstruction) aims to investigate satisfaction and HRQOL in Japanese patients with breast cancer who undergo immediate breast reconstruction (IBR).

Methods and analysis: This ongoing prospective, observational multicenter study will assess 406 patients who had unilateral breast cancer and underwent mastectomy and IBR, recruited from April 2018 to July 2019. All participants were recruited from seven hospitals: Okayama University Hospital, Iwate Medical University Hospital, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Showa University Hospital, University of Tsukuba Hospital, Osaka University Hospital, and Yokohama City University Medical Center. The patients will be followed up for 36 months postoperatively. The primary end point of this study will be the time-dependent changes in BREAST-Q satisfaction with breasts subscale scores for 12 months after reconstructive surgery, which will be collected via an electronic PRO system.

Ethics and dissemination: This study will be performed in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by Japan's Ministry of Education, Science and Technology and the Ministry of Health, Labour and Welfare, and the modified Act on the Protection of Personal Information, and the Declaration of Helsinki. This study protocol was approved by the institutional ethics committee at the Okayama University Graduate School of Medicine, Dentistry on 2nd February, 2018 (1801-039), and all other participating sites. The findings of this trial will be submitted to an international peer-reviewed journal.

Registration: This trial is registered in the UMIN Clinical Trials Registry: UMIN000032177.

Protocol version: 1.2. 1st, January, 2020.

Strengths and limitations of this study

- The SAQLA will be the first prospective, multicenter study in Japan to investigate satisfaction and HRQOL after immediate breast reconstruction.
- Time-dependent changes in BREAST-Q scores after reconstructive surgery will be informative and aid patients in decision-making.
- The Decision Regret Scale has been added to better understand the impact of breast implant recall.
- The results of this study may represent the satisfaction and HRQOL of patients in relatively good condition after IBR.

INTRODUCTION

Background and rationale

Breast cancer is the most common type of cancer in Japanese women. One in eleven Japanese women will develop breast cancer over the course of her lifetime.[1] The number of newly diagnosed cases was over 76,000 in 2014,[1] and the incidence rate is increasing. In terms of age, the incidence begins to increase from the age of thirty and peaks in the forties to the sixties.[1] As the survival rate of breast cancer increases,[2] the health-related quality of life (HRQOL) of survivors has become more important in deciding the course of treatment.

Breast reconstruction (BR) after mastectomy is a surgical option to restore the breast shape. It has been recognized as a part of comprehensive breast cancer surgery to improve patients' HRQOL and satisfaction.[3-9] In Japan, autologous BR has been covered by the national healthcare insurance (NHI) since 2006, and implant-based reconstruction since 2013. The number of immediate BR (IBR) cases has rapidly increased since that time and reached 4700 in 2018, with 70% being implant-based procedures.[10-12]

Despite this, some problems remain for patients making BR decisions. BR has potential risks and additional burdens compared to mastectomy without BR. Insertion of a silicone breast implant involves risks of infection, rupture, and deformation caused by capsule contracture,[13-15] and autologous reconstruction involves the sacrifice of donor sites and the risk of flap necrosis.[16-18] Evidence-based information about the available reconstruction options is needed, including the possible complications, HRQOL prognosis, and patients' perception of cosmetic results to help patients know what to expect after BR.[19-21]

In the past decade, patient-reported outcomes (PROs) have been utilized to understand how BR impacts a patient's life and to measure the value of BR.[7, 22-26] Among these PROs, the BREAST-Q,[24] the first BR-specific instrument, has been most commonly used worldwide because of its high validity. It enables evaluation of the outcome of BR in terms of various aspects such as aesthetic satisfaction, physical well-being, psychosocial well-being, and satisfaction with care. Research conducted using the BREAST-Q has provided much of the important information about BR.[7, 8, 9] A recent large prospective cohort study in North America, the Mastectomy Reconstruction Outcome Consortium, enrolled over 4,400 women, and demonstrated that HRQOL and satisfaction after autologous reconstruction were higher than after implant-based reconstruction, and that post-mastectomy radiation therapy was better tolerated.[9, 27] They also investigated the recovery phase and reported that many participants may not be fully recovered at 3 months postoperatively, regardless of the reconstruction procedure, and that patients who underwent

abdominal-based autologous reconstruction had lesser chest and upper extremity morbidities.[21] Evidence regarding BR is being developed in Western countries, although there is very little evidence from Japan. Since there are physical, psychological, and cultural differences between Western and Japanese women, investigations in Japanese cohorts are essential to improve medical care.[4, 28, 29] The health care environment also differs between countries, and there are some limitations in terms of BR performed under medical insurance in Japan. The acellular dermal matrix that supports the lower pole of the breast in implant-based reconstruction,[30] which is more commonly used in other developed countries, is not available in Japan; therefore, most implant cases require a staged procedure. Risk-reducing mastectomy (RRM) for Hereditary breast and ovarian cancer (HBOC) has been covered by the NHI since April 2020 and is limited to women who have already developed breast or ovarian cancer; therefore, currently, fewer women in Japan undergo RRM and bilateral BR.[31] Types of implants covered under the NHI have been limited to Allergan products; therefore, Allergan's July 2019 recall of Biocell textured breast implants due to the risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)[32-35] had a significant impact on women who had undergone implant-based reconstruction in Japan, as well as those who were undergoing the reconstruction.

Objective

The aim of this study, the **Sa**tisfaction and **q**uality of **l**ife **a**fter immediate breast reconstruction (SAQLA) study, is to investigate the satisfaction and HRQOL in Japanese patients with breast cancer following mastectomy and IBR to further understand their experience. We will focus on differences due to the reconstructive procedure so as to provide useful information for decision-making in BR. This will be the first prospective, multicenter study in Japan to investigate the time-dependent change in BREAST-Q scores, which will contribute fundamental data for future clinical research leading to new hypotheses and evidence for Japanese breast cancer patients.

In addition, since Allergan's recall occurred during the study period, just before recruitment was closed, we will also explore how it affected our participants by watching for trends in participants opting out of reconstruction surgery or changing their chosen reconstruction procedure, and evaluating their regrets about their decision.

METHODS AND ANALYSIS

Design and setting

This study was designed as a multicenter, longitudinal, observational study. All participants were recruited from seven major BR hospitals: Okayama University Hospital, Iwate Medical University Hospital, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Showa

University Hospital, University of Tsukuba Hospital, Osaka University Hospital, and Yokohama City University Medical Center. The study is currently ongoing. Recruitment began in April 2018 and closed in July 2019. A total of 406 patients are enrolled in the study and they will be followed up for 36 months postoperatively.

Patients and recruitment

The eligible subjects are those diagnosed with initial unilateral breast cancer, and are planned for mastectomy and IBR. All participants receive regular treatment at their participating sites. The breast reconstructive procedures include implant-based reconstruction, latissimus dorsi flap, and abdominal flaps including deep inferior epigastric artery perforator flap, transverse rectus abdominus myocutaneous (TRAM) flap, and superficial inferior epigastric artery perforator flap, all of which are commonly practiced in Japan. Potential participants were recruited at each site before surgery if they fulfilled all the inclusion criteria. and did not meet any of the exclusion criteria (Table 1). The time between the diagnosis of breast cancer and recruitment into the study was not set. Consenting participants were then registered on the electronic data capture (EDC) system and study IDs were given.

Table 1. Eligibility criteria

Inclusion criteria
1. Pathological diagnosis of breast cancer.
2. Planned total mastectomy (including Bt, SSM, and NSM).
3. Breast surgeon determined an indication for breast reconstruction and immediate breast reconstruction is planned.
4. Aged between 20 and 75 years.
5. ECOG PS of 0 or 1.
6. Written informed consent provided.
Exclusion criteria
1. Reconstruction for breast conserving surgery.
2. History of breast conserving surgery.
3. History of ipsilateral breast reconstruction (re-reconstruction).
4. Heterochronic and simultaneous bilateral breast cancer.
5. Breast shape has been remarkably changed by previous surgery such as augmentation.
6. Difficulty participating in the study due to a mental condition.
7. Doctor indicates unsuitability for the study.
8. No possession of a device such as a smart phone, tablet, or PC, and inability to respond to the ePRO at home.

Bt, mastectomy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ePRO, electronic version of the patient-reported outcomes questionnaire; NSM, nipple-sparing mastectomy; PC, personal computer; SSM; skin-sparing mastectomy.

Loss to follow-up

Observation will be discontinued if a participant meets any of the following conditions: (1) cancellation of BR due to patient's intension or treatment plan; (2) reconstruction failure; (3) recurrence or metastasis of breast cancer; (4) contralateral breast cancer; (5) malignant diseases other than breast cancer; (6) death of participant; (7) withdrawal of consent; (8) researchers judge that it is inappropriate to continue observation.

In this study, reconstructive failure is defined as a condition in which the reconstructed breast is removed, i.e., flap loss and implant removal. Patients with reconstructive failure are rather devastated; we therefore regard the administration of a questionnaire about aesthetic satisfaction to be highly inappropriate in these patients. However, patients with other complications, such as hematomas, capsular contractures, or fat necrosis, which may lead to impaired aesthetic results, will be followed.

Outcomes

Primary and secondary outcomes

The primary endpoints of this study are the time-dependent changes in BREAST-Q satisfaction with breasts scores over 12 months after surgery. BREAST-Q evaluations will be performed at baseline, and at 1, 3, 6, and 12 months postoperatively, and the scores will be analyzed according to the BR procedure performed. The secondary endpoints include: (1) the time-dependent changes in BREAST-Q subscale scores including psychosocial well-being, physical well-being, and sexual well-being for 12 months after surgery; (2) the time-dependent changes in SF-8 (8-Item Short-Form Health Survey) summary score and physical and mental component summary score for 12 months after surgery;[36] (3) long-term patient satisfaction and HRQOL after IBR evaluated by BREAST-Q and SF-8 for up to 36 months; (4) the burden of IBR; (5) the complication rate; and (6) bilateral symmetry measured by the 4-point Harris scale[37] and Mamma Balance®.[38]

Patient-reported outcomes

We set the questionnaire items for satisfaction and HRQOL based on a core outcome set proposed by Potter et al.[39] BREAST-Q will be used for the measurement of satisfaction and HRQOL related to BR. The satisfaction with general health, which cannot be evaluated with BREAST-Q, will be measured using SF-8.[36] Ad-hoc questionnaires to investigate the patient burden associated with

IBR and motivation for further reconstructive procedures such as revision surgery or nipple reconstruction will also be used. Since depression and anxiety of preoperative patients may affect the level of postoperative satisfaction,[40] screening for depression/anxiety will be performed with HADS (Hospital Anxiety and Depression Scale)[41, 42] at baseline. The baseline questionnaire also includes data on the participants' social background such as education level, employment, income, and marital status.

Following the Allergan implant recall, the distress with regard to the decision of BR will be assessed using the Decision Regret Scale (DRS)[43, 44] 1 year after completing BR.

BREAST-Q

BREAST-Q is a self-administrated rating scale consisting of 15 subscales and 121 items that measures the effect of breast surgery on patient satisfaction and HRQOL. The recall period is the past week. There is a score for each subscale, and a higher score indicates a higher satisfaction level and QOL. The following subscales are used in this study: satisfaction with breasts, satisfaction with implant, psychosocial well-being, sexual well-being, adverse effects of radiation, physical well-being of chest and upper extremity, satisfaction with abdomen, physical well-being of abdomen, satisfaction with back appearance, and physical well-being of shoulder and back. A formal Japanese version was developed,[45] and the validation of the reconstruction module has been completed (Cronbach $\alpha > 0.7$, inter-rater reliability [ICC] > 0.8).

SF-8

This tool is a self-administered questionnaire consisting of eight items to evaluate HRQOL: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Based on the eight subscales, SF-8 can calculate two summary scores: a physical and a mental component summary.[36]

HADS

HADS is a 14-item questionnaire that evaluates depression and anxiety. There are seven depression items and seven anxiety items which are scored separately. Each item is scored from 0 to 3 points, with a maximum subscale score of 21. A subscale score of more than eight indicates anxiety or depression.[42]

DRS

DRS is a self-administered questionnaire consisting of five items that measures the distress or remorse after health care decisions. Possible score is 0–100, where higher scores indicate stronger regret. A formal Japanese version has been developed.[44] In this study, an item will be added to

determine whether the implant recall affected the response to DRS.

Medical history and physical examination

The following medical history and physical examination data will be collected by researchers from medical records: age, breast cancer clinical stage, adjuvant therapy, body mass index, smoking habits, HbA1c, American Society of Anesthesiologists classification, regular administration of steroids, and breast ptosis. Surgery-related factors to be collected on the day of surgery include reconstruction procedure, mastectomy procedure (nipple-sparing or skin-sparing mastectomy), axillary dissection or sentinel node biopsy, and weight of resected specimen. The factors that influence whether participants undergo additional reconstructive procedures such as nipple reconstruction, fat injection, revision of reconstructed breast, or mastopexy of the contralateral breast will be collected at 12 and 36 months after reconstruction.

Complications of surgery

Complications related to BR procedures will be divided into four categories as follows: (1) complications of the breast area common to all procedures: postoperative hemorrhage, hematoma, seroma, wound dehiscence, wound infection, and skin and nipple-areola necrosis; (2) systemic complications common to all procedures; (3) complications related to the tissue expansion (TE)/implant; infection or implant explantation; (4) autologous reconstruction-related complications: emergent additional surgery for blood flow insufficiency, flap necrosis, or donor-site complications. Complications will be graded according to the Japan Clinical Oncology Group postoperative complications criteria (Clavien-Dindo classification) version 2.0. Complications will be reviewed at 1, 12, and 36 months after surgery.

Cosmetic outcomes

Objective cosmetic outcomes of the breast will be evaluated by medical staff using photographs taken at 12 and 36 months after reconstruction. The following two methods will be used for evaluation: (1) Harris scale (4-point scale):[37] classification of the global cosmetic outcomes into four categories (excellent, good, fair, or poor) and (2) Mamma Balance®[38] software that digitizes the position difference between the left and right nipples and objectively evaluates bilateral symmetry. The ICC of this method is 0.78.

Sample size determination

The sample size was not calculated based on a statistical perspective. The number of target participants was determined as 400 patients based on the annual number of IBR cases in the participating seven sites and consideration of the eligibility criteria.

Data collection and timelines

This study will collect data using electronic data capture (EDC) systems, Viedoc 4 and ePRO, Viedoc me (PCG Solutions, Sweden). Data entry into the electronic case report forms will be performed by researchers using the EDC at each hospital. The PRO questionnaire will be administered to patients using ePRO at nine study time points: baseline, and at 1, 3, 6, 12, 18, 24, 30, and 36 postoperative months through the patient's own device. Participants will be given the timeline of the survey and will complete the questionnaire in the scheduled survey period by accessing the Viedoc me web-site from a browser of their own smartphone. If the patient desires, she can register her e-mail address or phone number in the Viedoc system and receive notifications to remind her of the survey. The central data manager will monitor the completion status of the questionnaire and notify the researchers at the respective sites of incomplete assessments. Thereafter, the researcher will contact the participant to request they complete the questionnaire within the survey period. Data regarding participants' medical history, physical examination, complications of surgery, and cosmetic outcomes will be gathered by medical staff and entered into the EDC system on the Web at each site and linked to the PRO data. The study timeline is shown in Tables 2 and 3.

Table 2. Study timeline: patient-reported outcomes

	Baseline	Time after breast cancer surgery							
		1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months
HADS	●								
BREAST-Q	●	●	●	●	●	●	●	●	●
SF-8	●	●	●	●	●	●	●	●	●
Burden of BR		●	●	●	●	●	●	●	●
Motivation for further revision									●
DRS					●*				

*12 months after the second operation for staged reconstruction patients

HADS: Hospital Anxiety and Depression Scale; SF-8, 8-Item Short-Form Health Survey; BR, breast

reconstruction; DRS: Decision Regret Scale

Table 3. Study timeline: clinician-reported outcomes

	Before breast cancer surgery	Day of surgery	After breast cancer surgery		After breast reconstruction*		
	Upon enrollment		1 month	12 months	1 month	12 months	36 months
Medical history and physical examination	●						
Surgery-related factors		●					
Review of complications			●		●	●	●
Review of adjuvant therapy				●			
Review of additional reconstructive procedure						●	●
Cosmetic outcome (photograph)						●	●

*Second operation for staged reconstruction

Data management, data monitoring, and auditing

The data center is located in the Department of Clinical Trial Data Management, Tokyo University Graduate School of Medicine, Tokyo, Japan. No personally identifiable information will be entered into the EDC to protect participants' privacy. Data management and central data monitoring will be performed using the EDC. There will be no data monitoring committee. Similarly, auditing is also not planned for this study. Following completion of the study, the fixed data will be exported, and then deleted from the EDC. The data will be stored in a public data repository.

Harms

No serious harm is expected in this observational study. Some patients might feel psychological distress when asked about their sexual well-being.[45] The estimated time to complete a survey is

about 10 minutes, and this may be a burden.

Statistical analysis

The primary analysis of this study will describe the time-dependent changes in satisfaction with breasts score of the BREAST-Q during the 12-month postoperative period. BREAST-Q evaluation will be performed at baseline, and at 1, 3, 6, and 12 months after surgery, and summary statistics at each time point will be calculated for each surgical procedure. General linear models, which include the reconstruction procedure, time point, and time-by-procedure interaction as explanatory variables, will be used to summarize the longitudinal change of the endpoints. Likelihood-based methods will be applied to analyze incomplete data. An unstructured covariance matrix will be assumed, and robust standard error will be calculated for estimated parameters. BREAST-Q and SF-8 scores will be adjusted for age, BMI, breast ptosis, radiation therapy, chemotherapy, complications, and other factors.

ETHICS AND DISSEMINATION

Research ethical approval

All investigators involved in the current research will conduct this study in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare, 2015).

Consent

Before enrolling patients into this study, the researchers gave the patients an informed consent form, and the details about this study were explained according to the Ethical Guidelines for Medical and Health Research involving Human Subjects. All the participants were informed that they had the right to withdraw consent without any disadvantages.

Trial registration

This study protocol and the informed consent form have been approved by the Institutional Review Boards at all the participating sites. The study was registered with the UMIN Clinical Trial Registry (UMIN000032177).

Access to data

Only clinical data managers at the central data center will have access to the reported case data through the EDC system during the study. Site investigators will have access to case data within all their sites. The data manager will transfer the final dataset to the principal investigator and the data

will be stored in electronic format.

Dissemination policy

The results will be analyzed and reported in a form in which individuals cannot be identified. The findings of the study will be presented at conferences and published in peer-reviewed medical journals domestically and internationally.

DISCUSSION

Although the number of cases of BR is increasing in Japan, the outcomes of BR have not been adequately evaluated due to the lack of established outcome measures. Considering that the purpose of BR is to improve patients' satisfaction and HRQOL, PROs are very useful and essential. SAQLA is the first multicenter study in Japan to evaluate BR from this perspective. Our data will provide time-dependent changes in BREAST-Q and SF-8 scores following mastectomy and IBR. Information on the recovery process is helpful for patients who are to make BR decisions, and can facilitate patient engagement in decision-making. It can also serve as fundamental data for future clinical research and contribute to improving healthcare surrounding BR.

Our patients were mainly recruited from university hospitals, although we included patients undergoing IBR with implant-based reconstruction, latissimus dorsi flap, and abdominal flaps, which are commonly used techniques in hospitals other than university hospitals. Thus, we believe that this study sample will represent Japanese women undergoing IBR adequately. BR procedures that are performed only in a limited number of facilities, such as gluteal artery perforator flaps, total breast reconstruction with fat graft, and BR for breast conserving surgery, were not included. Since the trend of the surgical procedure for BR will change with the times, further research plans are expected for cases that are not included in this study but are expected to increase, such as bilateral RRM and BR.

Implant recall has had a significant impact on the field of BR in Japan. We cannot rule out the possibility that the fear of developing BIA-ALCL might decrease satisfaction and HRQOL of our participants, and therefore, the study results will be skewed. To account for that, DRS has been added to help us understand the psychological impact of implant recall while also paying attention to the discontinuation of reconstruction cases caused by the recall. We also considered making a comparison between outcomes of patients with recalled implants and those with other types of implants.

There are a few limitations to this study protocol. First, this is a hypothesis-generating observational study. The number of target participants has not been set statistically, but is based on the actual number of cases in the participating seven sites instead. Therefore, although we will describe the time-dependent changes in PROs following reconstruction procedures, this study will not determine

the difference between the procedures. Second, it was discussed whether the time-dependent changes in staged reconstruction should start from the primary operation (TE insertion) or the second operation (change to permanent implant or autologous tissue). The latter can be better at evaluating the recovery period of the second operation. However, we believe that it would be more beneficial to evaluate the physical and psychological well-being of patients from the primary operation itself since the extent of distress during TE insertion is one of the main concerns of patients who need to select an IBR procedure or prepare for surgery. Focusing on 12 months, we assume that cases with staged reconstruction would have a lower level of satisfaction since the downtime occupies a longer period. We would like to investigate any differences in the final aesthetic satisfaction between one-stage and staged reconstruction procedures over a 3-year follow-up period. Third, we cannot obtain results of all participants. Patients lost to follow-up may have low satisfaction and HRQOL, which can lead to bias. That is, the results of this study may represent the satisfaction and HRQOL of patients in relatively good condition, rather than represent all cases of IBR. Presumably, another research plan will be needed to understand how such "loss-to-follow-up" patients cope with the situation, in order to have a wholistic picture of IBR. Finally, our participant group includes only women who choose BR. It would be more informative to include women who undergo other breast cancer surgeries such as mastectomy without BR and breast conserving surgery. This will be investigated in a future study.

Authors' contributions

M Saiga and YK devised the project and the main conceptual ideas. M Saiga, YH, YK, KT, YA, MM, MH, TK, TM, TY, AG, and TK contributed to design of this study protocol with supervision from SW, SZ, M Sekido, M Sakuraba, TS, HD and YK.TK, TM, and YK will contribute to data management and planned data analysis.

M Saiga, YH, HU, YK, SW, KT, YA, MM, AG, TK, KM, TK, TY, MT and YT carried out acquisition of data. M Saiga wrote the manuscript with input from all authors. All authors will approve the final manuscript.

Funding statement

This research is supported by the AMED (Japan Agency for Medical Research and Development) under Grant Number JP19ck0106325.

Competing interests: None declared.

Acknowledgments: We are grateful to Sawaizumi M. for our long-term collaboration and his

advice. We would like to thank Editage (www.editage.com) for their writing support on the Abstract.

Data availability: Data sharing not applicable as no datasets generated and/or analyzed for this study.

Patient and Public involvement: Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

REFERENCES

1 Cancer Statistics in Japan; Table download. Cancer Information Service. http://ganjoho.jp/reg_stat/statistics/dl/index.html. Date accessed: 29 Mar 2020.

2 Center for Cancer Control and Information Services, National Cancer Center. Monitoring of Cancer Incidence in Japan - Survival 2006-2008 Report.

3 Wellisch DK, DiMatteo R, Silverstein M, et al. Psychosocial outcomes of breast cancer therapies: lumpectomy versus mastectomy. *Psychosomatics* 1989;30:365–73.

4 Fobair P, Stewart SL, Chang S, et al. Body image and sexual problems in young women with breast cancer. *Psychooncology* 2006;15:579–94.

5 Elder EE, Brandberg Y, Björklund T, et al. Quality of life and patient satisfaction in breast cancer patients after immediate breast reconstruction: a prospective study. *Breast* 2005;14:201–8.

6 Dauplat J, Kwiatkowski F, Rouanet P, et al. Quality of life after mastectomy with or without immediate breast reconstruction. *Br J Surg* 2017;104:1197–206.

7 Winters ZE, Benson JR, Pusic AL. A systematic review of the clinical evidence to guide treatment recommendations in breast reconstruction based on patient- reported outcome measures and health-related quality of life. *Ann Surg* 2010;252:929–42.

8 Jeevan R, Browne JP, Gulliver-Clarke C, et al. Surgical determinants of patient-reported outcomes following postmastectomy reconstruction in women with breast cancer. *Plast Reconstr Surg* 2017;139:1036e–45e.

9 Pusic AL, Matros E, Fine N, et al. Patient-reported outcomes 1 year after immediate breast reconstruction: results of the mastectomy reconstruction outcomes consortium study. *J Clin Oncol* 2017;35:2499–506.

10 Oda A, Kuwabara H, Fushimi K. Disparities associated with breast reconstruction in Japan. *Plast Reconstr Surg* 2013;132:1392–9.

11 Tanakura K, Sawaizumi M, Miyashita H, et al. The impact in an institute of social insurance coverage for breast reconstruction using silicone breast implants. *Oncoplastic Breast Surgery*

2017;2:40–5.

12 Annual report of the Japan Society of Plastic and Reconstructive Surgery Database. https://jsprs.or.jp. Date accessed: 1 May 2020.

13 Sbitany H, Wang F, Peled AW, et al. Immediate implant-based breast reconstruction following total skin-sparing mastectomy: defining the risk of preoperative and postoperative radiation therapy for surgical outcomes. *Plast Reconstr Surg* 2014;134:396–404.

14 Spear SL, Murphy DK; Allergan silicone breast implant U.S. core clinical study group. Natrelle round silicone breast implants: core study results at 10 years. *Plast Reconstr Surg* 2014;133:1354–61.

15 Fischer JP, Wes AM, Tuggle CT 3rd, et al. Risk analysis of early implant loss after immediate breast reconstruction: a review of 14,585 patients. *J Am Coll Surg* 2013;217:983–90.

16 Sailon AM, Schachar JS, Levine JP. Free transverse rectus abdominis myocutaneous and deep inferior epigastric perforator flaps for breast reconstruction: a systematic review of flap complication rates and donor-site morbidity. *Ann Plast Surg* 2009;62:560–3.

17 Gill PS, Hunt JP, Guerra AB, et al. A 10-year retrospective review of 758 DIEP flaps for breast reconstruction. *Plast Reconstr Surg* 2004;113:1153–60.

18 Selber JC, Kurichi JE, Vega SJ, et al. Risk factors and complications in free TRAM flap breast reconstruction. *Ann Plast Surg* 2006;56:492–7.

19 Hoffman AS, Cantor SB, Fingeret MC, et al. Considering breast reconstruction after mastectomy: a patient decision aid video and workbook. *Plast Reconstr Surg Glob Open* 2019;7:e2500.

20 Flitcroft K, Brennan M, Spillane A. Making decisions about breast reconstruction: a systematic review of patient-reported factors influencing choice. *Qual Life Res* 2017;26:2287–319.

21 Weichman KE, Hamill JB, Kim HM, et al. Understanding the recovery phase of breast reconstructions: Patient-reported outcomes correlated to the type and timing of reconstruction. *J Plast Reconstr Aesthet Surg* 2015;68:1370–8.

22 Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. *J Clin Oncol* 1997;15:974–86.

23 Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;14:2756–68.

24 Pusic AL, Klassen AF, Scott AM, et al. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg* 2009;124:345–53.

25 Kanatas A, Velikova G, Roe B, et al. Patient-reported outcomes in breast oncology: a review of validated outcome instruments. *Tumori* 2012;98:678–88.

26 Cohen WA, Mundy LR, Ballard TN, et al. The BREAST-Q in surgical research: a review of

the literature 2009-2015. *J Plast Reconstr Aesthet Surg* 2016;69:149–62.

27 Jagsi R, Momoh AO, Qi J, et al. Impact of radiotherapy on complications and patient-reported outcomes after breast reconstruction. *J Natl Cancer Inst* 2018;110:157–65.

28 Albornoz CR, Bach PB, Mehrara BJ, et al. A paradigm shift in U.S. breast reconstruction: increasing implant rates. *Plast Reconstr Surg* 2013;131:15–23.

29 Zelken J, Cheng MH. Asian breast augmentation: a systematic review. *Plast Reconstr Surg Glob Open* 2015;3:e555.

30 Sheflan M, Brown I. Immediate implant-based breast reconstruction using variable lower pole support. In: Urban C, Rietjens M, eds. Oncoplastic and reconstructive breast surgery. Milan: Springer 2013:235-52

31 Yoshimura A, Okumura S, Sawaki M, et al. Feasibility study of contralateral risk-reducing mastectomy with breast reconstruction for breast cancer patients with BRCA mutations in Japan. *Breast Cancer* 2018;25:539–46.

32 Calobrace MB, Schwartz MR, Zeidler KR, et al. Long-term safety of textured and smooth breast implants. *Aesthet Surg J* 2017;38:38–48.

33 Collett DJ, Rakhorst H, Lennox P, et al. Current risk estimate of breast implant–associated anaplastic large cell lymphoma in textured breast implants. *Plast Reconstr Surg* 2019;143:30S–40S.

34 McCarthy CM, Loyo-Berrios N, Qureshi AA, et al. Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE): initial report of findings, 2012–2018. *Plast Reconstr Surg* 2019;143:65S–73S.

35 Marra A, Viale G, Pileri SA, et al. Breast implant-associated anaplastic large cell lymphoma: a comprehensive review. *Cancer Treat Rev* 2020;84:101963.

36 Ware JE, Kosinski M, Dewey JE, et al. How to Score and Interpret Single-item Health Status Measures: A Manual for Users of the SF-8™ Health Survey. Lincoln, RI: Quality-Metric Incorporated 2001.

37 Harris JR, Levene MB, Svensson G, et al. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1979;5:257–61.

38 Mukai Y, Watanabe S, Matsumoto M, et al. Reliability and validity of Mamma Balance®: novel software to assess the symmetry of the nipple-areola-complex position. *J Plast Reconstr Aesthet Surg* 2017;70:1147–9.

39 Potter S, Holcombe C, Ward JA, et al. Development of a core outcome set for research and audit studies in reconstructive breast surgery. *Br J Surg* 2015;102:1360–71.

40 Unukovych D, Johansson H, Brandberg Y. Preoperative psychosocial characteristics may predict body image and sexuality two years after risk-reducing mastectomy: a prospective

study. *Gland Surg* 2017;6:64–72.

41 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.

42 Kugaya A, Akechi T, Okuyama T, et al. Screening for psychological distress in Japanese cancer patients. *Jpn J Clin Oncol* 1998;28:333–8.

43 Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003:23:281–92.

44 Tanno K, Bito S, Isobe Y, et al. Validation of a Japanese version of the Decision Regret Scale. *J Nurs Meas* 2016;24:E44–54.

45 Saiga M, Taira N, Kimata Y, et al. Development of a Japanese version of the BREAST-Q and the traditional psychometric test of the mastectomy module for the assessment of HRQOL and patient satisfaction following breast surgery. *Breast Cancer* 2017;24:288–98.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.