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Long-term outcomes of two-stage, immediate and delayed breast reconstruction with polyurethane-covered versus textured implants: protocol of a prospective, multicentre randomised controlled trial (TIPI trial)

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ABSTRACT

Introduction Two-stage implant-based breast reconstruction is the most commonly performed postmastectomy reconstructive technique. During the first stage, a tissue expander creates a sufficiently large pocket for the definite breast implant placed in the second stage. Capsular contracture is a common long-term complication associated with implant-based breast reconstruction, causing functional complaints and often requiring reoperation. The exact aetiology is still unknown, but a relationship between the outer surface of the implant and the probability of developing capsular contracture has been suggested. The purpose of this study is to determine whether polyurethane-covered implants result in a different capsular contracture rate than textured implants.

Methods and analysis The Textured Implants versus Polyurethane-covered Implants (TIPI) trial is a multicentre randomised controlled trial with a 1:1 allocation rate and a follow-up of 10 years. A total of 321 breasts of female adults undergoing a two-stage breast reconstruction will be enrolled. The primary outcome is capsular contracture at 10-year follow-up which is graded with the modified Baker classification. It is analysed with survival analysis using a frailty model for clustered interval-censored data, with both an intention-to-treat and per-protocol approach. Secondary outcomes are other complication rates, surgical revision rate, patient satisfaction and quality of life and user-friendliness. Outcomes are measured 2 weeks, 6 months, 1, 2, 3, 5 and 10 years postoperatively. Interim analysis is performed when 1-year, 3-year and 5-year follow-up is completed.

Ethics and dissemination The trial has been reviewed and approved by the Medical Research Ethics Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2018-126) and locally by each participating centre. Written informed consent will be obtained from each study participant. The results will be disseminated by publication in peer-reviewed journals.

Trial registration NTR7265.

Strengths and limitations of this study

- Designed as a randomised controlled trial, the highest quality clinical study design.
- Follow-up is sufficiently long, namely 10 years.
- Neither patient nor physician is blinded to treatment allocation.
- Some complications are subjectively scored lacking an objective diagnostic tool.

INTRODUCTION

One in every seven women is diagnosed with breast cancer of whom approximately a third undergoes a mastectomy.[1–3] Breast reconstruction can improve the quality of life and is an important and integrated optional part of the treatment offered to women.[4] Various breast reconstruction techniques exist; however, a two-stage silicone implant-based breast reconstruction remains the most commonly used procedure.[5 6] A tissue expander (TE) is temporarily placed and gradually inflated during routine visits to the outpatient clinic to create sufficient space for a definite breast implant placed during a second operation several months later.[7] Although excellent aesthetic results can be obtained using this technique, there are various short-term and long-term complications related specifically to the use of breast implants. Capsular contracture is a notorious complication with reported rates ranging from 0% to 30% and one of the main reasons for explantation.[8–14] If the internal scar tissue, which always develops around the breast implant as a result of a foreign body reaction, forms a tight and constricting capsule, the breast becomes

deformed and firm, deteriorating the aesthetic results. If the capsular contracture progresses, the breast may also become painful.

The aetiology of capsular contracture is not well understood. Most likely, it is a multifactorial process and various risk factors have been identified.[8 12 15] One aspect to this is the type of surface of the breast implant. Traditionally, three types of surfaces are distinguished, that is, smooth, textured (in varying degrees of roughness) and polyurethane covered. It is generally accepted that smooth implants are associated with a higher rate of capsular contracture than textured implants. The difference between textured silicone implants (TI) and polyurethane-covered silicone implants (PI) with regard to capsular contracture rates is less clear, but a recent review showed that the use of PI's may reduce the risk of capsular contracture, with reported rates of 1.8% and 3.4% after a follow-up of 8 and 4 years, respectively.[10 13 16] Another recent study reported a rate of 8.1% after a median follow-up of 9 years[17] and one study showed that PI's result in 10% less capsular contractures after 10 years compared with TI's.[11] This reduction is attributed to the polyurethane surrounding the implant, causing the collagen fibrils to arrange more randomly because of an interaction with the sponge-like structure of the polyurethane. By preventing an organised and parallel alignment of collagen fibrils, these cannot interact and the strength required for capsular contracture cannot occur.[8 10 18]

The choice for an implant type is a trade-off between various risks and benefits related to that type. Use of PI or TI may decrease risk for capsular contracture, but recent literature has reported an increased risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), a relatively rare but substantial adverse event (AE).[19–22] Reliable data are needed to weigh such factors appropriately and facilitate evidence-based implant choice.

However, the current literature about capsular contracture lacks prospective cohorts, comparative study designs and sufficiently long follow-up. The risk of capsular contracture accumulates over time and studies have indicated that a follow-up of at least 10 years is necessary to properly assess this complication.[11 23] Therefore, a prospective randomised controlled trial with adequate follow-up is needed to determine whether polyurethane covered silicone implants have the suggested positive effect on the chance of capsular contracture formation compared with standard textured silicone implants. We present the study protocol for the Textured Implants versus Polyurethane-covered Implants (TIPI) trial (V.3.0; 8 February 2019), in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[24]

Objectives

The primary objective of the TIPI trial is to determine whether textured silicone implants (TI) produce a different capsular contracture rate than polyurethane covered silicone implants (PI) in two-stage breast reconstruction after mastectomy.

The secondary objectives are to compare TI's and PI's with regard to the rates of other complications and revision surgery, patient satisfaction and quality of life (PS-QoL), and user-friendliness.

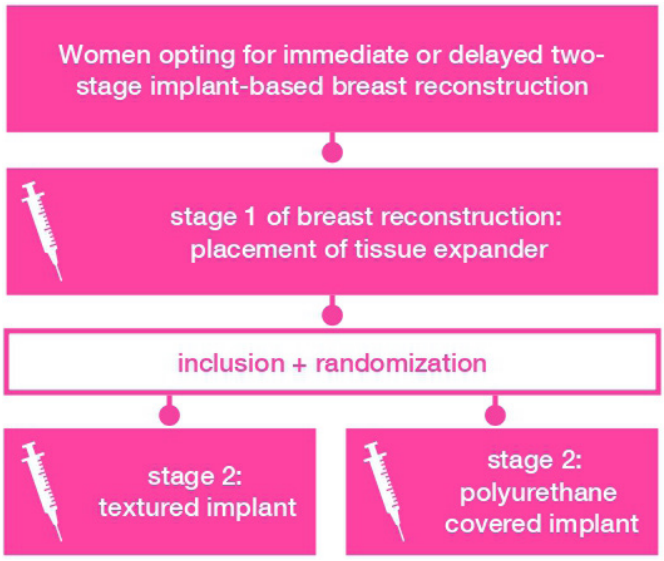

Figure 1 Study design of the TIPI trial. TIPI, Textured Implants versus Polyurethane-covered Implants.

METHODS

Design

The TIPI trial is designed as a multicentre prospective randomised controlled, parallel group, two-arm, comparative trial with a 1:1 allocation ratio. A summary of the trial is depicted in figure 1.

Setting

This study is led by the department of Plastic and Reconstructive Surgery at the Erasmus MC, University Medical Center Rotterdam in the Netherlands. Fifteen study sites will participate, both academic and general hospitals in the Netherlands.

Population

All patients interested in breast reconstruction following their mastectomy are referred to a plastic surgeon. These patients are the source population for this study if they opt for a two-stage implant-based breast reconstruction. Inclusion is done per breast after a successful first stage of TE insertion and inflation.

Inclusion criteria

In order to be eligible to participate in this study, a breast must meet all of the following criteria

- Female patient, aged 18 years or older
- Mastectomy is performed
- Undergoing immediate or delayed breast reconstruction

- Eligible for two-stage implant-based breast reconstruction in accordance with the Dutch national breast reconstruction guideline
- First step of two-stage submuscular implant-based breast reconstruction (placement of TE) is successfully completed
- Patient is able to understand the patient information sheet, to complete questionnaires and to provide written informed consent

Exclusion criteria

If any of the following criteria are met, a subject is not eligible for inclusion:

- Additional use of autologous tissues to reconstruct the breast (eg, latissimus dorsi flap)
- The use of an acellular dermal matrix or a synthetic mesh
- Prior irradiation of the breast or an indication for postoperative radiotherapy
- Revision surgery or tertiary breast reconstruction
- Inflammatory carcinoma.
- Evidence of distant metastases.
- Active infection at the surgical field or distant locations

Interventions

Surgical technique

All patients will undergo a mastectomy, performed by a surgical oncologist, followed by a two-stage immediate or delayed breast reconstruction using breast implants. During the first stage, a TE is placed in a (partial) submuscular pocket in order to create enough space for the definite implant. In selected patients a de-epithelialized caudal skin flap is used for additional cover of the implant. Postoperatively, the TE is inflated during regular outpatient clinic visits until the desired volume is reached.

During the second stage, the TE is replaced by a definite implant, which differs for the intervention and control cohort (see 'Breast implants' below). After removal of the TE, the capsule surrounding it is scored ('capsulotomy') and may be partially removed ('capsulectomy'), to stimulate tissue adherence to the implant. The definite implant is then placed in a partial (at least below the pectoralis major) or total submuscular pocket as chosen by the surgeon.

With both surgeries, perioperative hygienic measures will be taken to minimise the risk of infection, conform national guidelines and institutional protocols. This includes, among other things: timely prophylactic intravenous antibiotics consisting of a single dose of 1–3 g cefazolin, glove change before placing the implant, one touch technique, pocket and implant wash with an antibiotic solution (2 g cefazolin and 80 mg gentamicin in 500 mL saline) and a closed-door policy while implants are exposed to air. Drains are used at the discretion of the plastic surgeon. Patients are advised to wear a sports bra day and night for 6 weeks.

Breast implants

The TEs used in the first reconstructive stage are identical in both cohorts. All participating centres are allowed to use their routinely employed type and brand for all their breast reconstructions. However, brands and types might differ between hospitals.

For the intervention cohort, silicone breast implants with a micropolyurethane-foam cover (Microthane) are used, produced by POLYTECH Health and Aesthetics (Germany).

In the control cohort, patients receive textured silicone breast implants routinely used in the participating medical centre. These are all microtextured (10–50 µm) implants and brands or types may differ between centres.[25]

The breast implants in this study are not experimental, have a CE-marking and are only used according to intended use. They have an anatomical or round shape.

There are no predefined criteria for discontinuing or modifying allocated interventions.

Outcomes

Type and number of surgical as well as non-surgical complications, reoperations, PS-QoL and user-friendliness of both implant types are assessed conform the Core Outcome Set for breast reconstruction.[26] All complications are assessed 2 weeks, 6 months, 1, 2, 3, 5 and 10 years postoperatively by a well-trained member of the participating departments of plastic and reconstructive surgery (consultant, resident, research nurse or coordinating researcher), usually the operating plastic surgeon.

Primary outcomes

The primary outcome is capsular contracture. A capsular contracture is a clinical diagnosis assessed by the modified Baker classification.[27] Baker grade 3 or 4 capsular contractures are considered clinically relevant. A breast with a grade 3 contracture feels and looks moderately firm, and the implant is readily discernible. Although the patient may be dissatisfied, reoperation is not necessarily required. Grade 4 represents an excessively firm reconstructed breast, resulting in an unacceptable aesthetic result and/or significant patient symptoms such as pain. Surgical intervention is required.[27] Capsular contracture is scored dichotomously comparing Baker grades 3 and 4 to grades 1 and 2.

Secondary outcomes

Other complications and reoperations

The following complications will be scored: cutaneous rash, haematoma, seroma, infection, skin necrosis, implant rupture, malposition, breast animation, implant exposure, excessive visibility/palpability, ASIA syndrome (autoimmune/inflammatory syndrome induced by adjuvants) and BIA-ALCL (table 1). In addition, an open 'other complications'-category will be scored to register systemic and/or omitted breast complications.

Table 1 Descriptions for all complications scored explicitly in the TIPI trial

Complication	Description
Cutaneous rash	Erythema of the skin that is deemed abnormal.
Haematoma	Bruising, swelling and firmness of the breast leading to surgical exploration.
Seroma	Palpable lump suggesting liquid under the skin accompanied with tenderness.
Infection	Symptoms of abnormal erythema, warmness, swelling, tenderness and/or a body temperature exceeding 38 °C that either resolves with antibiotics (minor infection) or requires reoperation (major infection).
Skin necrosis	Darkening of the skin to dark blue or black. Treated conservatively by local wound management and healing by secondary intention (minor skin necrosis), or by surgical excision and closure or reconstruction (major skin necrosis).
Implant malposition	Malposition of the implant as judged by the plastic surgeon leading to inferior aesthetic result.
Breast animation	Abnormal distortion of the breast with muscle contraction.
Implant exposure	Implant is not completely covered by soft tissues so that it becomes visible.
Implant rupture or deflation	Is only scored when confirmed at the time of explantation.
Excessive implant visibility/ palpability	Deformity is significantly troublesome to the patient or requires reoperation.
ASIA syndrome	**Is diagnosed based on Shoenfeld's criteria.**[41]
BIA-ALCL	Late seroma or mass. Diagnosis is confirmed by histopathological examination.
Other complications	Category which will be scored to register systemic and/or omitted breast complications

ASIA syndrome, autoimmune/inflammatory syndrome induced by adjuvants; BIA-ALCL, breast implant associated anaplastic large cell lymphoma; TIPI, Textured Implants versus Polyurethane-covered Implants.

Severity of all complications will be assessed using the Clavien-Dindo classification[28] and data will be aggregated as proportions.

Reoperations will be registered together with the indication.

Patient satisfaction and quality of life

PS-QoL is scored using three validated questionnaires. Patients answer these before the second step of their breast reconstruction and again postoperatively after 2 weeks, 6 months and 1, 2, 3, 5 and 10 years.

The 36-Item Short Form Health Survey (SF-36), version 2, assesses the general health status of the patient.[29] It consists of eight scales yielding two summary measures: physical and mental health. Answers are converted into scores ranging from 0 to 100, with higher scores indicating better health.

The Reconstruction Module of the BREAST-Q, V.2, assesses PS-QoL specifically associated with breast reconstruction and consists of five domains regarding PS-QoL and four domains about patient experiences.[30] Answers for each domain result in an independent score from 0 to 100, with higher scores representing a better outcome. There is no overall BREAST-Q score.

The EuroQol five dimensions, five levels questionnaire (EQ-5D-5L) measures the generic health status and may be used in cost-utility analysis.[31]

User-friendliness

The user-friendliness of the definite implants is evaluated after each operation in which they are handled. Plastic surgeons fill in a non-validated questionnaire valuing different aspects of ease of handling during implantation or explantation of the definite implant on a 10-point Likert scale.

Baseline characteristics

Several baseline values are scored, that is, age, body mass index, breast size, smoking, skin type, allergies, medication, comorbidities, prior breast surgery, tumour histology and stadium, genetic predisposition for breast cancer, oncological treatment, details on the course of the first reconstructive phase, educational attainment, household composition and employment. In case of a genetic predisposition for breast cancer, the involved mutation is noted.

Statistical analysis

Primary outcome

The primary outcome will be analysed on breast level using survival analysis, because capsular contracture accumulates over time. This allows for staggered entry of cases into the trial and irregular loss to follow-up. 'Time to event' is defined as the time from placement of definite implant to diagnosis of a Baker grade 3 or 4 capsular contracture.[27] Breasts without a diagnosis of capsular contracture are censored at final follow-up.

A frailty model for clustered interval-censored data will be used for analysis, which will produce HRs. This model will treat patients, mastectomy indication and centre as clusters, thereby accounting for the correlation structure of the data (measurements within patients will be more related than measurements between patients)

and for stratification in the randomisation process (see 'Treatment allocation'). Also, this model allows for the possibility of interval censoring resulting from the study's design. Finally, it enables adjusting for potential confounders.

The primary study parameter will be analysed after 10 years of follow-up with both an intention-to-treat and a per-protocol analysis. With the intention-to-treat analysis, patients will not be censored in case of surgical manipulation of the capsule. With the per-protocol analysis, if a breast requires an operation in which the capsule is opened during an operation for which the indication is not capsular contracture, the breast is censored in the primary analysis. Also, if a breast changes cohort for any reason, it will be censored.

The model will adjust for covariates that have a substantial influence on capsular contracture development as the number of observed events allows it. They will be identified at the time of analysis with a hypothesis led approach based on literature/expert opinion.

Finally, breasts that suffer more than one capsular contracture will be analysed using descriptive statistics.

Secondary outcomes

Time to capsular contracture will also be analysed as secondary outcome at 1-year, 3-year and 5year follow-up.

All other complications are presented as categorical variables. Binary/ordinal outcomes will be analysed with multilevel (centre, indication, patient) generalised linear mixed effect models (logistic/ordinal mixed effect models). A hypothesis led approach will be used to construct the model; whereby potential confounders are included based on literature/expert opinion. No adjustment of the alpha-level for multiple hypothesis testing will be made in the secondary outcome measures will be interpreted in agreement with their secondary nature.

The results of the SF-36 and Breast-Q will be shown as means with SD and CI or as medians with first and third interquartile ranges, depending on skewedness. Anticipating variability in baseline scores, differences between preoperative and the postoperative measurement points will be compared between the two arms of the trial with non-parametric tests (Mann-Whitney U test). Multilevel linear mixed effects models will be used to compare both cohorts over time while also accounting for between-patient and between-centre variability and to assess the effect of prior breast cancer and complications and/or reoperations. The comparison of these latter subgroups will also be shown through descriptive statistics.

The health states derived by the EQ-5D-5L will be presented using descriptive statistics.

User-friendliness will be compared between the two study arms with a Mann-Whitney U test.

The continuous baseline characteristics that are collected will be presented as means with SD for both cohorts. Categorical data will be presented as both absolute numbers and percentages of the total for both cohorts.

No interim analysis will be performed during the accrual period. When 1-year, 3-year and 5-year follow-up will be completed, an analysis will be done for the secondary outcome measures in order to publish results over these first intervals. If these analyses show significant differences, follow-up is still continued according to protocol. Inclusion has already been finished by then and continuing the study only requires a few outpatient clinic visits. As described in the introduction, the development of capsular contracture is time depended with the risk accumulating over time and it is important to obtain information for this complication for a follow-up of 10 years.

CIs of 95% will be used and all tests will be two-sided with statistical significance defined as $p<0.05$.

Sample size calculation

The literature is lacking sufficient reliable data to run a simulation for the purposed model and therefore the sample size was determined using a simpler two-sided, two sample proportion test for a range of feasible effect sizes.

As mentioned in the introduction, the capsular contracture rates vary widely in literature. Few studies have reported on these rates in breast reconstruction after long-term follow-up specified to the type of implants used in this trial. The best available studies at the time of the sample size calculation reported rates between 1.8% and 8.1% after 3–9 years follow-up[10 13 16 17] for PI's. For textured implants, most available data came from Food Drug and Administration studies with rates between 8.2% and 24% after 4–10 years follow-up.[13 32–36] Extrapolating to a 10-year follow-up period for both cohorts, we assumed capsular contracture rates in the range of 5%–7% for PI's and 16%–19% for textured implants. These ranges were used to calculate samples sizes using R-software (V.1.0.153) and the TrialSize package (V.1.3) based on a two-sample, two-sided proportion test with an alpha of 0.05, a power of 0.80 and a group size ratio of 1. Because the present study will have a 10-year follow-up, 20% lost to follow-up was taken into account.[37] From the resulting sample size ranges, we conservatively selected a total sample size of 321 breasts implants which we regard both a feasible number and should provide sufficient power (table 2). Since some patients will receive bilateral implants, fewer patients will be included.

Patient recruitment and timeline

Only after completion of the first reconstructive stage (placement of a TE), the patient is informed about the trial. This is feasible because this first stage is standard of care and identical in both cohorts. This moment is chosen for two reasons. First, the period in which breast cancer or a genetic predisposition for breast cancer is diagnosed, is stressful and demanding for patients. We aim to avoid additional patient burden by postponing sharing study information and the decision on participation until calmer times. Second, we reason that patients

Table 2 Results of the sample size calculations for combinations of various survival rates based on a two-sample, two-sided proportion test

α	Power	Group size ratio	Survival rate 1	Survival rate 2	Total sample size	Total sample size adjusted for lost to follow-up: 20%
0.05	0.8	1	0.95	0.81	161	202
0.05	0.8	1	0.94	0.81	195	245
0.05	0.8	1	0.93	0.81	239	299
0.05	0.8	1	0.95	0.82	181	227
0.05	0.8	1	0.94	0.82	222	278
0.05	0.8	1	0.93	0.82	276	345
0.05	0.8	1	0.95	0.83	206	257
0.05	0.8	1	0.94	0.83	256	321
0.05	0.8	1	0.93	0.83	324	405
0.05	0.8	1	0.95	0.84	236	295
0.05	0.8	1	0.94	0.84	300	375
0.05	0.8	1	0.93	0.84	387	484

The green row indicates the conservatively selected sample size deemed both feasible and enough to reject the null hypothesis given the current literature.

are more likely to participate in the present study if they are less burdened by other worries and have completed an important part of their oncological treatment (eg, mastectomy and (neo)adjuvant therapy). We anticipate this will positively affect the inclusion process.

In this phase, the patient visits the outpatient clinic regularly to fill the TE which provides ample time for informing the patient and well-advised decision making. First, written and verbal information is given by a member of the reconstructive team (consultant or resident), usually the operating plastic surgeon. A follow-up with the coordinating researcher by (video)call may be offered to minimise any threshold for asking questions or requesting additional information. Patients get a minimal reflection period of 7 days. Before informed consent is obtained any remaining questions are answered. Subsequently, the patient will be randomised followed by a consultation to select the optimal dimensions of the assigned breast implant type.

After exchanging the TE for the definite implant, the patient will visit the outpatient clinic for follow-up after 2 weeks, 6 months, 1, 2, 3, 5 and 10 years. 4, 6, 7, 8 and 9 years postoperatively, patients receive a digital questionnaire inquiring after possible symptoms suggesting complications and changes in their contact information. This is thought to improve patient adherence and retention. Also, participants will receive restitution of parking and travel costs for study related follow-up.

A summary of the participant timeline is portrayed in figure 2.

Treatment allocation

Computer-generated permuted-block randomisation lists (block size 2, 4 or 6) were generated through a website by an independent researcher and saved in a spreadsheet file.[38] Stratification was done by participating centre and mastectomy indication (oncologic or prophylactic). Two independent researchers have exclusive access to these lists. They allocate treatment to participants (note: not to individual breasts) in order of study enrolment, which is done by the study site investigator (the patient' s plastic surgeon) and communicated through the coordinating investigator. Both breast implants will be of the same type

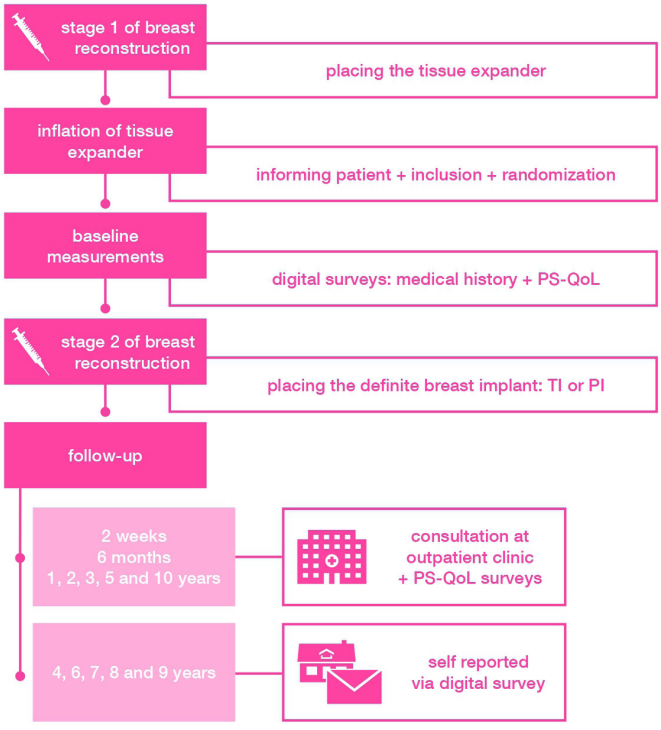

Figure 2 Summary of the participant timeline. PI, polyurethane-covered breast implant; PS-QoL, patient satisfaction and quality of life; TI, textured breast implant.

if a patient receives bilateral implants, even if only one breast is included in the trial. The allocated treatment is made known to the surgeons and patients at least 3 days prior to surgery, so neither is blinded.

Data collection and management

All data will be collected with GemsTracker, a software package for distribution of digital questionnaires and forms. Both patients and physicians enter data. Patients receive emails with a secured link to GemsTracker's website to answer digital questionnaires at the appropriate times, both for measuring QoL and collecting baseline characteristics. These emails as well the reminders are sent automatically if questionnaires remain incomplete.

Physicians each have a personal account providing access to GemsTracker to enter data through various predefined forms for baseline characteristics and follow-up.

Mainly predefined answer categories are used on these forms to ensure data quality. Answering all essential questions is mandatory before the form can be submitted in order to ensure data completeness.

The collected data are stored in an electronic database through GemsTracker which automatically encodes as prespecified. This database is stored on a secure server of the coordinating study site and has an adequate backup system.

The coordinating researcher will regularly monitor whether all data are registered timely and properly, by both participants and surgeons, to promote data completeness.

(Serious) adverse events

AEs are defined as any undesirable experience occurring to a subject during the study, whether or not considered to be related to the PI. All AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All AEs will be followed until they have abated, or a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

A serious adverse event (SAE) is any untoward medical occurrence or effect that: results in death, is life threatening (at the time of the event), requires hospitalisation or prolongation of hospitalisation, results in persistent or significant disability or incapacity, or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based on appropriate judgement by the physician. An elective hospital admission will not be considered as an SAE. The physician will report all SAEs to the coordinating investigator without undue delay after obtaining knowledge of the events. The coordinating investigator will report the SAEs to the accredited Medical Research Ethics Committee (MREC) that approved the protocol timely in accordance with regulations.

Data monitoring

The conduct of the study will be monitored in accordance with Erasmus MC guidelines assuming a medium risk. Monitoring will be done by a resident or PhD candidate of the Plastic and Reconstructive Surgery Department of the Erasmus MC who is independent from this study. Monitoring is done 2–3 times per year per centre depending on inclusion rate and previously observed deviations. During a visit, inclusion and dropout rates are checked, as well as informed consent, inclusion and exclusion criteria, protocol compliance and reporting of SAE's for roughly 25% of participants. Detailed frequencies and procedures are found in the Erasmus MC Monitoring plan (version date: 19 February 2013).

There will be no data monitoring committee, because this study does not involve a life-threatening disease or a vulnerable population, and because the intervention is not experimental but rather standard of care and is not expected to have a significant risk of potential harm for the patient.[39]

Patient and public involvement

Patients and the public were not involved in the study design. However, information about this trial has been approved and is distributed through the website 'www.kanker.nl', an initiative by The Dutch Federation of Cancer Patient Organisations (NFK) that provides reliable information about cancer to patients and their relatives.[40]

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the Declaration of Helsinki (version: October 2013, Fortaleza, Brazil) and in accordance with the Medical Research involving Human Subjects Act (WMO).

The trial has been reviewed and approved by the MREC of the Erasmus MC, University Medical Centre Rotterdam (MEC-2018-126). All amendments will be notified to the MREC that gave a favourable opinion, and relevant parties through email.

Written informed consent will be obtained from each study participant by their physician or the coordinating investigator by mail. This is done at least 1 week after written and verbal study information was shared, and after answering any questions of the patient to satisfaction (online supplemental appendix 1). The informed consent form also stipulates how participants data are stored, shared and used.

The database will not be anonymous, but restrictions will be placed on the rights of different types of users. The principal investigator, coordinating investigator, auditor and ICT-team will have access to all data. The treatment team will only have access to data of its own patients in the database. If data are shared with other party than the above, data will be pseudonymised.

The department of Plastic and Reconstructive and Hand Surgery of the Erasmus MC received funds for

conducting the TIPI trial from the manufacturer of the investigational product, POLYTECH Health & Aesthetics GmbH based in Germany. It was contractually ensured that this party does not have any rights to influence the study protocol, study execution or publishing of any results. POLYTECH does have the right to be informed through regular progress updates, and about any protocol changes or upcoming publications.

No provisions about ancillary and post-trial care are in place as the healthcare system in the Netherlands ensures all participants get the care they need through health insurance. In accordance with Dutch law, each study site has a liability insurance and the coordinating centre has a human subject insurance which provides cover for damage to research subjects through injury or death caused by the study until 4 years after its conclusion.

The results of this study will be disclosed unreservedly through publications in peer-reviewed journals. Patients will be informed about any publication accompanied by a brief summary in Dutch.

When publishing, we will adhere to the journal's authorship eligibility guidelines. In general, we accept every individual judged to have made a substantial intellectual or practical contribution to the publication to be an eligible author. This includes anyone who has made a significant contribution to the conception or design of the project or the acquisition, analysis, or interpretation of data and/or writing and revising the manuscript. All participating plastic surgeons will at least be part of a collaborative authorship.

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Contributors JXH and MAM conceived the study concept and design. JXH, MAM, KPC and EMLC contributed to implementation of the study protocol, patient screening, data acquisition and analysis. E-RA provided statistical expertise. JXH and KPC prepared the first draft of the manuscript. All authors provided critical revisions and approved the final version.

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Competing interests The TIPI trial is investigator-initiated. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. The Department of Plastic & Reconstructive Surgery of Erasmus MC received funding from POLYTECH Health & Aesthetics GmbH in the form of financial support for personnel costs for one PhD candidate (no grant number available).

Patient consent for publication Not required.

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