CLINICAL PROTOCOL

PRADAIIBE

Protocol no CTO23023GZA

ClinicalTrials.Gov NCT06739655

Version 4.0 24-DEC-2025

ZAS vzw

Kempenstraat 100
2030 Antwerpen

Trial title, protocol version and registration

English title: Preoperative Radiation Therapy and Immediate Breast Reconstruction, a phase 3 randomised controlled trial in the Belgian population. (PRADAIIBE)

Dutch title: Preoperatieve bestralingstherapie en onmiddelijke borstreconstructie, een fase 3 gerandomizeerde gecontrolleerde klinische studie in de Belgische populatie (PRADAIIBE)

French title: Radiothérapie préopératoire et reconstruction mammaire immédiate, un essai contrôlé randomisé de phase 3 dans la population Belge

Current protocol: Version 4 - 24-DEC-2025

Trial registration

Registry	Unique Id	Date of first registration
Local trial registry (central IEC)	CTO23023GZA	22-APR-2024
ClinicalTrials.gov	NCT06739655	17-DEC-2024

Statement of compliance

This study will be conducted in compliance with this clinical study protocol, the current International Conference on Harmonization guidelines for Good Clinical Practices (ICH - GCP E6 R3), the principles of the Declaration of Helsinki (version 2024) and any applicable regulatory requirements.(1,2) Enrolment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

Confidentiality Statement

Roles and responsibilities

Coordinating team and centre (ZAS Augustinus)

Prof. Dr. Melanie Machiels, Radiation oncologist in ZAS – Iridium Netwerk[1]	Principal Investigator (PI), involved in Protocol development and trial management[a]
Dr. Tom Quisenaerts, Plastic-Reconstructive surgery resident and PhD-candidate[1]	Sub-investigator (SI), Project manager, involved in Protocol development and trial management[a]
Prof. Dr. Philip Poortmans, Radiation oncologist in ZAS – Iridium Netwerk[1]	Sub-investigator (SI), involved in Protocol development and trial oversight
Ilse Van Der Auwera, Project manager ZAS CTO[1]	Project manager, involved in Protocol development and trial management[a]

Trial sponsor and funding

Ziekenhuis aan de Stroom (ZAS) vzw, represented by CEO **Willeke Dijkhoffz[2]**	Sponsor, delegates trial responsibilities to the PI and their delegates
Kom op tegen kanker (KOTK) vzw, represented by CEO **David Vansteenbrugge[3]**	Funder, delegates trial responsibilities to the PI and their delegates. Requests annual updates in order to assess correct trial conduct and viability.

Trial Steering Committee (TSC)[b]

Prof. Dr. Philip Poortmans, Radiation oncologist in ZAS – Iridium Netwerk[1]	TSC president
Prof. Dr. Melanie Machiels, Radiation oncologist in ZAS – Iridium Netwerk[1]	TSC member
Prof., Dr. Filip Thiessen, Plastic-Reconstructive surgeon in ZAS – Clinic12b[1,4]	TSC member
Prof. Thierry Tondu, Plastic-Reconstructive surgeon in ZAS – Clinic12b[1,4]	TSC member
Dr. Zainab Amajoud, Surgical Oncologist (Gynaecologist) in ZAS[1]	TSC member
Dr. Kevin Punie, Medical Oncologist in ZAS[1]	TSC member
Dr. Tom Quisenaerts, Plastic-reconstructive surgery resident and PhD-candidate in ZAS[1]	TSC member
Dries Reynders, Senior statistician, Stat-Gent – Ghent University[5]	TSC member

Trial writing committee

Prof. Dr. Melanie Machiels, Radiation oncologist in ZAS – Iridium Netwerk[1]	Writing of the study report and scientific or public disseminations
Dr. Tom Quisenaerts, Plastic-reconstructive surgery resident and PhD-candidate[1]	Writing of the study report and scientific or public disseminations

[a]: Trial management will include overseeing data collection and handling, data analysis (supported by a statistician consultant), data interpretation.
[b]: The TSC will also take upon itself the role of overseeing end point adjudication and will advise on data management
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Funding

This clinical trial is financially funded by “Kom op tegen kanker vzw” (KOTK), providing a grant covering all direct study related expenses. This grant results from the KOTK “Call for proposals 2022 - Clinical trials”. KOTK is a non-profit organisation focused on supporting patients with cancer and research in the field of oncology.

The indirect/overhead costs such as the functioning of the ZAS Augustinus clinical trial office, and additional (unforeseen) costs will be covered by “Iridium network vzw” and “Ziekenhuis aan de Stroom vzw” (ZAS).

Sponsor's Approval

Protocol title: Preoperative Radiation Therapy and Immediate Breast Reconstruction, a phase 3 randomised controlled trial in the Belgian population. (PRADAIIBE)

Version number and date: 4.0 24-DEC-2025

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated below.

Sponsor Representative:

Signature: _____ Date: _____

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Signature: _____ Date: _____

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Investigator Agreement

Protocol title: Preoperative Radiation Therapy and Immediate Breast Reconstruction, a phase 3 randomised controlled trial in the Belgian population. (PRADAIIBE)

Version number and date: 4.0 24-DEC-2025

I have read the protocol, appendices, and accessory materials related to the *"Preoperative Radiation Therapy and Immediate Breast Reconstruction, a phase 3 randomised controlled trial in the Belgian population. (PRADAIIBE)"* clinical trial and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R3)
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study specific procedures or administering investigational products to those participants
- To maintain records of each participant's participation and all data required by the protocol

Signature: _____ Date: _____

Name: _____

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List of Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALND	Axillary Lymph Node Dissection
AR	Adverse Reaction
BCS	Breast Conserving Surgery
BCT	Breast Conserving Therapy
BMI	Body Mass Index
BP	Bisphosphonates
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBR	Delayed Breast Reconstruction
DCIS	Ductal Carcinoma In Situ
DFS	Disease-free survival
DIEP	Deep Inferior Epigastric Perforator
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EHR	Electronic Health Record(s)
EMA	European Medicine Agency
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level
EU	European Union
EVF	Eligibility Verification Form
FU	Follow-up
GEE	Generalised Estimating Equation
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IBR	Immediate Breast Reconstruction
ICE	Inter-Current Event(s)
ICF	Informed consent form
ICH	International Counsil for Harmonisation
IEC	Independent Ethics Committee
IQR	Inter-Quartile Range (statistics)
ITT	Intention-to-treat population/analysis
KM	Kaplan-Meier
LMM	Linear Mixed Model(s)
LPLV	Last Patient Last Visit
LST	Last study visit (last treatment instance of RT of Onco/Recon surgery, finalising treatment; systemic therapies are not taken in consideration in this respect)
ME	Mastectomy, broad term which covers all forms.
NACT	Neoadjuvant chemotherapy
MCAR	Missing Completely At Random
MRM	Modified Radical Mastectomy
MWU	Mann Whitney U (statistical test)

NCI-CTCAE	**National Cancer Institute Common Terminology Criteria for Adverse Events**
NSM	**Nipple Sparing Mastectomy**
OAR	**Organs At Risk (Radiotherapy related term)**
OS	**Overall Survival**
pCR	**Pathological Complete Response**
PMRT	**Postmastectomy radiotherapy**
Postop-RT	**Postoperative radiation therapy**
Preop-RT	**Preoperative radiation therapy**
PROM	**Patient Reported Outcome Measure**
RT	**Radiation therapy**
SAE	**Serious Adverse Event**
SAR	**Serious Adverse Reaction**
SAP	**Statistical Analysis Plan**
SD	**Standard Deviation (statistics)**
SNP	**Sentinel Node Procedure**
SoC	**Standard of Care (therapy)**
SoE	**Schedule of Events**
SSM	**Skin Sparing Mastectomy**
SUSAR	**Suspected Unexpected Adverse Reaction**
TE	**Tissue Expander**
TT	**Targeted Therapy**
TTE	**Time-To-Event (statistics)**
UAR	**Unexpected Adverse Reaction**
VAS	**Visual Analogue Scale**

Amendments

History of the protocol and its amendments	
Protocol version	**Date of IEC application**
Protocol v1.0, original protocol	22-APR-2024
Protocol v2.0, amendment	25-OCT-2024
Protocol v3.0, amendment	17-JUN-2025
Protocol v4.0, amendment	24-DEC-2025

Protocol v4.0, amendment

Purpose of this amendment:

1. A new BREAST-Q scale was added, the "satisfaction with breasts" scale from the "Mastectomy" module was added to the IMFU visit, in order to capture the BREAST-Q score at the moment after mastectomy, and before reconstructive surgery.
2. After developing and discussing the statistical analysis plan some minor discrepancies existed between the statistical methods described in the previous protocol version, and the SAP. This amendment will correct these discrepancies. These changes do not reflect major changes in the hypotheses posed in this trial, nor their conclusions.
3. More in-depth discussion of the recruitment process
4. The randomisation process was moved from section 6, to section 5 where it is more appropriately placed as it is an integral part of the study procedures.
5. The eligibility criterium concerning a history of breast cancer/radiation therapy is more specifically defined as ipsilateral, as the previous wording could be interpreted as excluding contralateral disease/radiation therapy history as well.
6. A transformation of the EQ-5D-5L index score to the 0 to 1 scale was added, due to the fact that this scale is proposed by the EQ-5D-5L documentation, and improves interpretability.
7. The BREAST-Q outcome variable was removed from the secondary variables. Initially the BREAST-Q was included as both the primary and a secondary variable due to the fact that the initially planned statistical assessment would be different. After reforming the SAP this is no longer necessary as all outcomes will be assessed using both a LMM and MWU-test.
8. The analysis of the pathological response outcome variable was changed to account for the fact that Preop-RT can be regarded as a preoperative therapy, eliciting response assessment, even when there was no preoperative-systemic therapy administration. Since the time between Preop-RT and oncological surgery is 2-6 weeks, we don't expect this to impact the pathological response at this short interval. Which would lead to an inflation of the 'No signs of response (Pinder 3)' category in the experimental arm.
   This will be handled by defining that this outcome will only be assessed in the group of patients receiving preoperative systemic therapy.
   However, all reported pathological response categories will be recorded and these will be presented in the safety data, next to the previously defined outcome.

A summarised list of key changes is provided in appendix 6: amendment history

Synopsis

Title	Preoperative Radiation Therapy and Immediate Breast Reconstruction, a phase 3 randomised controlled trial in the Belgian population. (PRADAIIBE)
Protocol number	CTO23023GZA
Study sites	The study will be conducted at multiple centres across Belgium. Please refer to the study sites list for an up to date listing of participating study sites. This is available upon motivated inquiry.
Disease under study	Breast cancer
Study Objectives and Endpoints	
Objective	**Endpoint**
Primary	
Satisfaction with breasts, PROM (BREAST-Q)	**Operationalisation (measurement variable):** The satisfaction with breasts outcome variable is operationalised through the "satisfaction with breasts" scale from the BREAST-Q (v2) 'Reconstruction', 'Breast Conserving Treatment', or 'Mastectomy' modules (as applicable). The answers from the questionnaire are then transformed into a 'BREAST-Q Score', using the provided conversion scales.(3) The BREAST-Q score can range from 0 to 100. The BREAST-Q v2 questionnaires are discussed in section 5.4.4, and added in appendix 2. **Analysis metric:** The transformed value of the BREAST-Q score will be used for analysis. **Method of aggregation:** Mean, SD, median, IQR, and range will be reported. For comparisons and estimands, please refer to the SAP. **Time point(s):** A baseline assessment is performed during the screening visit, followed by repeated measurements during the IMFU (if applicable), 3M, 1Y, 2Y, 5Y, and 10Y follow-up visits. The primary endpoint is assessed at 1 year of follow-up after the last study treatment (LST). **Rationale:** The BREAST-Q is a validated and widely accepted tool for assessing different PROMs in women after (oncological) breast surgery. The 'Satisfaction with breasts' scale offers a relatively short (max 15 items) yet complete (assessing feel, comfort, cosmesis, etc.) assessment of the patient's satisfaction with their breasts after reconstructive surgery (or BCS/ME).
Secondary	
Quality of Life, PROM (QoL, EQ-5D-5L VAS and Index score)	**Operationalisation (measurement variable):** 'Quality of Life' will be assessed using the EQ-5D-5L questionnaire. From this questionnaire the VAS-score and Index-score will be derived. The VAS-score can be used as recorded. The index score is derived from the answers to each of the 5 Liker-scale items, using a formula validated in the Belgian population. The EQ-5D-5L VAS-score can range from 0 to 100, while the Index-score can range from -0.533 to 0.962.(4,5) The EQ-5D-5L questionnaire is discussed in section 5.4.5, and added in appendix 3.

	Analysis metric: The VAS-score will be used as recorded. The Index-score will be transformed to a scale between 0 and 1, proportional to its original distribution. This transformation will be achieved using the following formula, where f(IS) represents the transformed score, IS the index score, 0.533 is the correction of the lowest value to zero, and 1.495 is the range difference: $$f(IS) = (IS + 0.533)/1.495$$ The rationale for this transformation, is to adhere to the scale proposed by the EQ-5D-5L documentation, and improve interpretability of the index score. **Method of aggregation:** Mean, SD, median, IQR, and range will be reported. For comparisons and estimands, please refer to the SAP. **Time point(s):** A baseline assessment is performed during the screening visit, followed by repeated measurements during the IMFU (if applicable), 3M, 1Y, 2Y, 5Y, and 10Y follow-up visits. **Rationale:** The EQ-5D-5L questionnaire offers a very short (6 items) validated questionnaire assessing QoL, offering an index score based on 5 domains using 5 level Likert-scales, as well as a general QoL assessment using a VAS item.
Breast cosmesis, objective assessment (AIS – TAS)	**Operationalisation (measurement variable):** Breast cosmesis will be assessed through a blinded panel of experts, using the 'Aesthetic Items Scale' to score a set of photographs taken during study visits. This set will consist of 4 2D digital photographs. The AIS has 5 items, each are scored from 1 to 5. These items are then summed to derive the 'Total Aesthetic Score' (TAS). The TAS can range from 5 to 25. (6,7) These are discussed in section 5.4.6, and appendix 4. **Analysis metric:** The derived value of the Total Aesthetic Score (TAS) from each assessor will be averaged to derive the TAS of each set of photos. **Method of aggregation:** Mean, SD, median, IQR, and range will be reported. For comparisons and estimands, please refer to the SAP. **Time point(s):** Photographs are taken during the screening visit, followed by repeated photographs during the IMFU (if applicable), 3M, 1Y, 2Y, 5Y, and 10Y follow-up visits. Expert panel assessment will take place at a later moment. A more detailed description is included in Appendix 4. **Rationale:** The use of photographs was included to be able to assess cosmesis in a more objective way. In order to achieve this objectiveness an expert panel will be used. The AIS-tool was selected due to its simplicity and good inter-rater validity in professionals.

Frequency and severity of adverse events (AEs)	**Operationalisation (measurement variable):** During the study all adverse events (AEs) codes and grades will be recorded in the eCRF, based on the 'National Cancer Institute Common Terminology Criteria for Adverse Events' (NCI-CTCAE) v5.0 reporting system.(8) The NCI-CTCAE v5.0 and (S)AE registration is discussed in section 5.4.8 and section 7, and added in appendix 5. **CAVEAT:** Not all postoperative complications are *explicitly* listed in the CTCAE v5.0 framework, for example: capsular contraction, implant malposition, reconstructive failure, etc. are not listed but need to be recorded. These will be registered under "Injury, poisoning and procedural complications - Other, specify" CTCAE term **Analysis metric:** Tabulation of AE frequency, type and severity. As well as the highest grade AE for each participant. **Method of aggregation:** AEs will be aggregated based on their grades. Two composite measures will be reported, consisting of 1) any AE vs. no AE, and 2) grade ≥ 3 AEs vs. no or grade <3 AEs. Tables presenting both frequency and proportions of each grade and the composite measures will be presented. Proportions will be reported as AEs compared to 'highest grade per patient', and to 'total set of AEs'. For comparisons and estimands, please refer to the SAP. **Time point(s):** AEs will be assessed and recorded continuously, with explicit querying during all follow-up visits. **Rationale:** In order to assess safety and to ensure that the experimental treatment does not differ significantly from the Standard of Care (SoC)/control treatment regarding AEs, the AEs were adopted as a secondary outcome variable. The NCI-CTCAEv5 was selected due to its uniformity in reporting and wide adoption in oncological research.
Frequency and severity of adverse events (AEs), related to surgery	**Operationalisation (measurement variable):** Cfr. 'Frequency and severity of adverse events (AEs)' (supra). For this outcome variable only the AEs related to surgical study interventions will be taken into consideration. This relationship is registered when the AE is recorded in the eCRF. **Analysis metric:** Tabulation of surgical AE frequency, type and severity. As well as the highest grade surgical AE for each participant. **Method of aggregation:** Surgical AEs will be aggregated based on their grades. Two composite measures will be reported, consisting of 1) any AE vs. no AE, and 2) grade ≥ 3 AEs vs. no or grade <3 AEs, relating to surgical AEs. Tables presenting both frequency and proportions of each grade and composite measures will be presented. Proportions will be reported as surgical AEs compared to 'highest grade per patient', and to 'total set of surgical AEs'. For comparisons and estimands, please refer to the SAP. **Time point(s):** Cfr. 'Frequency and severity of adverse events (AEs)' (supra).

	Rationale: In addition to the rationale mentioned for AEs in general, we wanted to look at the surgical AEs specifically as we believe that this subgroup is the most important one to monitor in this study.
Treatment duration	**Operationalisation (measurement variable):** The dates of diagnostic, study, and treatment milestones will be recorded in the eCRF. Time intervals expressed in days, will be assessed for: - Randomisation to last study treatment (LST) - Randomisation to oncological breast surgery - Oncological breast surgery to last study treatment (LST) As discussed in section 5.4.11. **Analysis metric:** The 'randomisation to last study treatment (LST)' time interval, expressed in days. **Method of aggregation:** KM-estimates and derived estimates for central tendency and spread will be provided. For comparisons and estimands, please refer to the SAP. **Time point(s):** These outcome variables will be continuously recorded as the participant progresses through the study and the data is entered in the eCRF. **Rationale:** The experimental treatment theoretically leads to a shorter treatment duration. In order to prove this theoretical assumption in practice, the treatment duration was adopted as a secondary outcome.
Pathological (complete) response rate (pCR)	**Operationalisation (measurement variable):** Patients receiving preoperative therapy undergo pathological response assessment of the removed breast tissues (SoC assessment). The reported response Pinder-classification or 'No preoperative therapy' will be recorded in the eCRF.(9) The assessment of pathological tumour response is discussed in section 5.4.10. **Analysis metric:** The response category as described in the pathology report will be recorded for all participants, but this outcome will only be assessed in participants receiving preoperative-systemic therapy (with, or without Preop-RT). Therefore, the response category value of participants receiving Preop-RT without preoperative-systemic therapy will not be included in this outcome due to the fact that no response is expected at 2-6 weeks after radiation therapy monotherapy, which would result in an unfair comparison. Both this subset of the ITT set, and the complete safety set will be used in the safety assessment, as described in the SAP. **Method of aggregation:** The frequency and proportion of the response categories will be presented in a table. For comparisons and estimands, please refer to the SAP. **Time point(s):** This outcome variable will be assessed after the pathology report of the removed breast tissues is available. This is checked intermittently during the treatment phase, or at least during the 3 months follow-up visit.

	Rationale: The pathological response rate was added as a secondary outcome in order to assess the effects of preoperative radiotherapy on this parameter. On the one hand as a method of assessing the experimental treatment does not negatively impact oncological safety. While on the other hand assessing the potential synergistic effects on preoperative systemic therapy.
Tertiary	

Oncological survival and time-to-event data:	**Operationalisation (measurement variable):**
	The oncological survival and TTE data are operationalised as time-to-event intervals for the events of interest listed below. These events are recorded according to the 2015 DATECAN consensus: (10)
	- Death
	  ○ All-cause mortality
	  ○ Death from breast cancer
	- Any recurrence vs. none.
	  If any recurrence has occurred it will be recorded using the subtypes:
	  ○ Invasive ipsilateral breast tumour recurrence/progression
	  ○ Local invasive recurrence/progression
	  ○ Regional invasive recurrence/progression
	  ○ Appearance/occurrence of metastasis/distant recurrence
	  ○ Ipsilateral DCIS
	
	The following TTE/survival metrics will be reported according to the 2015 DATECAN consensus: Overall Survival (OS), Breast Cancer-Specific Survival (BCSS), Relapse-Free Survival (RFS), Locoregional Relapse-Free Survival (L-RFS), and Distant-Relapse Free Survival (D-RFS).(10)
	As discussed in section 5.4.10.
	Analysis metric:
	The TTE data is registered in days from randomisation (Rz). Censoring will be used for participants without events at the end of their follow up.
	Method of aggregation:
	KM-estimates with derived estimates for central tendency and spread, as well as proportions free from events at follow-up visit timepoints will be reported. The non-aggregated data will be used for survival analysis. For comparisons and estimands, please refer to the SAP.
	Time point(s):
	Oncological TTE data will be registered at 1, 2, 5, and 10 years of follow-up after the last study treatment (LST). However, the exact dates of diagnosis/death will be used.
	Rationale:
	These oncological survival parameters were added as a tertiary outcome variable in order to assess oncological safety of the experimental treatment. These variables will be pooled with other international parallel studies, as it is likely that results from this study will be underpowered.

Study Design	
Study design synopsis	The PRADAIIBE trial is a multicentric, prospective, open-label, phase-III interventional, randomised controlled trial in patients with breast cancer for whom a skin/nipple-sparing mastectomy (SSM/NSM) and postoperative radiation therapy (Postop-RT) are indicated and who have a wish for a breast reconstruction. After providing informed consent, patients will be randomised in one of the following treatment arms: - **Standard treatment arm:** Standard of Care (SoC) treatment: Mastectomy (ME) combined with an immediate or delayed breast reconstruction (IBR/DBR) followed by radiation therapy (Postop-RT). - **Experimental treatment arm:** Preoperative radiotherapy (Preop-RT) followed by ME combined with immediate breast reconstruction (IBR), or BCS (in the unlikely event of downstaging). The primary objective of the PRADAIIBE trial is to investigate whether Preop-RT followed by ME combined with an immediate breast reconstruction (implant based or autologous) improves the patient's satisfaction with the breast reconstruction when compared to the standard of care therapy, with ME followed by Postop-RT and immediate or delayed breast reconstruction. Participation in the study will comprise a screening period, where the screening assessments must be completed before participants are enrolled and randomised. Eligible, consenting participants will then undergo treatment according to their assigned treatment group. Following the treatment period, safety (AEs, survival, pCR) and efficacy (breast satisfaction, cosmetic outcome and quality of life) are assessed during a follow-up period of 10 years.
Sample size	n=180
Eligibility criteria	Screening assessments, including review of all study eligibility criteria must be completed before enrolment and randomisation. **Inclusion criteria:** In order to be eligible to participate in this study, a participant must meet all of the following criteria: 1. Women ≥18 years with histopathologically confirmed breast cancer who: a. require SSM/NSM for any reason (e.g. extensive disease) b. require postoperative radiation therapy of at least the chest wall c. have a wish for a breast reconstruction 2. An Eastern Cooperative Oncology Group (ECOG) performance status grade ≤ 2 3. Participant is able and willing to provide written informed consent, which includes compliance with and ability to undergo all study procedures, and attend the scheduled follow-up visit(s) per protocol. **Exclusion criteria:** A potential participant who meets any of the following criteria will be excluded from participation in this study: 1. A previous history of breast cancer or irradiation of the chest wall for any other indication, on the other side (ipsilateral). A bilateral SSM/NSM + reconstruction (e.g. in case of a contralateral prophylactic SSM/NSM), or previous contralateral breast cancer disease/treatment, do not fall under this criterium and are thus allowed. 2. Collagen synthesis disease

	3. Ongoing pregnancy 4. Actively breastfeeding 5. Smoking at time of inclusion (a history of smoking is allowed but needs to be registered in the eCRF). No interval between smoking cessation and study inclusion is defined, but the reconstructive surgeon needs to be willing to operate the patient using autologous tissue transfer. This generally translates to a smoking cessation of >3months preoperatively. 6. BMI > 35 kg/m2 7. cT4d tumour, metastatic disease or any reason making SSM/NSM not indicated NOTE: If neoadjuvant chemotherapy is given, and if the indication for adjuvant systemic treatment is dependent on the presence or absence of a pathological complete tumour response pCR (such as in patients with a triple negative or Her2 positive tumour), centres can choose - to exclude these patients, - only to include these patients when a non-pCR is proven via a biopsy prior to the start of the RT. - to include these patients after the end of neoadjuvant chemotherapy, since earlier studies in partial breast RT showed that pCR rate of Preop-RT only, followed by surgery <6-8 weeks is very low in the general breast cancer population (17 of the 110), whilst it seems to be higher in patients with triple negative (6/8) and Her2 positive (1/1) (11). However, the decision to include or exclude the patients which fall into this category, should be made before the participant is randomised.
Length of Participation and study visits	Follow-up visits to assess safety and efficacy will occur as delineated in the Schedule of Events (SoE). Participants in the standard arm, who underwent DBR, will be invited for an additional intermediate follow-up (IMFU) visit at 3 months after PMRT. The first follow-up visit occurs at 3 months of follow-up (after LST). The primary endpoint will be analysed at 1 year of follow-up after last study treatment (LST), defined as the last radiotherapy session or definitive (reconstructive) surgery. After reaching the primary endpoint, participant follow-up will continue at 2 years, 5 years and 10 years after LST.
Study Interventions /treatments	**Radiation therapy** Preop-RT must be planned to commence as quickly as reasonably possible after randomisation, at the discretion of the Investigator, treating physician, or no longer than 6 weeks after the last dose of neoadjuvant chemotherapy (if applicable) or randomisation. Postop-RT will be initiated 6-12 weeks after oncological breast surgery. Patients will be treated according to departmental protocol, these protocols should follow current guidelines and deliver a radiation dose of 40Gy in 15 fraction, over 3 weeks, or a biologically equivalent dose (i.e. 26Gy/5 fx). Radiation techniques and quality assurance procedures are identical to the SoC radiation therapy techniques applied in Post-Mastectomy RT (PMRT) or Whole Breast RT (WBRT), and should fulfil the criteria as defined by this protocol. **Oncological breast Surgery** In accordance with SoC, a skin-sparing (SSM), nipple-sparing mastectomy (NSM), or modified radical mastectomy (MRM) will be performed within 6 weeks after randomisation or last dose of neoadjuvant chemotherapy (if applicable) for patients

	in the standard treatment arm. Patients in the experimental treatment arm proceed to SSM/NSM/MRM or a breast-conserving surgery (in case of downstaging after Preop-RT), at 2-6 weeks after the last radiation fraction. This timing can be delayed if necessary, e.g. in case of severe acute toxicity after RT or logistical reasons, but this needs to be documented as a protocol deviation. **Breast reconstruction surgery** The type/technique of breast reconstruction performed is at the discretion of the patient and the treating plastic/reconstructive surgeon, within the bounds of the assigned randomisation/treatment group. The options include implant-based (+/- in two steps with a temporary tissue expander), autologous tissue -based (e.g.: Deep Inferior Epigastric Perforator (DIEP) flap), or a combined technique using both autologous tissue and an implant/TE. Adjuvant reconstruction techniques such as fat grafting, or an acellular dermal matrix can also be used in addition to the primary technique. In the standard treatment arm, both immediate (IBR) and delayed breast reconstruction (DBR) techniques can be used according to SoC and patient/surgeon preferences. In the experimental treatment arm, only immediate breast reconstruction (IBR) techniques are allowed. An exception is made for two-stage implant-based reconstruction, in which case a tissue expander is placed at the time of the oncological surgery, followed by a later definitive breast reconstruction, within the study this will be considered as IBR. If there are unforeseen conditions, in which immediate reconstruction is not in the best (medical/safety) interests of the patient, the treating physician and medical team should act in the best interest of the patient, if this leads to a protocol deviation, it should be recorded as such.
Statistical Methods	The sample size has been calculated to detect a difference in 'satisfaction with breasts' as operationalised by the BREAST-Q score ('Satisfaction with Breasts' scale from the Breast Q v2 'Reconstruction', 'Breast Conserving Therapy', or 'Mastectomy' modules; appendix 2), measured at 1 year follow-up, between patients in the control group, receiving the standard treatment (Postop-RT) and the experimental group/treatment (Preop-RT+IBR). Based on previous studies assessing general BREAST-Q score means after breast reconstructions, we expect a mean score of 58 (SD 18) in the standard arm. Based on minimally important differences from previous BREAST-Q literature, we consider a difference of 8 points between groups to be realistic and clinically relevant.(12) To detect a difference of at least 8 points with 80% power and a two-sided alpha of 0.05 using the Students' t-test, we need to include n=81 women in each treatment arm. To account for dropout of at least 10%, we aim to randomise n=90 women per treatment arm, resulting in n=180 patients in total. Statistical methods will be further outlined in a Statistical Analysis Plan (SAP). All analyses will be performed on the entire population as per the intention-to-treat (ITT) principle. The methodology and standards of 'The Estimands Framework' will be used to ensure correct reporting of hypothesis tests, and to correct for intercurrent events (ICE).(13)

Schedule of Events

The Schedule of events (SOE) is presented in Table 1.

Table 1A. Schedule of events for patients in the control treatment arm

Period	**Ref.**	**Screening**	**Treatment period**			**Follow-up Period**				**Closeout**
Visits		**Screening visit**	**Oncological breast surgery +/- IBR[e]**	**Postop-RT[f]**	**Definitive breast reconstruction**	**IMFU visit**	**3 Months FU visit**	**1 Year FU visit**	**2, 5, 10 Year FU visits**	**Closeout visit[g]**
Study Visit number		1	-	-	-	[2x]	2	3	4, 5, 6	
Scheduling		≤10 bd of ICF	Rz or NACT +≤6w	Onco surg + 6-12w	As planned	If DBR; RT+3M	LST + 3M	LST+1Y	LST+2/5/10Y	
Window						±1M	±1M	±1M	±6M	
ICF[a]	9.2	Before visit								
Enrolment										
Eligibility screening	4.2,4.3	x								
Demographics	5.4.1	x								
Health data	5.4.2, 5.4.7	x								
Concomitant medications	5.4.2	x								
Clinical assessments	5.4.3									
Height		x								
Body weight		x								
ECOG score		x								
Randomisation(Rz)[b]	6.4.3	x								

Assessments (baseline, treatment and follow-up)										
BREAST-Q (pre-op)	5.4.4	x								
BREAST-Q (post-op)	5.4.4					x	x	x	x	(x)
EQ-5D-5L	5.4.5	x				X	x	x	x	(x)
Photographs	5.4.6	x				x	x	x	x	(x)
AE assessment[c]	5.4.8	x	x	x	x	x	x	x	x	x
Data on systemic therapy, RT and surgery	6.5		x	x	x		x			(x)
Data on pathology and pathological tumour response	5.4.9	x	x				x			(x)
Data on oncological survival[d]	5.4.10							x	x	(x)
Study related interventions/treatments										
Oncological surgery	6.2		x							
Radiotherapy	6.1			x						
Breast reconstruction	6.3		(x)		(x)					

Abbreviations: Ref. = reference within this document; IBR = Immediate Breast Reconstruction; RT = Radiation Therapy; IMFU = InterMediate Follow-Up; FU = Follow-Up; bd = business days; ICF = Informed Consent Form; Rz = Randomisation; NACT = NeoAdjuvant ChemoTherapy; Onco Surg = Oncological surgery; DBR = Delayed Breast Reconstruction; LST = Last study treatment; w= week; M = month (30 days); Y = Year (365 days); ECOG = Eastern Cooperative Oncology Group; pre-op = Preoperative; post-op = postoperative; AE = Adverse Event.

a. Informed consent from the patient must be documented before any study specific procedure, including procedures for screening, are undertaken.
b. Patients can be randomised as soon as eligibility has been confirmed by the Coordinating Investigator.
c. Elicitation of all AEs will occur at each interaction with the patient from the time of informed consent onwards. Patients will be questioned regarding AEs at each visit, and will be instructed to inform the Investigator or staff of any AEs or intercurrent events/illnesses experienced at any time during the trial. Adverse events will be coded and graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0).
d. Oncological follow-up of patients will be planned according to local institutional guidelines.
e. Oncological breast surgery should be performed within 6 weeks of patient randomisation (Rz) or within 6 weeks of the last dose of neoadjuvant chemotherapy (NACT).
f. Post-mastectomy/Postoperative radiation therapy will be initiated 6-12 weeks after oncological breast surgery.
g. In the case of premature discontinuation from study participation, the participant should be asked to return to the clinic/study site and complete an early termination visit. The indicated assessments can be considered depending on the status of the participant, timing of discontinuation and the consent of the participant.

Note: additional unscheduled visits may occur at the discretion of the Investigator, i.e. if considered necessary for clinical safety reasons.

Table 1B. Schedule of events for patients in the experimental treatment arm

Period	**Ref.**	**Screening**	**Treatment period**			**Follow-up Period**				**Closeout**
Visits		**Screening visit**	**Preop-RT[e]**	**Oncological breast surgery +IBR[f]**	**(Definitive breast implant)**	**IMFU visit**	**3 Months FU visit**	**1 Year FU visit**	**2, 5, 10 Year FU visits**	**Closeout visit[g]**
Study Visit number		1	-	-	-	NA	2	3	4, 5, 6	
Scheduling		≤10 bd of ICF	Rz or NACT +≤6w	Preop RT + 2-6w	As planned	NA	LST + 3M	LST+1Y	LST+2/5/10Y	
Window						NA	±1M	±1M	±6M	
ICF[a]	9.2	Before visit								
Enrolment										
Eligibility screening	4.2,4.3	x								
Demographics	5.4.1	x								
Health data	5.4.2, 5.4.7	x								
Concomitant medications	5.4.2	x								
Clinical assessments	5.4.3									
Height		x								
Body weight		x								
ECOG score		x								
Randomisation(Rz)[b]	6.4.3	x								

Assessments (baseline, treatment and follow-up)										
BREAST-Q (pre-op)	5.4.4	x								
BREAST-Q (post-op)	5.4.4						x	x	x	(x)
EQ-5D-5L	5.4.5	x					x	x	x	(x)
Photographs	5.4.6	x					x	x	x	(x)
AE assessment[c]	5.4.8	x	x	x	x		x	x	x	x
Data on systemic therapy, RT and surgery	6.5		x	x	x		x			(x)
Data on pathology and pathological tumour response	5.4.9	x	x				x			(x)
Data on oncological survival[d]	5.4.10							x	x	(x)
Study related interventions/treatments										
Oncological surgery	6.2			x						
Radiotherapy	6.1		x							
Breast reconstruction	6.3			x	(x)					

Abbreviations: Ref. = reference within this document; IBR = Immediate Breast Reconstruction; RT = Radiation Therapy; IMFU = InterMediate Follow-Up; FU = Follow-Up; bd = business days; ICF = Informed Consent Form; Rz = Randomisation; NACT = NeoAdjuvant ChemoTherapy; Onco Surg = Oncological surgery; DBR = Delayed Breast Reconstruction; LST = Last study treatment; w= week; M = month (30 days); Y = Year (365 days); ECOG = Eastern Cooperative Oncology Group; pre-op = Preoperative; post-op = postoperative; AE = Adverse Event.

a) Informed consent from the patient must be documented before any study specific procedure, including procedures for screening, are undertaken.
b) Patients can be randomised as soon as eligibility has been confirmed by the Coordinating Investigator.
c) Elicitation of all AEs will occur at each interaction with the patient from the time of informed consent onwards. Patients will be questioned regarding AEs at each visit, and will be instructed to inform the Investigator or clinic staff of any AEs or intercurrent events/illnesses experienced at any time during the trial. Adverse events will be coded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0).
d) Oncological follow-up of patients will be planned according to local institutional guidelines.
e) Preoperative Radiation Therapy should be initiated within 6 weeks of Randomisation (Rz) or within 6 weeks of the last dose of neoadjuvant chemotherapy (NACT).
f) Oncological breast surgery should be performed within 2-6 weeks after preoperative radiotherapy.
g) In the case of premature discontinuation from study participation, the participant should be asked to return to the clinic/study site and complete an early termination visit. The indicated assessments can be considered depending on the status of the participant, timing of discontinuation and the consent of the participant.

Note: additional unscheduled visits may occur at the discretion of the Investigator, i.e. if considered necessary for clinical safety reasons.

1. Introduction

1.1 Background

In the past decades, there has been a two- to threefold increase in patients with breast cancer receiving immediate breast reconstruction (IBR) combined with postmastectomy radiotherapy (PMRT). This is best explained by the increasing number of patients opting for IBR due to concerns with cosmesis and its wider availability, as well as the broader application of PMRT due to changing guidelines and insights (14–19). One of the reasons for an increase in PMRT, is that regional RT is preferred over axillary lymph node dissection when 1-3 lymph nodes are found to be positive.(20,21)

This shifting paradigm poses challenges, since regardless of breast reconstruction technique, PMRT leads to an increase in complications, with the frequency of any complication at 23% in non-irradiated vs. 28.9% in irradiated patients.(22) These complications are also known to result in diminished patient satisfaction.(23,24) Furthermore, postoperative complications following IBR leads to an average RT delay of 19.7 days (61.62 days if no complications vs. 81.32 days if any complication), which is a statistically significant difference ($p=0.021$).(25) PMRT induced increases in the complication rates is further compounded when combined with IBR, and is highest for implant-based IBR, with complication rates of up to 38.9%, compared to 21.8% without PMRT, at 2 years of follow-up.(22) This increase is observed on both the short and long term, complications include loss of reconstruction, pain, infection, postoperative bleeding, hematoma, capsular contracture, fibrosis, implant malpositioning, seroma, impaired cosmetic results, and lower patient satisfaction.(26–31) The prevalence of Baker grade 3 or 4 capsular contracture when PMRT is administered to either a tissue expander or permanent implant was reported to be 37.5% in an n=1286 meta-analysis of 9 studies.(32) In the case of autologous IBR on the other hand, no statistically significant difference was seen in the rate of complications between those who did and did not receive PMRT. For example, a prospective observational study with n=199 (Autologous +RT) and n=332 (Autologous, no RT) patients reported a complication rate of 25.6% and 28.3% respectively.(26)

1.2 Rationale for Use of Preop-RT to improve IBR outcomes

The high complication rate and impaired cosmetic results, following from IBR and PMRT, have led to practice variations and controversy in breast reconstruction practices when PMRT is indicated.(33,34) As a result, in some centres, only autologous reconstructions are being offered when PMRT is indicated. In other centres IBR is withheld when PMRT is indicated, and only delayed breast reconstructions (DBR) are offered. However, IBR does have several distinct advantages over DBR: 1) Improved skin and sometimes even nipple sparing options, resulting in a superior cosmetic outcome (35,36); 2) No period without a (reconstructed) breast, waiting for DBR (usually about 6-12 months after PMRT); 3) Overall treatment duration is significantly (at least 6-12 months) shorter; 4) A single major surgery, in contrast to two surgeries with accompanying revalidation periods (without additional aesthetic corrections).

A promising alternative approach, with the hope of improving IBR outcomes in patients requiring PMRT, is to change the RT sequence from postoperative (Postop-RT) to preoperative (Preop-RT). This approach would allow for irradiated breast tissues to be removed during surgery and avoids irradiation of the reconstructed tissues and/or prothesis. Preop-RT is routinely used for several other types of cancer, such as e.g. rectal cancer (37), oesophageal cancer (38), and sarcomas (39,40), with improved options for tissue-preserving surgeries and higher rates of complete pathologic response. Several studies showed no oncologic disadvantages for Preop-RT versus Postop-RT in breast cancer, with some studies suggesting

lower recurrence rates, but no difference in overall survival (OS).(41–46) These studies include two prospective studies demonstrating that preoperative RT is safe and technically feasible in node-positive and locally advanced breast cancer.(44,45)

1.3 Benefit-risk assessment

1.3.1 Complication rates

When consulting the currently available literature, the Preop-RT followed by ME and IBR approach does not seem to significantly increase the rate of complications, when compared to the ME, PMRT and DBR sequence.(47–52) A retrospective observational study by the American College of Surgeons, with a study population of n=77902 (ME-only 61039 vs. ME+IBR 16863), assessed the impact of Preop-RT on 30-day postoperative morbidity after ME with or without IBR. From the study population n=266 ME-only, and n=75 ME+IBR patients were identified as having received preoperative RT. In the ME-only group, the subgroup with Preop-RT experienced 'any type of morbidity' in 9.4% of cases, vs. 11.1% without Preop-RT (p=0.48). While in the ME+IBR group this was 14.7% vs. 11.2% (p=0.22). In both the ME-only and ME+IBR groups, preoperative RT was not associated with a significantly increased risk of complications upon multivariate regression analysis.(47) Another study compared preoperative chemo-radiation therapy followed by ME and IBR (Latissimus dorsi flap + breast implant) n=26 to ME followed by postoperative chemo-radiation therapy and DBR (Latissimus dorsi flap + breast implant) n=78. They reported no significant difference in both early (p=0.645) and late (p=0.362) complications.(45) Similarly, two observational studies of n=83 and n=111 patients, observed low rates of skin necrosis (6% and 5.4%, respectively) in patients receiving preoperative chemo-radiation therapy followed by ME and implant-assisted latissimus dorsi flap IBR.(53,54) Although, when looking at patients who underwent Preop-RT and NACT followed by ME and IBR, a retrospective study observed higher rates of skin necrosis (within 30 days) in a transverse rectus abdominis musculocutaneous (TRAM)-flap subgroup (33.9%), compared to other reconstruction options (17.5%) consisting of a latissimus dorsi flap with or without breast implant, or breast implant alone. The authors of this study reported a relative risk (RR) of 1.9 for early complications and a RR of 6.4 for the occurrence of flap necrosis (of any degree) in a TRAM-flap based IBR compared to other IBR options.(55) These results seem to advise against the use of TRAM-flaps in the setting of Preop-RT and IBR. However, there was no direct comparison of the Preop-RT to Postop-RT or no RT groups, making it harder to put these findings into perspective.

The PRADA pilot study demonstrated that Preop-RT followed by skin-sparing mastectomy (SSM) and immediate microvascular DIEP-flap reconstruction is technically feasible and safe. This multicentric, phase-II, prospective feasibility study showed that in the study sample of n=33, 4 (12%) open wounds (>1cm) occurred, of which 3 were minor wounds treated conservatively and 1 needed debridement and skin grafting. As well as 6 (18%) events of limited fat necrosis occurred, all with minimal cosmetic impact. It can be concluded that the rate of open wounds, mastectomy skin necrosis, fat necrosis, and unplanned returns to the operating theatre were low, with no DIEP flap failures. Twelve months after surgery, the patients in the PRADA-trial reported high levels satisfaction with the breast reconstruction, and very good aesthetic outcomes were observed on panel assessment.(56)

A similar pilot study came to an equivalent conclusion, that Preop-RT followed by ME and IBR was deemed to be both feasible and safe. Out of n=48 patients receiving ME with IBR, 41 had microvascular autologous tissue IBR, 5 received a pedicled latissimus dorsi flap, and 2 patients had tissue expanders implanted at

the moment of ME. There were no reconstructive failures, 8 patients (18.2%) had some degree of partial autologous flap necrosis of which only 1 (2.27%) needed re-intervention.(42)

1.3.2 Oncological outcomes

Concerning oncological outcomes, the literature seems to show no significant differences between Preop-RT and Postop-RT concerning local/locoregional recurrence, overall survival, and disease-free survival, with a general trend in favour of Preop-RT. (48,57–61)

A large retrospective observational study based on the Surveillance, Epidemiology, and End Results (SEER) database, included n=250195 female patients with early-stage breast cancer, of which n=2554 received Preop-RT, and n=247641 Postop-RT. This study concluded that the disease-free survival and mortality were not significantly different in both groups, only the oestrogen receptor positive subgroup showed a significant Hazard Ratio (HR) of 0.64 ($p<0.0001$) which was in favour of Preop-RT for second primary tumours.(59) Another retrospective observational study in n=315 Preop-RT and n=329 Postop-RT patients found that the 10-year relapse-free survival was not significantly different between the Preop-RT (67.96%), and Postop-RT (66.31%) groups. For the 10-year overall survival the Preop-RT (68.59%) and Postop-RT (64.96%) groups were again not significantly different, while the Preop-RT group did have a non-significant trend for better outcomes (HR=0.813; p=0.1037).(61) The PRADA I pilot-study also showed no local or locoregional recurrences during a 23.6 month median follow-up period, with 4 (12%) cases of distant metastatic disease, and 2 (6%) cancer related deaths, resulting in an overall survival of 93.9%, and disease-free survival of 84.8%.(48) In a retrospective study with a cohort of n=30 patients treated with Pre-operative radiotherapy for locally advanced breast cancer, propensity-score matched to a cohort of n =81 control patients treated with Postop-RT, the pathological complete response (pCR) rate was 22.6% vs. 14.9% ($p<0.001$), disease-free survival at 3 years of follow-up was 81% vs. 69% (p=0.186), overall survival at 3 years of follow-up was 89% vs. 74% (p=0.162), in Preop-RT vs. Postop-RT groups, respectively.(62) Another observational study of n=111 patients receiving Preop-RT for locally advanced breast cancer, found that after a median follow-up time of 31.6 months, there was a recurrence rate of 9%. This 9% consisted of 0.9% local recurrence and 8.1% distant metastatic disease, as a % of the study sample. At 5 years of follow-up the disease-free survival was 93.2%, and overall survival was 98.3%. While this study lacks a comparison group, it shows very low local recurrence rates and high levels of 5 year disease-free, and overall survival compared to known rates for Postop-RT in the general literature.(54)

1.4 Concluding the introduction

The current study (PRADAIIBE) will now compare efficacy and safety outcomes of Preop-RT followed by ME and IBR, to these outcomes in the conventional SoC treatment consisting of ME followed by PMRT and either IBR or DBR (according to local practices), in a randomised controlled trial (RCT). It is our hypothesis that Preop-RT will improve patient reported satisfaction with breasts, quality of life (QoL), and cosmesis, while not leading to more complications, worse pCR rates, nor worse oncological outcomes. Preop-RT is also projected to streamline the treatment timeline by minimising delays associated with Postop-RT and shortening treatment duration. In addition, Preop-RT might theoretically achieve an antitumour immune response directed at subclinical disease, potentially decreasing the odds of recurrence, through the abscopal effect, which in turn may open avenues to other adjunct treatment modalities.(63,64) Which should be investigated through additional fundamental and translational research projects.

2. Objectives and Endpoints

Study Objectives and Endpoints	
Objective	**Endpoint**
Primary	
Satisfaction with breasts, PROM (BREAST-Q)	**Operationalisation (measurement variable):** The satisfaction with breasts outcome variable is operationalised through the "satisfaction with breasts" scale from the BREAST-Q (v2) 'Reconstruction', 'Breast Conserving Treatment', or 'Mastectomy' modules (as applicable). The answers from the questionnaire are then transformed into a 'BREAST-Q Score', using the provided conversion scales.(3) The BREAST-Q score can range from 0 to 100. The BREAST-Q v2 questionnaires are discussed in section 5.4.4, and added in appendix 2. **Analysis metric:** The transformed value of the BREAST-Q score will be used for analysis. **Method of aggregation:** Mean, SD, median, IQR, and range will be reported. For comparisons and estimands, please refer to the SAP. **Time point(s):** A baseline assessment is performed during the screening visit, followed by repeated measurements during the IMFU (if applicable), 3M, 1Y, 2Y, 5Y, and 10Y follow-up visits. The primary endpoint is assessed at 1 year of follow-up after the last study treatment (LST). **Rationale:** The BREAST-Q is a validated and widely accepted tool for assessing different PROMs in women after (oncological) breast surgery. The 'Satisfaction with breasts' scale offers a relatively short (max 15 items) yet complete (assessing feel, comfort, cosmesis, etc.) assessment of the patient's satisfaction with their breasts after reconstructive surgery (or BCS/ME).
Secondary	
Quality of Life, PROM (QoL, EQ-5D-5L VAS and Index score)	**Operationalisation (measurement variable):** 'Quality of Life' will be assessed using the EQ-5D-5L questionnaire. From this questionnaire the VAS-score and Index-score will be derived. The VAS-score can be used as recorded. The index score is derived from the answers to each of the 5 Liker-scale items, using a formula validated in the Belgian population. The EQ-5D-5L VAS-score can range from 0 to 100, while the Index-score can range from -0.533 to 0.962.(4,5) The EQ-5D-5L questionnaire is discussed in section 5.4.5, and added in appendix 3. **Analysis metric:** The VAS-score will be used as recorded. The Index-score will be transformed to a scale between 0 and 1, proportional to its original distribution. This transformation will be achieved using the following formula, where f(IS) represents the transformed score, IS the index score, 0.533 is the correction of the lowest value to zero, and 1.495 is the range difference: $$f(IS) = (IS + 0.533)/1.495$$ The rationale for this transformation, is to adhere to the scale proposed by the EQ-5D-5L documentation, and improve interpretability of the index score.

	Method of aggregation: Mean, SD, median, IQR, and range will be reported. For comparisons and estimands, please refer to the SAP. **Time point(s):** A baseline assessment is performed during the screening visit, followed by repeated measurements during the IMFU (if applicable), 3M, 1Y, 2Y, 5Y, and 10Y follow-up visits. **Rationale:** The EQ-5D-5L questionnaire offers a very short (6 items) validated questionnaire assessing QoL, offering an index score based on 5 domains using 5 level Likert-scales, as well as a general QoL assessment using a VAS item.
Breast cosmesis, objective assessment (AIS – TAS)	**Operationalisation (measurement variable):** Breast cosmesis will be assessed through a blinded panel of experts, using the 'Aesthetic Items Scale' to score a set of photographs taken during study visits. This set will consist of 4 2D digital photographs. The AIS has 5 items, each are scored from 1 to 5. These items are then summed to derive the 'Total Aesthetic Score' (TAS). The TAS can range from 5 to 25. (6,7) These are discussed in section 5.4.6, and appendix 4. **Analysis metric:** The derived value of the Total Aesthetic Score (TAS) from each assessor will be averaged to derive the TAS of each set of photos. **Method of aggregation:** Mean, SD, median, IQR, and range will be reported. For comparisons and estimands, please refer to the SAP. **Time point(s):** Photographs are taken during the screening visit, followed by repeated photographs during the IMFU (if applicable), 3M, 1Y, 2Y, 5Y, and 10Y follow-up visits. Expert panel assessment will take place at a later moment. A more detailed description is included in Appendix 4. **Rationale:** The use of photographs was included to be able to assess cosmesis in a more objective way. In order to achieve this objectiveness an expert panel will be used. The AIS-tool was selected due to its simplicity and good inter-rater validity in professionals.
Frequency and severity of adverse events (AEs)	**Operationalisation (measurement variable):** During the study all adverse events (AEs) codes and grades will be recorded in the eCRF, based on the 'National Cancer Institute Common Terminology Criteria for Adverse Events' (NCI-CTCAE) v5.0 reporting system.(8) The NCI-CTCAE v5.0 and (S)AE registration is discussed in section 5.4.8 and section 7, and added in appendix 5. **CAVEAT:** Not all postoperative complications are *explicitly* listed in the CTCAE v5.0 framework, for example: capsular contraction, implant malposition, reconstructive failure, etc. are not listed but need to be recorded. These will be registered under "Injury, poisoning and procedural complications - Other, specify" CTCAE term **Analysis metric:** Tabulation of AE frequency, type and severity. As well as the highest grade AE for each participant.

	Method of aggregation: AEs will be aggregated based on their grades. Two composite measures will be reported, consisting of 1) any AE vs. no AE, and 2) grade ≥ 3 AEs vs. no or grade <3 AEs. Tables presenting both frequency and proportions of each grade and the composite measures will be presented. Proportions will be reported as AEs compared to 'highest grade per patient', and to 'total set of AEs'. For comparisons and estimands, please refer to the SAP. **Time point(s):** AEs will be assessed and recorded continuously, with explicit querying during all follow-up visits. **Rationale:** In order to assess safety and to ensure that the experimental treatment does not differ significantly from the Standard of Care (SoC)/control treatment regarding AEs, the AEs were adopted as a secondary outcome variable. The NCI-CTCAEv5 was selected due to its uniformity in reporting and wide adoption in oncological research.
Frequency and severity of adverse events (AEs), related to surgery	**Operationalisation (measurement variable):** Cfr. 'Frequency and severity of adverse events (AEs)' (supra). For this outcome variable only the AEs related to surgical study interventions will be taken into consideration. This relationship is registered when the AE is recorded in the eCRF. **Analysis metric:** Tabulation of surgical AE frequency, type and severity. As well as the highest grade surgical AE for each participant. **Method of aggregation:** Surgical AEs will be aggregated based on their grades. Two composite measures will be reported, consisting of 1) any AE vs. no AE, and 2) grade ≥ 3 AEs vs. no or grade <3 AEs, relating to surgical AEs. Tables presenting both frequency and proportions of each grade and composite measures will be presented. Proportions will be reported as surgical AEs compared to 'highest grade per patient', and to 'total set of surgical AEs'. For comparisons and estimands, please refer to the SAP. **Time point(s):** Cfr. 'Frequency and severity of adverse events (AEs)' (supra). **Rationale:** In addition to the rationale mentioned for AEs in general, we wanted to look at the surgical AEs specifically as we believe that this subgroup is the most important one to monitor in this study.
Treatment duration	**Operationalisation (measurement variable):** The dates of diagnostic, study, and treatment milestones will be recorded in the eCRF. Time intervals expressed in days, will be assessed for: - Randomisation to last study treatment (LST) - Randomisation to oncological breast surgery - Oncological breast surgery to last study treatment (LST) As discussed in section 5.4.11. **Analysis metric:** The 'randomisation to last study treatment (LST)' time interval, expressed in days. **Method of aggregation:** KM-estimates and derived estimates for central tendency and spread will be provided. For comparisons and estimands, please refer to the SAP.

	Time point(s): These outcome variables will be continuously recorded as the participant progresses through the study and the data is entered in the eCRF. **Rationale:** The experimental treatment theoretically leads to a shorter treatment duration. In order to prove this theoretical assumption in practice, the treatment duration was adopted as a secondary outcome.
Pathological (complete) response rate (pCR)	**Operationalisation (measurement variable):** Patients receiving preoperative therapy undergo pathological response assessment of the removed breast tissues (SoC assessment). The reported response Pinder-classification or 'No preoperative therapy' will be recorded in the eCRF.(9) The assessment of pathological tumour response is discussed in section 5.4.10. **Analysis metric:** The response category as described in the pathology report will be recorded for all participants, but this outcome will only be assessed in participants receiving preoperative-systemic therapy (with, or without Preop-RT). Therefore, the response category value of participants receiving Preop-RT without preoperative-systemic therapy will not be included in this outcome due to the fact that no response is expected at 2-6 weeks after radiation therapy monotherapy, which would result in an unfair comparison. Both this subset of the ITT set, and the complete safety set will be used in the safety assessment, as described in the SAP. **Method of aggregation:** The frequency and proportion of the response categories will be presented in a table. For comparisons and estimands, please refer to the SAP. **Time point(s):** This outcome variable will be assessed after the pathology report of the removed breast tissues is available. This is checked intermittently during the treatment phase, or at least during the 3 months follow-up visit. **Rationale:** The pathological response rate was added as a secondary outcome in order to assess the effects of preoperative radiotherapy on this parameter. On the one hand as a method of assessing the experimental treatment does not negatively impact oncological safety. While on the other hand assessing the potential synergistic effects on preoperative systemic therapy.

Tertiary	

Oncological survival and time-to-event data:	**Operationalisation (measurement variable):**
	The oncological survival and TTE data are operationalised as time-to-event intervals for the events of interest listed below. These events are recorded according to the 2015 DATECAN consensus: (10)
	- Death
	  o All-cause mortality
	  o Death from breast cancer
	- Any recurrence vs. none.
	  If any recurrence has occurred it will be recorded using the subtypes:
	  o Invasive ipsilateral breast tumour recurrence/progression
	  o Local invasive recurrence/progression
	  o Regional invasive recurrence/progression
	  o Appearance/occurrence of metastasis/distant recurrence
	  o Ipsilateral DCIS
	
	The following TTE/survival metrics will be reported according to the 2015 DATECAN consensus: Overall Survival (OS), Breast Cancer-Specific Survival (BCSS), Relapse-Free Survival (RFS), Locoregional Relapse-Free Survival (L-RFS), and Distant-Relapse Free Survival (D-RFS).(10)
	As discussed in section 5.4.10.
	Analysis metric:
	The TTE data is registered in days from randomisation (Rz). Censoring will be used for participants without events at the end of their follow up.
	Method of aggregation:
	KM-estimates with derived estimates for central tendency and spread, as well as proportions free from events at follow-up visit timepoints will be reported. The non-aggregated data will be used for survival analysis. For comparisons and estimands, please refer to the SAP.
	Time point(s):
	Oncological TTE data will be registered at 1, 2, 5, and 10 years of follow-up after the last study treatment (LST). However, the exact dates of diagnosis/death will be used.
	Rationale:
	These oncological survival parameters were added as a tertiary outcome variable in order to assess oncological safety of the experimental treatment. These variables will be pooled with other international parallel studies, as it is likely that results from this study will be underpowered.

Table 2 Objectives and Endpoints

3. Overall Study Design

3.1 General Scheme of Study Design

The PRADAIIBE study is a multicentric, prospective, randomised controlled, open-label, phase-III interventional clinical trial in patients with breast cancer for whom a skin/nipple-sparing mastectomy (SSM/NSM) and Postop-RT are indicated and who have a wish for a breast reconstruction. After providing informed consent and verifying eligibility, data collection starts and patients will be randomised in one of the following treatment arms:

- **Standard treatment arm**: Standard of Care (SoC) treatment: ME combined with an immediate or delayed breast reconstruction (IBR/DBR) followed by radiation therapy (Postop-RT).
- **Experimental treatment arm**: Preoperative radiotherapy (Preop-RT) followed by ME combined with immediate breast reconstruction (IBR), or BCS (in the unlikely event of downstaging).

The primary objective of the PRADAIIBE study is to investigate whether Preop-RT followed by ME combined with an IBR (implant based or autologous) improves the patient's satisfaction with the breast reconstruction when compared to the SoC therapy, with Postop-RT, and IBR or DBR.

Participation in the study will comprise a screening period, where the screening assessments must be completed before participants are enrolled and randomised. Eligible, consenting participants will then undergo treatment according to their assigned treatment group.

The intervention consists of a change in the therapy sequence, where radiation therapy is provided in the preoperative setting as compared to the usual postoperative setting. Due to this changed sequence the breast reconstruction surgery can be performed concurrently with the ME (immediate breast reconstruction; IBR), avoiding irradiation of the reconstructed breast, and the fear of complications or inferior aesthetic results associated with it. In the unlikely event of downstaging due to Preop-RT, BCS could be performed, but this is not expected to occur. This treatment sequence consists of the SoC therapy for both the surgical and radiotherapeutic treatments, as appropriate for their specific situation, with only a change in the sequence in which these therapies are administered.
In the standard treatment group there will be no manipulation of the treatment (sequence), the participants will receive their breast cancer treatment in the same manner and sequence as they would when they wouldn't have enrolled in this clinical trial.

Chemotherapeutic or other systemic treatments, either in the neo-adjuvant/preoperative or adjuvant/postoperative setting will be left to the discretion of the treating medical team, there will be no manipulation of this treatment in this clinical trial. Therefore systemic therapies will not be considered study related treatments. However, the treatment details will be recorded in the eCRF for statistical analysis.

In the intervention group there is a slight chance of downstaging due to Preop-RT, in this case breast conserving surgery (BCS) can be performed. However, we expect that this will be a minority of cases as the timing of surgery at 2-6 weeks after Preop-RT is deemed to be too short to expect significant downstaging. We debated excluding these patients as they will not undergo breast reconstruction surgery and are therefore not a fair comparison for our research question, we came to the conclusion that due to the intention-to-treat (ITT) principle we need to include these patients, but in the handling of intercurrent events (ICE), these patients will be excluded from the analysis.

With regards to the standard treatment (control) group, the choice of immediate vs. delayed breast reconstruction surgery is left at the discretion of the treating plastic/reconstructive surgeon and the patient. However, we expect that the choice for IBR will be a smaller group and will mainly entail the placement of a tissue expander during oncological surgery. We expect that a substantial amount of these control-group patients will undergo DBR, in which case they will typically have to wait 6-12 months until receiving their DBR. In order to provide proper study participant follow-up, and to assess safety and efficacy outcomes in the intermediate period (after oncological treatment, before breast reconstruction), an additional study visit (InterMediate Follow-Up; IMFU) is provided at 3 months after conclusion of Postop-RT. This visits (IMFU) is specific to control group participants undergoing DBR, and includes a BREAST-Q 'satisfaction with breasts' from the 'Mastectomy' module assessment (Section 5.4.4; Appendix 2); QoL assessment using the EQ-5D-5L questionnaire (Section 5.4.5; Appendix 3); Photographs of the chest anatomy, which will be evaluated by an expert panel (Section 5.4.6; Appendix 4); and AE/SAE registration according to the CTCAE V5 (Section 7; Appendix 5).

After the treatment period is finalised, safety and efficacy are assessed during a follow-up period of 10 years. Follow-up visits will occur at 3 months, 1 year, 2 years, 5 years and 10 years after treatment finalisation, also known as 'last study treatment' (LST). During this follow-up period, the AEs/SAEs will be registered using the CTCAE V5 (Section 7; Appendix 5). Oncological outcomes will be reported from the +1 year follow-up visit onwards and registered based on patient interview and Electronic Health Record (EHR) review (Section 5.4.10). The cosmesis and satisfaction with breasts will be evaluated using the self-reported 'Satisfaction with breasts' scale of the BREAST-Q v2 'Reconstruction', 'Breast Conserving Therapy', or 'Mastectomy' modules (as applicable for the current situation), as well as through photographs evaluated by a panel of blinded experts (Section 5.4.6; Appendix 4). The QoL will be assessed using the self-reported EQ-5D-5L questionnaire (Section 5.4.5; Appendix 3).

The screening, treatment and follow-up schedule is shown in the Schedule of Events (SoE; Table 1).

A schematic presentation of the study design is shown in Figure 1 (Concise overview) and Appendix 7 (Detailed overview).

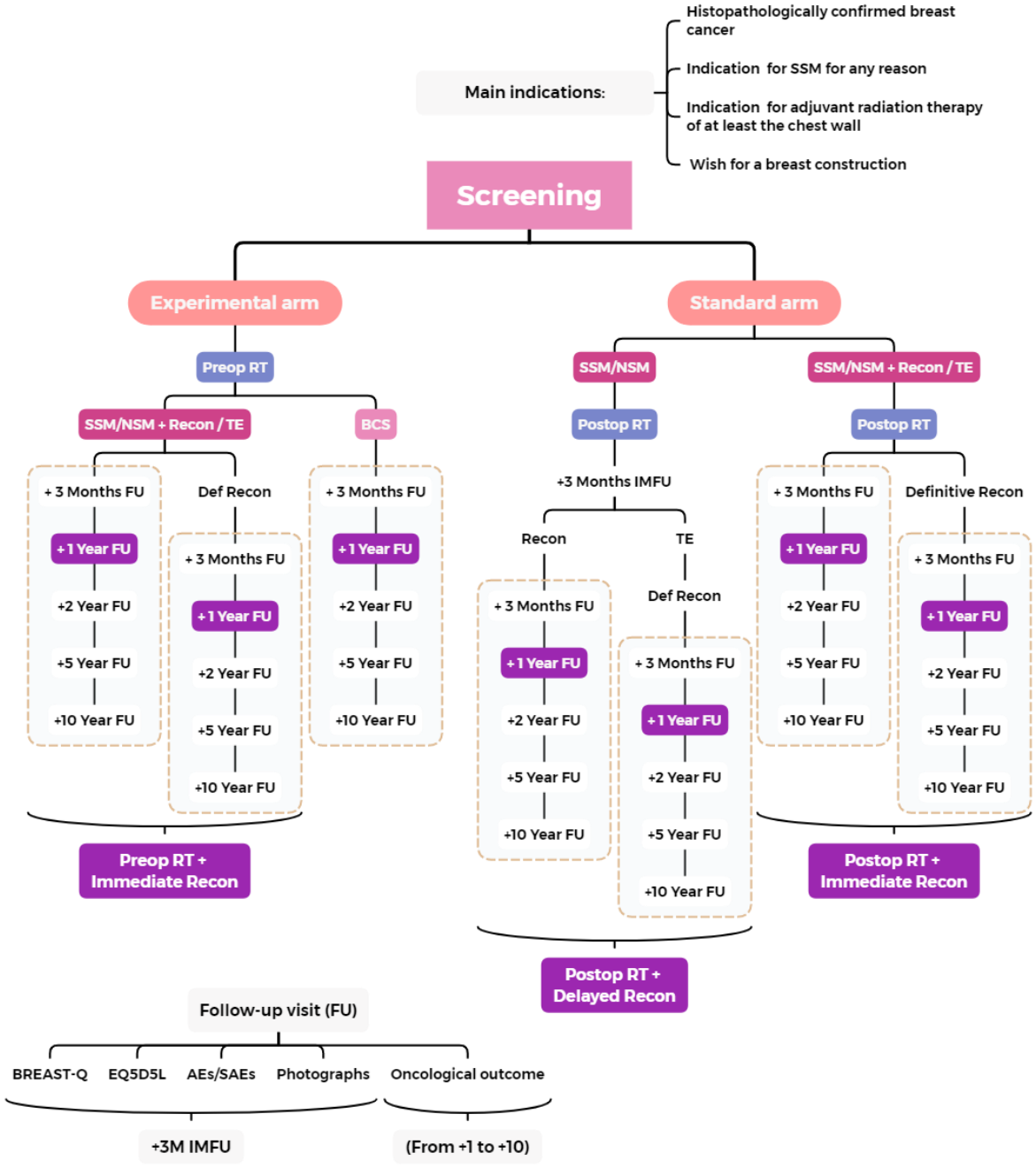

Figure 1: Study design

3.2 Study Duration, Enrolment and Number of Sites

3.2.1 Duration of Study Participation

Following study enrolment and randomised allocation to a study treatment group, participants will receive their assigned treatment. After the study related treatments have been concluded (variable length), there will be a follow-up period of 10 years.

3.2.2 Total Number of Study Sites/Total Number of Participants Projected

The study will be conducted at multiple study sites in Belgium. In total, n=180 patients will be enrolled in the study. The study will be closed when the last patient completes their last visit. We project a total of 10 study sites. An up to date list of participating study sites is kept in a separate document, which will be submitted to the central EC whenever a site is added or removed. This document is available upon request.

We expect a patient accrual period of 3 years. Total study duration is therefore projected to be 13 years.

4. Population

4.1 Definitions

Participants officially enter the screening period following provision of informed consent. Screening assessments must be completed before enrolment and randomisation.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following sections. Enrolment will occur only if the participant meets all study eligibility criteria, or if an eligibility criteria deviation permission is provided by the central PI, and has been assessed by the Investigator as being an appropriate candidate for study participation. If there is a question about any of these criteria, the Investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a participant in the study. If a participant's clinical status changes (including any available test/diagnostic/etc. results or receipt of additional medical records) after screening but before randomisation such that they no longer meet all eligibility criteria, then the participant should be excluded from participation in the study.

An enrolled participant is one who has provided informed consent, has been screened and deemed eligible, but who has not yet been assigned to a treatment group through randomisation.

Before randomisation, the local Investigator should submit a signed and dated Eligibility Verification Form (EVF) to cancertrials@zas.be. The central Investigator will reply by email to confirm eligibility within 1 business day. After eligibility has been centrally confirmed, patients can be randomised (see Section 6.4.3). After treatment allocation through the randomisation procedure in the eCRF, the patient is defined as (enrolled and) randomised.

4.2 Participant Inclusion Criteria

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

1. Women ≥18 years with histopathologically confirmed breast cancer who:
    a. require SSM/NSM for any reason (e.g. extensive disease)
    b. require postoperative radiotherapy of at least the chest wall
    c. have a wish for a breast reconstruction
2. An Eastern Cooperative Oncology Group (ECOG) performance status grade ≤2
3. Participant is able and willing to provide written informed consent, which includes compliance with and ability to undergo all study procedures, and attend the scheduled follow-up visit(s) per protocol.

4.3 Participant Exclusion Criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

1. A previous history of breast cancer or irradiation of the chest wall for any other indication, on the ipsilateral side. A bilateral SSM/NSM + reconstruction (e.g. in case of a contralateral prophylactic SSM/NSM), or previous contralateral breast cancer disease/treatment, do not fall under this criterium and are thus allowed.
2. Collagen synthesis disease
3. Ongoing pregnancy
4. Actively breastfeeding
5. Smoking at time of inclusion (a history smoking is allowed but needs to be registered in the eCRF). No interval between smoking cessation and study inclusion is defined, but the reconstructive surgeon needs to be willing to operate the patient using autologous tissue transfer. This generally translates to a smoking cessation of >3months preoperatively.
6. BMI > 35 kg/m2
7. cT4d tumour, metastatic disease or any reason making SSM/NSM not indicated

NOTE: If neoadjuvant chemotherapy is given, and if the indication for adjuvant systemic treatment is dependent on the presence or absence of a pathological complete tumour response pCR (such as in patients with a triple negative or Her2 positive tumour), centres can choose
- to exclude these patients,
- only to include these patients when a non-pCR is proven via a biopsy prior to the start of the RT.
- to include these patients after the end of neoadjuvant chemotherapy, since earlier studies in partial breast RT showed that pCR rate of Preop-RT only, followed by surgery <6-8 weeks is very low in the general breast cancer population (17 of the 110), whilst it seems to be higher in patients with triple negative (6/8) and Her2 positive (1/1) (11).
However, the decision to include or exclude the patients which fall into this category, should be made before the participant is randomised.

4.4 Study Restrictions

Participants will be informed and reminded of all study restrictions during recruitment, the informed consent process, and during screening and other scheduled assessments. Compliance with all restrictions will be required for the duration of the study.

4.4.1 Contraceptive Requirements

Local recommendations related to contraception and pregnancy testing must be followed, to avoid potential problems associated with radiation exposure to the unborn child, as per standard of care. The study is not responsible for contraceptive measures or pregnancy testing.

4.4.2 Other Lifestyle Considerations and Study Restrictions

The patient is not allowed to be an active smoker for the duration of the study, defined as from the moment of inclusion until at least the assessment of the primary outcome (follow-up visit at 1 year after LST). The smoking cessation eligibility criterium does not define a minimal cessation period, but the plastic/reconstructive surgeon must be (at least theoretically) willing to perform microsurgical breast reconstruction on the participant, based on their smoking cessation status. Active smoking is defined as the active use/consumption of any tobacco products or nicotine replacement products.

No other lifestyle restrictions apply.

4.4.3 Prior and Concomitant Therapies

There are no restrictions on the use of medication during the study.

4.5 Screen Failures

A screen failure is a consenting participant who has been deemed ineligible during screening, on the basis of the eligibility criteria, or who has withdrawn consent prior to randomisation. Rescreening must be discussed with and approved by the Sponsor on a case-by-case basis.

The Investigator agrees to complete a participant identification and enrolment log to permit easy identification of each participant during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness. The participant identification log will be treated as confidential and will be filed by the investigator in the investigator study file (ISF). To ensure participant confidentiality, no copies will be made. All reports and communications relating to the study will identify all participants by participant identification, redacting all other direct identifiers (e.g. participant first/last name, email address, or their exact date of birth).

5. Study Conduct

5.1 Study Procedures

As noted in Section 3.1, participation in the PRADAIIBE study will comprise a screening period, where screening assessments must be completed before participants are enrolled and randomised. Eligible, consenting participants will then be randomised and undergo treatment according to their assigned treatment group, with a post-treatment follow-up period to assess safety and efficacy. The visit schedule and all study procedures and assessments are presented in the SoE (table 1).

The results of all assessments and procedures will be documented in the participant's medical record and in the study documentation, including the electronic case report form (eCRF), as applicable.

5.1.1 Recruitment

Recruitment will mainly rely on local investigators (or their assigned deputies) being present in multidisciplinary meetings where all patients with breast cancer being diagnosed/treated at that study site are being discussed, in order to raise the question of study participation. When a potential study participant is identified, the treating physician and local trial team (investigators and clinical trial office) will be notified. If all parties agree upon apparent study eligibility, the best method and moment of approaching the patient will be discussed and enacted. If the patient is willing, they will be invited to discuss the Informed Consent Form (ICF) with a study investigator trained in the ICF-procedure. The potential participant will be given adequate opportunity and time to reflect and ask questions concerning the ICF and study participation. If the potential candidate agrees to participate in the study, and signs the ICF, they will be invited to the screening visit. During the ICF-procedure, the patient will be adequately informed of the study related risks and benefits, their rights and the expected commitments, as well as the fact that they are able to retract their informed consent and discontinue the study at any point, without prejudice or a negative impact on their further treatment options. In providing the ICF and planning the screening visit, careful consideration will be taken as not to apply undue pressure to the patient in making their decision on study participation.

Additionally, there will be dissemination of public information concerning the PRADAIIBE trial, through channels of patient support groups, flyers, and websites.

5.1.2 Assignment of the Participant Identification Number

At screening, each consenting study participant will be assigned a participant identification number that will be retained as the primary identifier for the participant throughout the study. The participant-id consists of a sequential 6-digit number (comprised of a 3-digit study site number: 110, 120, etc.- and a 3-digit number incremental per centre representing the sequential order in which participants are screened: 110-0001, 110-0002, etc.), so that each participant is numbered uniquely across the entire study and eCRF database. Upon signing the ICF, the participant is assigned to the next sequential participant-id available to the Investigator through the electronic data capture system. Each site keeps an updated participant identification log, in which the name of the participant is linked to their assigned study-id. This log is kept in a designated secured location with restricted access, managed by the local study personnel. The link between the participant name and study-id will never be shared outside of the local study team, except for monitoring or auditing purposes, as indicated. If a participant is a screen failure, their study-id will not be re-used and it will remain unique to them.

5.1.3 Screening Period

Screening of consenting patients, confirmation of eligibility by the central investigator, and randomisation will be performed within 10 business days after a patient has provided informed consent to participate in this clinical trial. This deadline serves the purpose of avoiding treatment delays, which could compromise oncological outcomes. If this time interval is not respected, a protocol deviation must be logged.

Written informed consent by the patient must be documented before any study specific procedure, including procedures or data collection for screening purposes, are undertaken. The patient will be adequately informed that screening visit cancellation and withdrawal of informed consent is possible at any point, without the necessity of providing a reason for withdrawal, in order to withdraw. A reason will be asked for registration purposes, but answering this question is not mandatory.

Screening evaluations for this study will include the following:

- Review of the study inclusion/ exclusion criteria (see Section 4.2 and Section 4.3)
- Collecting demographic information (see Section 5.4.1)
- Review of medical history and concomitant medications (see Section 5.4.2 and Section 4.4.3)
- Clinical assessment includes the evaluation of performance status (ECOG), and measurement of body weight and height (see Section 5.4.3).
- Assessment of baseline breast cancer disease characteristics (see Section 5.4.7)
- Assessment of baseline 'satisfaction with breasts' using the preoperative 'Satisfaction with Breasts' scale of the BREAST-Q v2 questionnaires, which is uniform among modules (see Section 5.4.4).
- Assessment of baseline QoL using the EQ-5D-5L questionnaire (see Section 5.4.5).
- Four digital photographs of the breasts (see Section 5.4.6).
- Elicitation of all Adverse Events (AEs) will be recorded from the moment of inclusion until study conclusion, and recorded according to the NCI-CTCAE v5.0 (see Section 7).

All results must be available for review and verification prior to participant enrolment to the study.

The Investigator should submit a signed and dated Eligibility Verification Form (EVF) to cancertrials@zas.be. The central investigator will reply by email to confirm eligibility within 1 business day. After eligibility has been confirmed, patients can be randomised using the eCRF in Castor EDC (see Section 6.4.3).

5.1.4 Study participant randomisation

5.1.4.1 Stratification

The randomisation will be balanced according to clinical trial site. More factors were considered, however the decision was made not to add more stratification parameters due to the risk of treatment group imbalances. Post-hoc subgroup analysis will be used to compensate for this decision.

5.1.4.2 Randomisation

Participants will be randomised using a computer generated permuted block randomisation. The randomisation scheme is further discussed in a separate file, to avoid bias due to predictability following from randomisation scheme knowledge. This separate file is included in the ethical commission application of this study protocol.

Randomisation of a participant can be performed by the site staff using the electronic randomisation tool built into the eCRF (Castor EDC), as soon as patient eligibility has been confirmed by the central investigator. The randomisation tool consists of an automatic calculation which checks if all eligibility and baseline assessment data are entered into the eCRF and if the patient is eligible for participation. When all pre-requisites are met, the eCRF will unlock the randomisation option. The study personnel performing the randomisation will press a button after which a dialogue box opens, displaying the randomisation arm, which is from then on also displayed in the participant's eCRF overview page. The study personnel are not able to change any settings of this randomisation process, nor are they able to see the sizes of the permutated blocks.

Participants will be randomised in a 1:1 ratio to one of the two treatment groups (SoC treatment, the control group, or experimental treatment, the intervention group).

5.4.1.3 Blinding

There is no blinding of the participants, nor research personnel in this study. This decision is made due to the consideration that blinding of the administration of Preop-RT and breast reconstruction timing are both impractical and may raise ethical concerns regarding oncological safety and informed consent. There is blinding of the expert panels scoring the photographs using the aesthetic items scale (AIS). Due to the nature of this assessment there is no need for an unblinding protocol.

5.1.5 Treatment period

Following randomised allocation to a study treatment group, the participant will start their assigned treatment. See Section 6 for the timing and a detailed description of the study interventions.

During the treatment period no study related visits are planned, except for the participants in the standard treatment group, receiving DBR. In this group of participants an additional intermediary follow-up (IMFU) study visit is planned at 3 months after the last Postop-RT treatment session. During this visit the following investigations will be performed:

- Assessment of 'satisfaction with breasts' using the 'Satisfaction with Breasts' scale from the 'Mastectomy' module of the BREAST-Q v2 questionnaire (see Section 5.4.4).
- Assessment of QoL using the EQ-5D-5L questionnaire (see Section 5.4.4).
- Four digital photographs of the breast-area (see Section 5.4.6).
- Elicitation of all (S)AEs and their potential links to study treatments. Adverse events will be graded according to the NCI-CTCAE v5.0 (see Section 5.4.8, and Section 7).

For all participants, the following data should be recorded in the eCRF during, or after conclusion of the treatment period:

- Treatment characteristics of radiation therapy (Section 6.1; 6.5.1).
- Treatment characteristics for oncological and reconstructive breast surgery (Section 6.2; 6.5.2).
- Treatment characteristics of (pre-/postoperative) systemic therapy (if applicable) (Section 6.5.3)
- Pathological tumour response as evaluated on the resection specimen (Section 5.4.9)
- Pathological staging (p/ypTNM) as evaluated on the resection specimen (Section 5.4.9).

5.1.6 Follow-up Period

Participants will return to the site during the follow-up period to complete the following assessments. The follow-up period starts after 'last study treatment' (LST), which is defined as the last radiotherapy session or definitive (reconstructive) surgery. Follow-up visits will be defined in relation to this point in time.

At 3 Months after last study treatment (LST)

The first follow-up visit occurs at 3 (+/-1) months after the last study treatment (LST). The following investigations should be performed:

- Assessment of satisfaction with breasts using the 'Satisfaction with Breasts' scale from the postoperative 'Reconstruction', 'Breast Conserving Therapy', or 'Mastectomy' modules of the BREAST-Q v2 questionnaire, as appropriate for the clinical situation (see Section 5.4.4).
- Assessment of QoL using the EQ-5D-5L questionnaire (see Section 5.4.5).
- Four digital photographs of the breasts (see Section 5.4.6).
- Elicitation of all (S)AEs and their potential links to study treatments. Adverse events will be graded according to the NCI-CTCAE v5.0 (see Section 5.4.8, and Section 7).
- Checking of treatment characteristics registration, as defined in section 5.1.5.

At 1, 2, 5 and 10 years of follow-up (after LST)

Visits during the follow-up period are to be conducted within ± 1 month of the nominal time point for the visit at 1 year after LST and ± 6 months for the visits at 2, 5 and 10 years after LST. The following investigations should be performed:

- Assessment of satisfaction with breasts using the 'Satisfaction with Breasts' Scale from the postoperative 'Reconstruction', 'Breast Conserving Therapy', or 'Mastectomy' modules of the BREAST-Q v2 questionnaire, as appropriate for the clinical situation (see Section 5.4.4).
- Assessment of QoL using the EQ-5D-5L questionnaire (see Section 5.4.5).
- Four digital photographs of the breasts (see Section 5.4.6).
- Elicitation of all (S)AEs and their potential links to study treatments. Adverse events will be graded according to the NCI-CTCAE v5.0 (see Section 5.4.8, and Section 7).
- Data on the regional, locoregional or metastatic tumour recurrence, or death must be collected. Used for TTE/survival assessment (see Section 5.4.11).

5.1.7 End of Study

End of study is defined as the last visit of the last patient (LPLV).

5.1.8 Unscheduled Visits

The Investigator or participant may request additional, unscheduled visits. Assessments at unscheduled visits will be undertaken as clinically indicated and registered in the eCRF.

5.1.9 Early Termination

In the case of premature discontinuation from study participation, the date and reason for termination (if willingly provided) should be documented in the eCRF, as discussed in section 5.2. The participant should return to the clinical site and complete an early termination visit (if they agree to this visit) as delineated in the SoE (Table 1).

5.2 Discontinuation or Withdrawal

5.2.1 Individual participants

5.2.1.1 Withdrawal from Study

In accordance with applicable regulations, a participant has the right to withdraw from the study, at any time and for any reason, without prejudice to their future medical care, nor having to provide a reason.

If a participant withdraws consent, the date and reason for consent withdrawal should be documented. This is documented by registering an 'Unscheduled visit' in the eCRF. If a participant does not wish to provide a reason for withdrawal, this will not have any consequence for the participant, their medical treatment, or their withdrawal from the study. Participant data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for early termination of individual participants may include:

- Protocol deviations or participant non-compliance (must be specified in the eCRF/deviation log)
- Adverse events
- The Investigator considers that it is in the participant's best interest to discontinue their participation in the study
- The participant is lost to follow-up
- The participant is deceased
- Other (must be specified and motivated)

If a participant is withdrawn because of an (S)AE, the Investigator should follow each (S)AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to the study, until a final outcome can be reported.
Wherever possible, the specified assessments should be performed for all participants who discontinue prior to the completion of the study.

5.2.1.2 Replacement of Participants

Participants who are enrolled and randomised but do not receive study treatment will not be replaced.

5.2.1.3 Participants Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for scheduled visits and are unable to be contacted by the study centre.

The following actions must be taken if a participant fails to return to the study centre for a required study visit:

- The study centre must attempt to contact the participant and reschedule the missed visit as soon as possible. The study centre must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or equivalent methods). These contact attempts should be documented in the participant's (e)CRF.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study, and will be classified as 'lost to follow-up'.

5.3 Study Termination

The study will be completed as planned unless:

- New information or other evaluations regarding the safety of the study treatment indicates a change in the known risk/benefit profile for the treatment, such that the risk/benefit is no longer acceptable for study participants. This may be determined by the Sponsor, the Investigator, the Trial Steering Committee (TSC), the Independent Ethics Committees (IEC) or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor, the IEC, the TSC, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by the investigational site during the course of termination or study suspension.

5.4 Study Assessments

5.4.1 Demographics

The following demographics will be recorded as part of the screening procedures.

- Date of screening visit
- Year of birth and age
- Biological sex
- Preferred language (Dutch, French or English)
- Height
- Weight
- BMI (calculated)
- Ethnicity

5.4.2 Medical History

The following details of the Medical history will be recorded during the screening visit:

- Confirmation of breast cancer diagnosis.
- Check if there is a history of breast cancer or radiotherapy of the chest wall or axilla.
- Check if the patient had any form of previous breast surgery, if so including a description.
- Check if the patient has a confirmed collagen synthesis disease/disorder.
- Smoking status and history.
- Check if the patient is currently pregnant or breastfeeding.
- Alcohol consumption habits.
- Use of illicit drugs
- Comorbidities
- Registration of concomitant medications (farmaca, route of administration, dosage, start/stop date)

5.4.3 Clinical Assessment

Clinical assessment includes the evaluation of the ECOG performance status, the measurement of body weight and height, and recording currently used (chronic) medications.

5.4.3.1 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status and the date of its assessment should be documented in the participant's medical record or study source documentation at the screening visit. A copy of the document is included in Appendix 1 (Eastern Cooperative Oncology Group Performance Status Assessment) for reference.

5.4.3.2 Height and Body Weight

Height (cm) and body weight (kg) will only be measured during the screening visit. The (calculated) BMI will also be recorded as part of the screening procedures.

5.4.3.3 Currently used (chronic) medication use

Patients will be questioned regarding concomitant medication use, only during the screening visit. The patient will be asked to report all the medication they currently use, especially those medications which are taken on a regular basis (chronic use). The substance, route of administration, dose, and start/stop date (if known) will be recorded.

All prior and concomitant systemic therapy (including neoadjuvant systemic chemotherapy, adjuvant systemic therapy, endocrine therapy, immune therapy, or any other forms of systemic therapy) for breast cancer are not recorded as concomitant medication, they must be recorded in the eCRF as discussed in Section 6.5.3.

5.4.4 BREAST-Q questionnaire

Satisfaction with breasts will be reported by patients using the Satisfaction with Breasts scale from the BREAST-Q v2 questionnaires.

Preoperative and postoperative versions of the 'Satisfaction with Breasts' scale from the 'Reconstruction', 'Breast Conserving Therapy', and 'Mastectomy' modules of the BREAST-Q Version 2.0 questionnaires will be used, as detailed above and supplied in appendix 2. These scales measure body image through patients' satisfaction with their breasts, based on questions about the comfort of the operated or reconstructed breasts, both clothed and unclothed. It also evaluates self-image, the comfort of wearing clothes, breast symmetry, smoothness, sensation, and size.

Participants will be asked to self-complete these BREAST-Q v2 questionnaires, they will be administered to patients on paper or via the Castor EDC platform (eCRF).

Since this study lets the patient and medical team decide on the preferred method of breast reconstruction (within the bounds of the randomisation group), there are a number of potential situations to take into account. All participants are set to receive a breast reconstruction, as this is an inclusion criterium, therefore the pre- and postoperative 'Satisfaction with Breasts' scale from the 'Reconstruction' module of the BREAST-Q v2 will be considered the standard module during this study. The preoperative questionnaire will be assessed during the screening visit and the postoperative questionnaire at each follow-up visit after treatment finalisation.

Considering the slight chance that Preop-RT may result in downstaging, we must consider the possibility that patients in the treatment group may become eligible for breast conservative surgery. The preoperative 'Satisfaction with Breasts' scale from the BREAST-Q v2 'Breast Conserving Therapy' Module is identical to that of the 'Reconstruction' module, and as such no extra questionnaire needs to be provided at the screening visit. During follow-up these patients will be evaluated with the postoperative 'Satisfaction with Breasts' scale from the BREAST-Q v2 'Breast Conserving Therapy' module.

Likewise, there is the possibility of patients not having received a breast reconstruction yet (in DBR patients, during the IMFU visit), the occurrence of flap failure, or the patient deciding not to go forward with breast reconstructive surgery. In these cases the 'Satisfaction with Breasts' scale from the BREAST-Q v2 'Mastectomy' module will be used. The preoperative questionnaire is again identical to those in the other modules.

Using the BREAST-Q documentation, the (raw) score for each scale is transformed into the corresponding BREAST-Q score, using the provided module-specific conversion scales. This BREAST-Q score can range from 0 (signifying the least possible level of satisfaction) to 100 (signifying the highest possible level of satisfaction).

5.4.5 European Quality of Life 5 Dimensions, 5 Levels (EQ-5D-5L) questionnaire

EQ-5D-5L is a widely used generic measure of QoL status consisting of two parts (see Appendix 3).

The first part assesses QoL in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which has five levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to). The patient is asked to indicate their QoL/health state by ticking the box next to the most appropriate statement in each of the five dimensions. This part of the EQ-5D-5L questionnaire provides a descriptive profile that can be used to generate a health state profile. For example, a patient in health state 12345 would have no problems with mobility, slight problems with self-care (washing or dressing), moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. Each health state can potentially be assigned a summary index score based on societal preference weights for the health state. Health state index scores generally range from 0 to 1, with 0 representing a health state equivalent to dead, and 1 is a perfect health state. Each population has an individually validated method of calculating the EQ-5D-5L index score. In this study the method validated in the Belgian population will be used, as recommended by the EuroQoL website and materials, and as published by Bouckaert et al., 2022.(65) This formula results in an index score ranging from -0.533 to 0.962. Since this validated formula to derive the index score in the Belgian population does not result in a score ranging from 0 to 1, the score will be transformed using the provided formula. This will increase interpretability of the score, and comparison to other populations.

Rescaling formula, where the rescaled score value is a function of the initially calculated index score (IS):

$$f(IS) = (IS + 0.533)/1.495$$

The second part of the questionnaire consists of a visual analogue (VAS) scale on which the patient rates their perceived health, on that specific day, from 0 (the worst imaginable health) to 100 (the best imaginable health).

Participants will be asked to self-complete the EQ-5D-5L questionnaire during study visits, at the screening visit (baseline), IMFU visit (for DBR patients), and during the follow-up visits at 3months, 1 year, 2 years, 5 years and 10 years after LST. The EQ-5D-5L questionnaire requires a low level of cognitive strain, consisting of 5 dimensions with 5 possible levels on a Likert answering scale and a single VAS-scale based question. It takes only a few minutes to complete. The self-complete version of the EQ-5D-5L questionnaires will be administered to subjects on paper or via the Castor EDC platform (eCRF).

5.4.6 Digital Photographs of the Breasts

Digital, two-dimensional, colour photographs of both breasts, will be taken during study visits, at the screening visit (baseline), IMFU visit (for DBR patients), and during the follow-up visits at 3months, 1 year, 2 years, 5 years and 10 years after LST. Each set of photographs will be assessed by a blinded panel of experts using the Aesthetic Items Scale (AIS; see Appendix 4).

It is of great importance that they are taken according to a standardised protocol to ensure comparability between visits and between participants. For this reason the following guidelines must be adhered to:

- Within each study site a certain location should be chosen to take these photographs. Ideally this location has:
    - 1) A blank (no frames, drawings, closets etc.) white wall or screen;
    - 2) No windows or the option to block out sunlight, as sunlight varies greatly depending on time-of-day and weather conditions;
    - 3) Adequate artificial light, so that a flash is not necessary, and these lighting options should always be available (e.g.: if a desk-lamp is used in the initial setup, this desk-lamp should always be available when taking photographs).
- Regarding the photography device, either a smartphone, or a dedicated camera device (DSLR, mirror-less, etc. camera) can be used. The following requirements apply:
    - 1) At least 10 Megapixels;
    - 2) Always use the same device, or verify that image quality is similar (before using the device);
    - 3) Use the automatic settings of the device;
    - 4) Always check the quality of the photographs after taking them, if needed repeat the photograph(s);
    - 5) Avoid using the Flash function, but it is allowed when the image quality/clarity is insufficient without the Flash.

Before the first patient, the location and device should be determined. Test photographs should be taken at the location, using the selected device (or multiple locations/devices to decide which are the best options). Take photographs according to these guidelines, using a stand-in model (clothed, preferably in a white/beige/brown top) in order to verify adequate image quality.

The participant should be positioned +/- 30-50cm from the background. The chest anatomy should be clearly visible, clothes and jewellery obstructing the view of the chest anatomy should be removed. Ensuring an unobstructed view for photographs which will be framed to include at least the low neck, upper border of the shoulders to the umbilicus in the cranio-caudal axis and the entire width and depth of the body in the sagittal and antero-posterior axes respectively.

The camera device should be positioned in such a way that the device is not tilted (no front/back and no left/right tilting), at least 50cm from the participant, increasing the distance as needed to correctly frame the participant within the view of the camera device.

Before the visit, please check the availability of the location and device. Check the standardised conditions and other prerequisites: lighting of the room, background, battery-life, storage capacity, camera settings.

Photograph 1: The participant is positioned in front of the camera in a 0°-angle. The arms should be down, next to the body with the hands placed on the gluteal region. Ensure correct framing of the photograph, including at least the low neck, upper border of the shoulders to the umbilicus in the cranio-caudal axis and the entire width of the body in the sagittal axis.

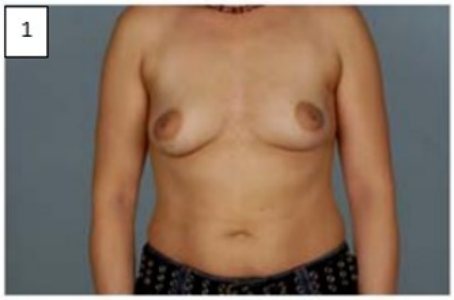

Figure 2.1: Photograph position 1, frontal view and arms down.

Photograph 2: The participant is positioned in front of the camera in a 0°-angle. The arms should be lifted up until the maximal height is achieved. Ensure correct framing of the photograph, including at least the low neck, upper border of the shoulders to the umbilicus in the cranio-caudal axis and the entire width of the body in the sagittal axis.

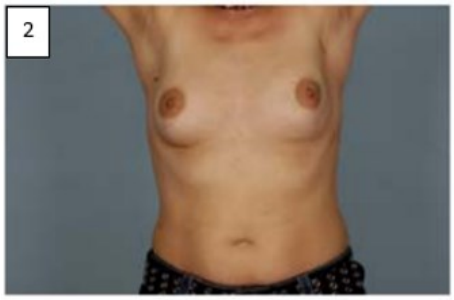

Figure 2.2: Photograph position 2, frontal view and arms up.

Photograph 3: The participant is positioned in front of the camera in a Right-facing 90°-angle, exposing the left flank. The arms should be lifted up at maximal height. Ensure correct framing of the photograph, including at least the low neck, upper border of the shoulders to the umbilicus in the cranio-caudal axis and the entire width and depth of the body in the sagittal and antero-posterior axes respectively.

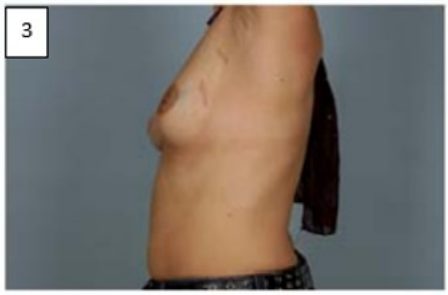

Figure 2.3: Photograph position 3, left lateral view and arms up.

Photograph 4: The participant is positioned in front of the camera in a Left-facing 90°-angle, exposing the right flank. The arms should be lifted up at maximal height. Ensure correct framing of the photograph, including at least the low neck, upper border of the shoulders to the umbilicus in the cranio-caudal axis and the entire width and depth of the body in the sagittal and antero-posterior axes respectively.

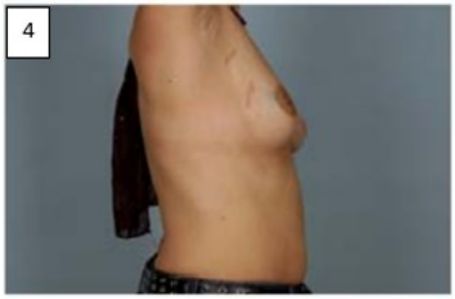

Figure 2.4: Photograph position 4, right lateral view and arms up.

Afterwards, please verify the image quality. Correctly name the photograph using the format: **"Photograph_[VISIT]_[Participant ID]_[#] of 4"**.

5.4.7 Disease baseline characteristics

The following information regarding aspects of the patient's breast cancer will be recorded in the eCRF

- Date of diagnosis
- Affected side
- Diagnostic measures performed (+ details such as amount and region of sampled lymph nodes)
- Signs of lymphovascular invasion (Pathology report)
- The c/ycTNM classification, as reported by the MDO
- Immuno-histochemical, molecular and/or genetic tests performed, including results
- Check if there is an indication for SSM/NSM
- Check if there is an indication for PMRT
- Check if there is a wish for breast reconstruction

5.4.8 Assessment of (S)AEs and Surgical AEs

The definition, registering and follow-up of (S)AEs is discussed in section 7.

Elicitation of general (S)AEs and surgical (S)AEs will occur at IMFU, 3 months, 1, 2, 5 and 10 years after LST. Surgical AEs are defined as any complication (AE or SAE) related to surgical treatment/intervention. In this study this pertains to both the oncological and reconstructive surgeries. Surgical (S)AEs/complications are reported using the Common Terminology Criteria for Adverse Events (CTCAE, version 5). During the reporting of an AE/SAE the relatedness to a study intervention is also registered, here the relatedness to surgical treatment/intervention will be registered. If an (S)AE is scored as 'Possibly related' or higher, relating to a surgical study treatment, then it will be considered as a surgical AE.

CAVEAT: Not all postoperative complications are listed in the CTCAE v5.0 database, for example: capsular contraction, implant malpositioning, reconstructive failure, etc. are not listed but need to be recorded. These can be registered under "Injury, poisoning and procedural complications - Other, specify" CTCAE term

5.4.9 Treatment duration

Throughout the study the dates of important treatment milestones will be recorded. These include the dates of diagnosis, screening visit, lymph node biopsy, randomisation, preoperative systemic therapy (start and stop), radiotherapy (start and stop), oncological surgery, reconstructive surgery(/-ies), postoperative systemic therapy (start and stop).

These parameters will be used to calculate the following outcome variables, expressed in days:

- Randomisation to last study treatment (LST)
- Randomisation to oncological breast surgery
- Oncological breast surgery to last study treatment (LST)

Other time intervals will be calculated in the eCRF, based on the aforementioned milestone dates. These will not be used in the primary statistical analysis, but could be used in the post hoc analysis.

5.4.10 Assessment of Pathological Tumour Response and resection specimen pathology TNM

Pathological tumour response, as assessed on the resection specimen, must be registered in the eCRF.

This outcome should always be reported when preoperative-systemic therapy was administered. Preop-RT without preoperative-systemic therapy, may also be seen as a reason to assess the tumour response category. However, at an interval of 2-6 weeks after radiation therapy we don't expect any effect on the pathological response. Therefore, if we would compare the response categories between the standard and experimental groups, this would result in an unfair comparison. For this reason this outcome will be assessed in a subset of the ITT set, which is defined as the population that received preoperative systemic therapy. In the safety set this will remain unchanged and in safety analysis of this outcome both sets will be analysed.

Response categories should be recorded according to the Pinder classification or 'no preoperative therapy': (9)

- No residual carcinoma nor DCIS (complete response) = Pinder 1i
- No residual carcinoma but DCIS present = Pinder 1ii
- Partial response (>90%) = Pinder 2i
- Partial response (50-90%) = Pinder 2ii
- Partial response (<50%) = Pinder 2iii
- No signs of response = Pinder 3
- No preoperative therapy

After oncological surgery it is standard of care for the pathologist to assess the resection specimen and resected lymph nodes if applicable. Resulting from this assessment a pathology-based TNM classification is reported (pTNM or ypTNM). The resulting pathology TNM and additional IHC or genetical testing results will be collected from the patient's EHR and registered in their (e)CRF.

5.4.11 Collection of Data on oncological survival

Oncological follow-up of patients will be planned according to local institutional guidelines.

During follow-up visits (from LST +1 year onwards) the oncological outcome parameters, as described below, will be registered in the patient's (e)CRF. Registration will be based on both patient interview during the follow-up visit, as well as EHR reviewing (source documents).

The following events must be recorded if applicable, as defined in the 2015 DATECAN consensus: (10)

- Death
    - All-cause mortality
    - Death from breast cancer
- Any recurrence vs. none.
  If any recurrence has occurred it will be recorded using the subtypes:
    - Invasive ipsilateral breast tumour recurrence/progression
    - Local invasive recurrence/progression
    - Regional invasive recurrence/progression
    - Appearance/occurrence of metastasis/distant recurrence
    - Ipsilateral DCIS

6. Study Intervention

6.1 Radiation Therapy

6.1.1 Timing

Postop-RT/PMRT will be initiated 6-12 weeks after the oncological breast surgery.

Preop-RT must be planned to commence as quickly as reasonably possible after randomisation, at the discretion of the Investigator, but no later than 6 weeks after randomisation or the last dose of preoperative chemotherapy (if applicable).

6.1.2 Patient Positioning and Imaging

All patients will undergo a radiation therapy-planning CT in a standard semi-supine position according to local protocols. Where indicated, patients will be imaged using a breath-hold technique (again, according to local protocols). CT images should be acquired at no greater than 5mm intervals, but ideally at 3mm intervals.

6.1.3 Target Volume Definition

In general, the breast tissue from 5 mm beneath the skin surface to the pectoral fascia will be the clinical target volume in all cases. Whether regional nodes are included in the target volume will be based on the clinical situation of the individual patient, local treatment protocols, and multidisciplinary meeting advice.

6.1.4 Treatment Planning

Breast cancer RT-plans will be prepared according to local protocols, with the aim of covering the dosimetric parameters listed in Table 3 (in accordance with the Dutch national consensus guidelines of Hurkmans et al. 2021).(66)

6.1.5 Dose

Patients will be treated according to departmental protocol, 40Gy in 15 fraction, over 3 weeks, or a biologically equivalent dose (i.e. 26Gy/5 fx). Radiation techniques and quality assurance procedures are identical to the standard radiation techniques applied in PMRT or WBRT, and should fulfil the criteria as defined by this protocol.

6.1.6 Use of Bolus

The use of a bolus will be in accordance with ESTRO guidelines.(67) When Preop-RT is given for a cT4b/c tumour, bolus should be administered only on the part of the skin that will also be excised during oncological breast surgery.

Table 3 National consensus on dosimetric parameters and target volume names to be used in the evaluation of a breast cancer RT-plan (Hurkmans et al., 2021)(66)

	D98%	Dmean	D2%
PTV_Breast	≥ 95%	99–101%[a]	≤ 107%
PTV_Boost	≥ 95%	100%[b]	≤ 107%
PTV_N1n2pect[c]	≥ 95%	No target value given	No target value given
PTV_N3n4[c]	≥ 95%[d]	No target value given	No target value given
PTV_IMN[e]	≥ 90%[c]	No target value given	No target value given

[a] : With the exception of plans including a boost volume.
[b] : 100% is given as target value but may differ per patient. No consensus was reached what range of values would be acceptable.
[c] : These node levels can be jointly evaluated.
[d] : In case this PTV includes lung, a concession to this target value is allowed.
[e] : D98% should be ≥95% for CTV_IMN, also taking into account set-up uncertainty.

6.2 Oncological breast Surgery

At inclusion there should be an indication for skin-sparing (SSM) or nipple-sparing (NSM) mastectomy. However, for the actual oncological surgery, a SSM, NSM, breast-conserving surgery (BCS), or Modified Radical Mastectomy (MRM) could be performed, as indicated. The possibility of a BCS is believed to be very unlikely, but was added in order to accommodate the unlikely event that Preop-RT would lead to sufficient downstaging. For the purpose of this protocol we will refer to SSM, NSM, or MRM, as 'mastectomy' or 'ME', and if BCS is also included, as 'oncological surgery'.

ME will be performed within 6 weeks of randomisation or the last dose of neoadjuvant chemotherapy (if applicable) for patients in the standard treatment arm.

Patients in the experimental treatment arm proceed to oncological surgery at 2-6 weeks after the last fraction of Preop-RT.

The timing of oncological surgery can be delayed if necessary for patient safety, e.g. in case of severe acute toxicity after RT, or unforeseen logistical reasons, but this needs to be documented as a protocol deviation.

6.3 Breast Reconstruction surgery

The type/technique of breast reconstruction performed is at the discretion of the patient and the treating plastic/reconstructive surgeon, within the bounds of the randomisation groups. These options include reconstruction using an implant (+/- in two steps with a temporary tissue expander), using autologous tissue (e.g.: Deep Inferior Epigastric Perforator (DIEP) flap), or a combined technique using both autologous tissue and an implant/TE. Adjuvant reconstruction techniques such as fat grafting, or an acellular dermal matrix, could also be used in addition to the primary technique.
In the standard treatment arm both immediate and delayed (IBR or DBR) techniques can be used according to standard of care and patient/surgeon preferences. The placement of a tissue expander (TE) is considered an IBR approach within this study.
In the experimental treatment arm only immediate reconstruction (IBR) techniques are allowed, this could also consist of a TE placed during oncological surgery. If there are unforeseen conditions, in which IBR is not in the best (medical/safety) interests of the patient, the treating physician and medical team should act in the best interest of the patient, such events should be recorded as a protocol deviation.

6.5 Treatment Characteristics, Compliance and Adherence

6.5.1 Radiation therapy characteristics

The following characteristics regarding RT will be recorded in the eCRF:

- Setting (preoperative vs. postoperative)
- Start and stop dates
- Prescribed dose and fractioning for both breast/thorax and axillary regions
- Modality of RT employed, and if proton-based RT is used, the MeV delivered.
- Homogeneity of delivery
- Target volume parameters (PTV volume, D98%, Dmean, D02%) for both breast and axillary regions
- Organs At Risk (OAR) parameters (Dmean ipsilateral lung, V5Gy ipsilateral lung, Dmean heart, Dmean contralateral breast, Thyroid V30Gy)
- Whether DICOM file(s) will be locally stored for at least 10 years.

6.5.2 Surgery characteristics

The following characteristics regarding oncological surgery will be recorded in the eCRF:
- Date of surgery
- Type of surgery (SSM, NSM, MRM, BCS, None/other)
- Weight of removed breast tissues (pathology report)
- Type of lymph node procedure, including number removed and positive nodes

The following characteristics regarding reconstructive surgery will be recorded in the eCRF:
- Immediate vs. delayed breast reconstruction (IBR vs. DBR)
- Date of surgery(/-ies)
- Primary technique of reconstruction (Autologous, implant-based, or combined; +/- Tissue Expander)
- Tissue expander starting volume
- Breast implant details: positioning, shape, profile, volume, and texture
- Autologous flap details: type of flap, pedicled/free-flap, number of anastomoses, and stacked yes/no
- Adjuvant breast reconstruction techniques
- If applicable, reconstructive failure details

6.5.3 Systemic treatment characteristics

The following characteristics regarding systemic therapies will be recorded in the eCRF:
- Preoperative and/or postoperative administration of systemic therapy
- Types of systemic therapy used. (This includes, but is not limited to chemotherapy (ChT) regimens, endocrine therapy (ET), Immuno-therapy, targeted therapies (TT) and Bisphosphonates (BP))
- Start and stop dates
- Agents used

7. Safety Monitoring

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up (S)AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study (see Section 5.2).

7.1 Definition of Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant, temporally associated with the study intervention, whether or not considered related to the study intervention.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the study intervention.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (haematology, biochemistry, etc.) or other medical (safety) assessments (e.g., ECG, radiological scans, vital signs measurements, etc.), including results that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator, which are not (clearly) related to progression of any underlying disease.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/ or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

7.2 Definition of Adverse Reaction (AR)

Adverse reactions are all noxious and unintended responses to a study intervention. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the study intervention based on an analysis of available evidence.

7.3 Definition of Unexpected Adverse Reaction (UAR)

An adverse reaction, the nature or severity of which is not consistent with the available safety evidence for the study intervention.

7.4 Definition of Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

  Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

- **Is life-threatening**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**

  In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/ or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent disability/ incapacity**

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in a congenital anomaly/ birth defect**

  Report if you suspect that exposure to a medical product/treatment prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- **Results in other situations (important medical events)**

  Report when the event does not fit the other outcomes, but the event may jeopardise the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalisation. The development of drug dependence or drug abuse would also be examples of important medical events.

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in situations which were not explicitly mentioned, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such medical events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: If an event is not an AE per definition presented in Section 7.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/ symptoms of the disease under study, death due to progression of disease).

In determining whether a serious adverse event (SAE) is a serious adverse reaction (SAR), consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the study intervention based on an analysis of available evidence.

7.5 Severity or Intensity of an Adverse Event

AEs are to be recorded in the eCRF. Severity will be graded according to the NCI-CTCAE v 5.0, published November 27, 2017 (NCI-CTCAE v5.0 – see Appendix 5).

CAVEAT: Not all postoperative complications are listed in the CTCAE v5.0 framework, for example: capsular contraction, implant malpositioning, reconstructive failure, etc. are not listed but need to be recorded. These can be registered under "Injury, poisoning and procedural complications - Other, specify" CTCAE term

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the grades listed in the NCI-CTCAE v5.0. These grades generally follow this model:

- Grade 1: Mild; an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Grade 2: Moderate; an event that causes sufficient discomfort and interferes with normal everyday activities.
- Grade 3: Severe; an event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Caveat: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is graded as severe (grade 3).

7.6 Causal Relationship or Relatedness of an Adverse Event

The Investigator is obligated, and will use clinical judgment, to assess the relationship between the study interventions and each occurrence of each AE/ SAE. The AE must be characterised as unrelated, unlikely to be related, possibly related, probably related, definitely related, or unknown (unable to judge) to the study intervention (i.e. oncological breast surgery, radiation therapy and breast reconstruction surgery).

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The Investigator will also consult the available evidence on the safety of the study intervention in his/ her assessment.

For each AE/ SAE, the Investigator must document in the medical notes that he/ she has reviewed the AE/ SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor medical representative.

The Investigator may change his/her opinion of causality in light of follow-up information and complete an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The following definitions, and the content of Table 4, are general guidelines to help assign grade of attribution:

Adverse reaction (AR) – An AR is any AE caused by the study interventions

Serious adverse reaction (SAR) – An SAR is any SAE caused by the study interventions

Suspected unexpected serious adverse reaction (SUSAR) – An SAR for which there is a reasonable possibility that the study interventions caused the SAE. A "reasonable possibility" means there is evidence to suggest a causal relationship between the study intervention and the AE. SUSAR implies a lesser degree of certainty about causality than AR/SAR.

Unexpected – An event is considered unexpected if there is no evidence available for its occurrence with the particular interventions under investigation.

Table 4 Adverse Event Causal Relationship with Study Intervention

Definitely Related	Clear evidence to suggest a causal relationship with other possible contributing factors has been ruled out. The clinical event occurs within an acceptable time relationship to study treatment, improves when stopping the treatment, and re-appears when exposure resumes if necessary.
Probably Related	Facts, evidence, and/or arguments suggest a causal relationship, yet there is still room for doubt.
Possibly Related	The association of the AE with the study intervention is unknown; however, the AE is not reasonably supported by other conditions.
Unlikely to be Related	Only a remote connection exists between the study intervention and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
Unrelated	No reasonable possibility that the study intervention caused the AE.
Unknown	All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

7.7 Outcome

Outcome of an AE or SAE will be recorded in the AE report form and eCRF as follows:

- Recovered/ resolved
- Recovering/ resolving
- Recovered/ resolved with sequalae
- Not recovered/ not resolving
- Fatal
- Unknown

7.8 Method of Detecting Adverse and Serious Adverse Events

(S)AEs will be reported by the participant. Participants are able to report (S)AEs at any point during the duration of the study and follow-up, there will be formal inquiries regarding (S)AEs occurrence during all study related visits (cfr. SoE). Care will be taken not to introduce bias when detecting (S)AEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about (S)AE occurrences.

(S)AEs can also be reported by any involved physician if they have a mandate from the patient or if reporting the (S)AE is in the best interest of the patient and/or other participants. (S)AEs may also come to light when the patient file is being reviewed.

7.9 Recording of Adverse and Serious Adverse Events

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/ SAE information in the eCRF. Each event must be recorded separately. There may be instances when copies of medical records of specific cases are requested by the coordinating study staff or other authorised organisations. In this case, all direct identifiers of participant identity, with the exception of the participant study ID, will be redacted on the copies of the medical records before submission. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/ or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

7.10 Follow-up of Adverse and Serious Adverse Events

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor medical representative, to elucidate the nature and/or causality of the AE or SAE as thoroughly as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. If a participant dies during study participation or during a recognised follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if relevant and applicable. New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any (updated) SAE data to the sponsor representatives (through 'cancertrials@zas.be') within 24 hours of receipt of the information.

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up.

7.10.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the final study visit. All SAEs will be recorded and reported to the Sponsor within 24 hours. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. Investigators are not obligated to actively seek AE or SAE information after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has discontinued study participation/follow-up, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

7.11 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of study participants and the safety of a study treatment under clinical investigation are met.

The Sponsor will comply with European and country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC/IRB, and investigators.

Investigator safety reports must be prepared for each suspected unexpected serious adverse reactions (SUSAR), and serious adverse reactions (SAR), in accordance with European and local regulatory requirements and Sponsor policy, and forwarded to investigators as necessary. SUSARs are defined as all SAEs which are 'unexpected' and are suspected to be related to the study intervention. SARs are defined as all SAEs which are deemed to be related to the study intervention

All SAEs (initial and follow-up information) and pregnancies occurring during this study must be reported by emailing the completed initial report section of the SAE form within 24 hours after becoming aware of the SAE to: gza.safetycto@zas.be.

The IEC/IRB will be informed by the Sponsor about SAEs, SUSARs or safety issues according to the European Union Clinical Trial Regulation No 536/2014 and/ or local regulations.

7.11.1 Annual Safety Report

The Sponsor will provide annual safety reports to the Ethics Committee. This obligation starts with the first authorisation of the trial and concludes with the end of the trial.

7.12 Clinical Laboratory Findings

Abnormal laboratory findings (e.g., haematology or biochemistry) or other abnormal assessments (e.g., vital signs) are not necessarily reported as AEs. However, those abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (or recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as (S)AEs.

The Investigator should exercise his/her medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near future, to be considered clinically significant.

8. Statistical Considerations

8.1 Justification of Sample Size

This trial will assess the efficacy of Preop-RT and the fact that it enables IBR. Therefore, the level of satisfaction of women with their reconstructed breasts was selected as its primary outcome variable. This will be assessed at 1 year of follow-up after LST, and compared to the standard of care treatment (Postop-RT and IBR or DBR).

The sample size was thus calculated to detect a difference in satisfaction with breasts as operationalised by the BREAST-Q score ('Satisfaction with Breasts' scale from the Breast Q v2 'reconstruction', 'BCT', or 'Mastectomy' module; appendix 2), between patients in the experimental and control groups. Based on previous studies assessing the mean BREAST-Q score after breast reconstructions, we expect a mean score of 58 (SD 18) in the standard treatment/control arm.(12) The minimally important difference in the BREAST-Q score for satisfaction with breasts (reconstruction module) was found to be 4, based on earlier research.(12) This would however lead to an exceedingly high sample size. Therefore an 8 point difference was selected as a balance between a workable sample size and a difference in BREAST-Q scores which is achievable, detectable and clinically relevant.

To detect a difference of at least 8 points (expected $\bar{x} \geq 66$) with 80% power and a two-sided alpha of 0.05, using the Students' t-test for two independent sample means, we need to include n=81 women in each treatment arm. To account for a dropout rate of 10%, we aim to randomise n=90 women per treatment arm, resulting in n=180 patients in total.

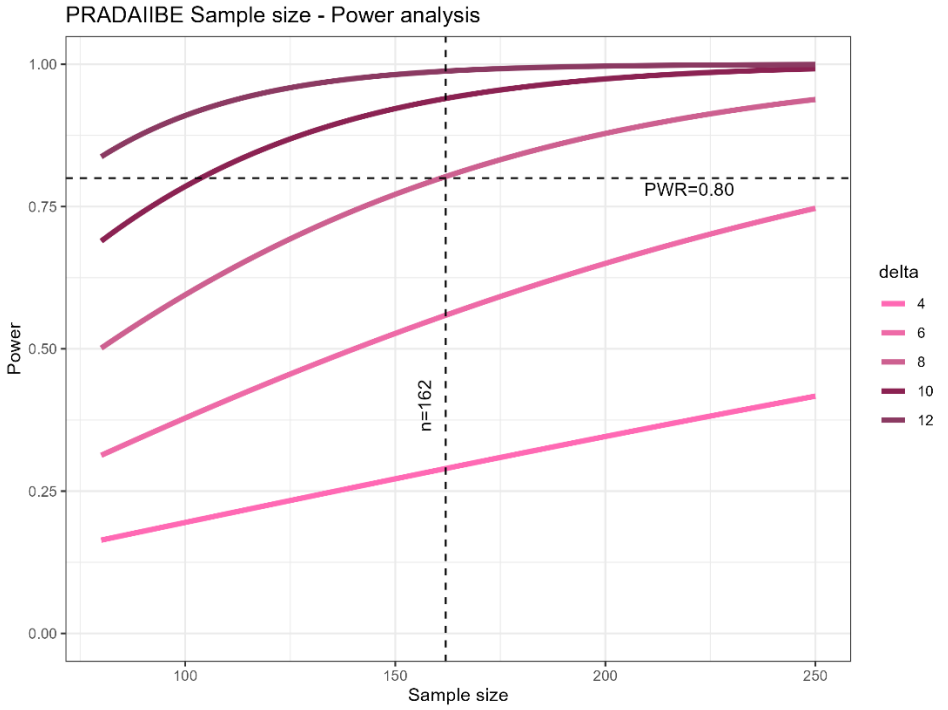

Figure 3: Power (y-axis) vs. Sample size (x-axis), per difference in means (legend)

8.2 Analysis Populations

The primary population for all statistical analyses is the Intention-To-Treat Population (ITT). The ITT population consists of all enrolled and randomised participants whether or not they received any study treatment. 'The Estimands Framework' will be used to define an inter-current events (ICE) strategy, which is described in the SAP.

8.3 Statistical Methods for Analysing Primary, Secondary, and Tertiary Outcomes

Statistical analysis will be performed under the authority of the Sponsor. A brief description of the main statistical principals, methods and considerations will be discussed in this study protocol. The full details concerning data handling and statistical analyses will be provided in the Statistical Analysis Plan (SAP), which is available upon request.

Continuous outcomes

All continuous primary and secondary outcomes (*BREAST-Q, EQ-5D-5L VAS, EQ-5D-5L Index Score, AIS-TAS*) will be analysed using Linear Mixed Models (LMM) regression analysis with a Wald-test of the grouping variable for formal hypothesis testing. This model will define study centre and participant levels as random effect factors, taking multiple measurements per participant into account. Fixed effect factors (regressors) are defined in the SAP and will be added to the model, in the primary statistical analysis there will be no post hoc adjustments of the predefined model. This is supplemented by a Mann-Whitney U (MWU) test which will be hierarchically inferior to the conclusions from the LMM, unless the assumptions of the LMM are not met. Data analysis occurring after 1Y of follow-up, will be based on a 'Generalised Estimating Equation' (GEE). These tests and the reported statistics will be further discussed in the SAP.

Dichotomous outcomes

The dichotomous secondary outcomes (General AEs, Surgical AEs, pathological Complete Response rate) will be assessed using a two-sided Z-test comparing two independent sample proportions. In the safety assessment an Agresti-Caffo corrected 95% Confidence Interval of the difference in proportions will be used. These tests and the reported statistics will be further discussed in the SAP.

Time-To-Event outcomes

The TTE secondary and tertiary outcomes (*Treatment duration , Overall Survival, Breast Cancer Specific Survival, Relapse-Free Survival, Locoregional Relapse-Free Survival, and Distant-Disease Free Survival*) will be assessed using survival analysis methods. These will consist of the construction of a Kaplan-Meier (KM) curve and estimates, and the performance of a cox-regression analysis comparing the treatment groups. These tests and the reported statistics will be further discussed in the SAP.

8.3.1 Primary Endpoint

For the primary endpoint, the 'Satisfaction with Breasts' scale from the Breast Q v2 'reconstruction', 'Breast conserving therapy', or 'Mastectomy' module (as applicable for the clinical situation) (appendix 2), at 1 year of follow-up after the last study treatment (LST), will be used. To score a BREAST-Q scale, the raw scores for the set of items in a scale are added together to produce a total raw score. If missing data is less than or equal to 50% of the scale's items, the within person mean for the completed items can be imputed. If more than 50% of the scale's items are missing, the summed score for this participant cannot be computed and will be classified as missing data. Once a total raw score for the scale is computed, the

BREAST-Q conversion table will be used to convert the raw score into a BREAST-Q score, which ranges from 0 (worst) to 100 (best).

8.3.2 Secondary Endpoints

Health related quality of life

The EQ-5D-5L questionnaire contains a VAS-scale ranging from 0 (worst) to 100 (best) to reflect the participant's overall QoL/health assessment at that point in time, this score is used without transformation. The Index score is calculated from the answers to the 5 items of the questionnaire. The raw scores per item are weighted and then entered into a formula which has been validated in the Belgian population.(65) The resulting score is the index-score, ranging from -0.533 (worst) to 0.962 (best). This score is then transformed to a scale ranging from 0 to 1 using the following formula, where f(IS) represents the transformed score, IS the index score, 0.533 is the correction of the lowest value to zero, and 1.495 is the range difference:

$$f(IS) = (IS + 0.533)/1.495$$

This scoring and transformation is automatically applied in the eCRF, and the transformed index score will be used in statistical analysis.

Cosmetic outcome (AIS – TAS score)

The average Total Aesthetic Score (TAS) will be derived from a panel of independent observers (consisting of at least 2, ideally 5 physicians with a background in either plastic surgery, mammary surgery, or mammary radiation therapy) assessing the photographs per participant and study visit, using the 'Aesthetic Items Scale' (AIS). Inter- and intra-observer agreement of the ratings will be calculated and expressed as intraclass correlation coefficients (ICCs). An ICC of >0.7 will be considered to indicate a good inter-rater reliability.(68)

Adverse events

Clinician-reported AEs will be graded using NCI-CTCAE v5. The highest grade per participant will be recorded, and then used for the composite outcomes: proportion of participants experiencing no AE vs. any grade AE, and grade < 3 AE vs. grade $\geq$ 3 AE.

Surgical adverse events.

From the adverse events data (as described above), those related to the surgical study interventions (oncological surgery and breast reconstruction surgery) will be sourced and evaluated separately. The methods of outcome reporting and hypothesis testing will be the same as described for the general AEs.

Treatment pathway duration time

Each of the treatment duration variables (infra) are compared between treatment groups.

- Randomisation to last study treatment (LST)
- Randomisation to oncological breast surgery
- Oncological breast surgery to last study treatment (LST)

The time interval of 'Randomisation to last study treatment (LST)' will be used in hypothesis testing

Pathological response

Participants receiving preoperative systemic or radiation therapy treatment(s) undergo pathological response assessment of the removed breast tissues (SoC assessment). The reported Pinder-classification response or 'No preoperative therapy' will be recorded in the eCRF: (9)

- No residual carcinoma nor DCIS (complete response) = Pinder 1i
- No residual carcinoma but DCIS present = Pinder 1ii
- Partial response (>90%) = Pinder 2i
- Partial response (50-90%) = Pinder 2ii
- Partial response (<50%) = Pinder 2iii
- No signs of response = Pinder 3
- No preoperative therapy

The analysis of this secondary outcome will be performed on a subset of the ITT set, which is defined as those participants that received preoperative systemic therapy.
More details on the rationale can be found in section 5.4.10.

8.3.3 Tertiary Endpoints

Oncological survival and time-to-event data

The following TTE/survival outcomes will be reported: Overall Survival (OS), Breast Cancer Specific Survival (BCSS), Relapse-Free Survival (RFS), Locoregional Relapse-free Survival (L-RFS), and Distant-Relapse Free Survival (D-RFS). These TTE/survival outcomes and their events of interest are defined according to the 2015 DATECAN consensus.(10)

8.4 Interim Analyses

Interim Analyses will be performed when n=90 participants (50% of the target sample size) fulfil a follow-up visit assessment, and their data has been adequately monitored (at least remote monitoring of the eCRF). This analysis will be performed on the safety set (and ITT subset for the Pathological response outcome). During the interim analyses, only the safety outcomes will be assessed, these are: AEs, surgical AEs, Pathological response, and Oncological events/survival. Analysis will be performed according to the methods described in the primary statistical analysis of the SAP, except for the dichotomous outcomes, which will be analysed using an Agresti-Caffo 95% Confidence Interval. This is further discussed in the SAP under section '7. Safety evaluation'.

The results of the interim analyses will be discussed by the Trial Steering Committee (TSC), who will then advise on the need of adjustments or trial termination, if applicable. Interim analyses will be stopped when the treatment of the last participant is concluded, since at this point these analyses will no longer be able to influence any study related treatments. Further details on interim analyses will be provided in the SAP.

8.5 Handling of Missing Data

Efforts will be made to minimise and manage missing data to show a robust result. Since a LMM is used in the primary (and some of the secondary) outcome(s), this means that missing data will be implicitly handled as 'Missing at random' (MAR), and that implicit imputation is used. Additionally a 'Missing Not At Random' (MNAR) sensitivity analysis will be performed.

Further details on missing data handling will be provided in the SAP.

9. Study Management

9.1 Regulatory and Ethical Considerations

9.1.1 Regulations and Guidelines

The investigator is responsible for ensuring that the study is performed in compliance with this protocol, the principles of the Declaration of Helsinki (2024), the current IHC guidelines on Good Clinical Practice (ICH-GCP E6 R3) and all of the applicable regulatory requirements(1,69).(1,2)

9.1.2 Independent Ethics Committees (IEC)

The protocol, protocol amendments, ICF, participant information materials and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated, or before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients. A central IRB/IEC is appointed upon the initial request for approval, when setting up study sites, approval from the central, and applicable local IRB/IECs will be sought.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study centre and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or the Sponsor representative. The study will not start at any study centre at which the Investigator has not signed the protocol.

9.1.3 Insurance

The Sponsor will ensure sufficient insurance is available to enable them to indemnify and hold the Investigators and relevant staff as well as any hospital, Institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the investigational therapy but only to the extent that the claim is not caused by the fault or negligence of the participants or investigators. An insurance certificate will be supplied to the involved parties, including the Investigator(s).

The Sponsor has taken a no fault insurance for this study, in accordance with the relevant legislation (article 29, Belgian Law of May 7, 2004):

- Sponsor: GasthuisZusters Antwerpen vzw - Oosterveldlaan 22 – B-2610 Wilrijk
- Insurance details*:* MS Amlin Insurance SE - Koning Albert II-laan 37 - B-1030 Brussel

9.2 Informed Consent

For each study participant, informed consent will be obtained in writing before any protocol-related activities commence. As part of this procedure, the investigator must explain orally and in writing, by means of the ICF, the nature, duration, purpose of the study, number of visits, assessments being performed, procedures to undergo, and the action of the treatment in such a manner that the participant

is aware of the potential risks, inconveniences, or adverse effects that may occur. Participants should be informed that they may withdraw from the study at any time without any resulting disadvantage or prejudice to their standard treatment care. They will receive all information that is required by national regulations and current ICH GCP guidelines. The ICF contains additional provisions concerning the use of participant e-mail communications, data sharing for research purposes, and sharing unexpected health-related findings.

The participant and the investigator will sign the ICF. A copy will be provided to the participant. The originally signed ICF will remain at the study centre. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date and hour at which the written consent was obtained.

All participants will be insured against injury caused by their participation in the study according to the legal requirements. They will be informed about the insurance and the resulting obligations on their part.

A model ICF form is available upon motivated request.

9.3 Participant Identification, Enrolment and Screening Logs

The investigator agrees to complete a 'subject identification and enrolment log' to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrolment log will be treated as confidential and will be filed by the investigator in the ISF. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by their study-id.

9.4 Quality Control and Assurance

The sponsor will implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of the study with a focus on study activities essential to ensuring protection of participants and the reliability of study results. The quality management system will use a risk-based approach.

9.4.1 Data Monitoring

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised study centre personnel is accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

The Medical Monitor will act as the main point of contact for PIs and sites to assess participant eligibility and ongoing protocol/safety management issues.

The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (e.g., hospital medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and study-site personnel and are

accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

9.4.2 Audits

The study may be audited by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required participant records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring/auditing of all relevant study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically relevant.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

9.4.3 Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly documented and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant IECs for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter. When a protocol amendment is approved by both the central and local IECs, the local PIs will be contacted in order to adequately inform them of any changes. The local PI oversees dissemination of this information to their delegates/study personnel.

9.4.4 Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis before database lock. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the study, non-compliance, participant management, or participant assessment should be described. Protocol deviations will be listed on a protocol deviation log, and significant protocol deviations will be reported to the IEC.

9.4.5 Records

9.4.5.1 Data Capture and Management

Study data will be recorded in the provided eCRF (electronic case report forms) with regular back up and controls for further analyses. Study investigators and authorised study staff will be granted access to the eCRF, and will be identifiable by login.

9.4.5.2 Source Documentation

Source documentation will include the demographic data, visit dates, signed ICF, and study number relating to the eCRF, and will be kept in a secured location of the local study site, as defined during the site initiation visit of that site.

9.4.5.3 (Electronic) Case Report Forms

The Investigator should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the centre's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

All clinical data will be captured via electronic data capture. The Investigator's study centre staff will enter and edit the data via a secure network. Electronic CRFs will be used for all participants. The Investigator's data will be accessible from the Investigator's site throughout the study. The eCRF must be kept current to reflect participant status at each phase of the study. The eCRF will not capture directly identifying data. The Investigator must make a separate confidential record of directly identifying data (name and initials) on the participant identification and enrolment log. All changes to data are done by the investigator or designated site personnel through the electronic data capture system.

It is the responsibility of the principal investigator of the study centre to ensure that all participant discontinuations or changes in treatment entered on the participant's eCRF are also registered in the participant's medical records. The (e)CRFs for any participant leaving the study should be completed at the time of the final visit or shortly thereafter.

9.4.5.4 Confidentiality and Data Protection

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 30 July 2018 and 22 Aug. 2002].

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organisational measures to protect the personal data against unauthorised disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to their original medical records (source data/documents) for study-related monitoring, audit, ethics committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

9.4.5.5 Records Retention

In compliance with the ICH-GCP guidelines, the Investigator/Institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH-GCP E6 R3, and all study documents as specified by the applicable regulatory requirement(s). All essential documents will be retained according to ICH GCP for a minimum of 25 years after study termination and in compliance with all applicable legal and regulatory requirements.

The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/Institution must permit access to such reports.

9.5 Data management plan

All collected data are discussed in this protocol, including any transformations/coding, the use of derivative measures (e.g. mean, median, etc.) and ranges where applicable. Access to data is on an as-needed basis, the study personnel are listed on the delegation of responsibilities log and access to data is managed according to their responsibilities. As a general rule, the central trial team (central PI, SIs and project managers) will have access to all study related data except for the subject identification logs; local trial teams will have access to participant data of their own study site, as well as their subject identification log. Monitors and auditors will be permitted access to study data as-needed to fulfil their responsibilities. Access to the eCRF is managed by the central trial teams, logging who has which access, as well as the start and end dates of this access.
A more detailed data management plan, discussing data handling, security and storage, is available upon request.

9.6 Study Termination or Study Site Closure

The Sponsor, Investigator and the IEC reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the CRFs. The Investigator should notify the relevant IEC in writing of the study's completion or early discontinuation.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

10. Clinical Study Report

A CSR will be prepared in accordance with ICH Guidance E3.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

The full CSR, or where required the CSR synopsis, will be submitted to the IEC within 12 months from the end date of the study.

11. Publication Policy

The results from the participating institutions will be analysed together and published as soon as possible. Individual groups/clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Sponsor has published its report. The Sponsor will form the basis of the Writing Committee and will advise on the nature of all publications.

We will aim to publish this protocol both on a trial registry (e.g. ClinicalTrials.gov) before the start of the trial, including amendments after IEC approval, as well as in a peer-reviewed scientific journal before the first interim analysis is performed in order to avoid bias.

All local investigators will be co-authors when at least 5 patients are accrued. The 4 centres with the largest number of patients accrued will be allowed 2 co-authors. The first and/or senior author will be chosen by the Sponsor institution.

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Appendices

Appendix 1: Eastern Cooperative Oncology Group Performance Status Assessment

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 4: Assessment of Cosmetic Outcome

The cosmetics results of the study treatment will be evaluated centrally, by independent ratings by at least two observers (at least, one plastic surgeon and one radiation oncologist).

Physician-reported cosmetic outcome

Regarding physician-reported cosmetic outcomes, average scores from a blinded panel of independent observers (consisting of at least 2, ideally 5 physicians with a background in either plastic surgery, mammary surgery, or mammary radiation therapy), using the 'The aesthetic Items Scale' will be calculated. Inter- and intra-observer agreement of the ratings between the observers will be expressed as intraclass correlation coefficients (ICCs) with corresponding 95% confidence intervals. An ICC of >0.7 will be considered to indicate a good inter-rater reliability.(68)

Twenty randomly selected photographs (not included in the actual study) will be shown to the panel before scoring begins in order to avoid a learning-curve effect.

In the aesthetic items scale, the breasts are evaluated with respect to volume, shape, symmetry, scars, and nipple areola complex. For each of these items a 5-point Likert scale is used for scoring. This scale ranges from "very dissatisfied," "dissatisfied," "neutral," "satisfied," to "very satisfied." The Total Aesthetic Score (TAS), is derived by summing the score of the 5 items.(69) The TAS will be used for outcome operationalisation.

Item N°	Score:	1	2	3	4	5
1	Volume	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied
2	Shape	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied
3	Scars	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied
4	Nipple (areola complex)	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied
5	Symmetry	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied

Appendix 5: CTCAE V5

The Cancer Therapy Evaluation Program NCI-CTCAE version 5.0 (November 27, 2017) can be viewed online at the following NCI website:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

CAVEAT: Not all postoperative complications are listed in the CTCAE v5.0 framework, for example: capsular contraction, implant malpositioning, reconstructive failure, etc. are not listed but need to be recorded. These can be registered under "Injury, poisoning and procedural complications - Other, specify" CTCAE term

Appendix 6: Amendment history

All previous versions of amendments will be collected in this appendix, the overview of changes relating to the current version of the protocol will be displayed at the beginning of this document. All previous amendment overviews will be kept in this appendix.

History of the protocol and its amendments	
Protocol version	**Date of IEC application**
Protocol v1.0, original protocol	22-APR-2024
Protocol v2.0, amendment 1	25-OCT-2024
Protocol v3.0, amendment 2	17-JUN-2024
Protocol v4.0, amendment	24-DEC-2025

Protocol v2.0, amendment 1 24-NOV-2024

Purpose of this amendment:
1) Clarify that the intervention group will only include patients undergoing immediate breast reconstruction, not delayed reconstruction. For this purpose, patients undergoing two-stage implant based breast reconstruction, where the tissue expander (phase 1) is placed during oncological surgery, followed by a later definitive implant/prosthesis placement surgery (phase 2), is considered as immediate reconstruction.
2) A study visit is added for the patients in the control arm, undergoing delayed reconstruction. This visit will take place at 3 months after their last Postop-RT. It was added because we feel that this is important to gauge QoL changes at this point, as well as provide adequate follow-up, whereas these patients would otherwise be seen at +/- 1-1.5y after randomisation, compared to +/- 0.5y for most other patients.
3) Some minor changes to wording and methodology, made to improve the clarity of the protocol and study quality. All changes were tracked with the 'track changes' function in Word, as well as summarized in the following table.

Summarised list of key changes:

Section Number and Name	**Description of change and Brief Rationale**
Cover page	**Description of change:** - GZA was changed to ZAS, reflection the changes due to GZA-ZNA hospital network fusion. - Logo's: change for the PRADAIIBE study, GZA to ZAS and KOTK logo was added. **Brief rationale:** Updating to changed reality.
Statement of compliance	**Description of change:** Declaration of Helsinki version update **Brief rationale:** Most recent version

Confidentiality Statement	**Description of change:** GZA was changed to ZAS, reflection the changes due to GZA-ZNA hospital network fusion. **Brief rationale:** Updating to changed reality.
Sponsor's Approval	**Description of change:** - Changed title - Changed protocol version and date - Changing GZA to ZAS **Brief rationale:** The new title better represents the study type and population. Updated version to reflect this amendment. Updating to changed reality (ZAS)
Investigator Agreement	**Description of change:** - Changed title - Changed protocol version and date **Brief rationale:** The new title better represents the study type and population. Updated version to reflect this amendment.
Table of Contents	**Description of change:** Updated **Brief rationale:** To reflect changes due to amendments
List of In-text Tables and Figures	**Description of change:** - Addition of table representing the aesthetic items scale - Addition of figure, exemplifying the digital photographs to be taken **Brief rationale:** - New assessment scale - Updated version
List of Attachments	**Description of change:** - Specification of BREAST-Q versions - Added Appendix 6 (amendment history) **Brief rationale:** Clarity and follow-up.
List of Abbreviations	**Description of change:** Added BCS, BCT and Postop-RT **Brief rationale:** Clarity

Amendments	**Description of change:** Addition of 'Amendments' section **Brief rationale:** Provide an overview of changes in current amendment
Administrative Structure	**Description of change:** - GZA was changed to ZAS, reflection the changes due to GZA-ZNA hospital network fusion. **Brief rationale:** Update to reflect changed reality.
Synopsis - Title	**Description of change:** - Changed title **Brief rationale:** The new title better represents the study type and population.
Synopsis - Outcomes	**Description of change:** - Improved specifications - Addition of the BREAST-Q for patients undergoing Breast Conservative surgery. - Add the option of 'No preoperative therapy' to the pCR outcome evaluation. **Brief rationale:** - Clarity - To better represent this specific subgroup and operationalize changes in their breast satisfaction scores, making them comparable to other subgroups. - To reflect the group not receiving preoperative therapy
Synopsis – Study design	**Description of change:** - Improved specifications - Remove 'immediate reconstruction' from the experimental arm description **Brief rationale:** - Clarity - Only immediate reconstructions will be performed in the experimental arm.
Synopsis – Eligibility criteria; Length of participation	**Description of change:** - Improved specifications - Addition to the clause regarding adjuvant chemotherapy based on pCR, that the decision of a centre to include/exclude these patients should be made before randomisation. **Brief rationale:** - Clarity

	- The decision of this clause should be made before randomisation to avoid bias and ITT analysis conflicts.
Synopsis – Intervention	**Description of change:** - Improved specifications - Remove 'immediate reconstruction' from the experimental arm description **Brief rationale:** - Clarity - Only immediate reconstructions will be performed in the experimental arm.
Synopsis – Statistical Methods	**Description of change:** - Improved specifications (2-sided alpha for sample size calculation; ITT and PPA analysis) **Brief rationale:** - Clarity
Schedule of events	**Description of change:** - Improved specifications - Addition of Postop-RT + 3M study visit for the delayed reconstruction subgroup - Removal of medication history registration during follow-up visits (only at screening) - Addition of systemic treatment registration - Addition of the BREAST-Q 'breast conserving therapy' module **Brief rationale:** - Clarity - Improved follow-up - Removal of unnecessary data registration (lean) - Systemic treatment is important for subgroup and regression analysis - Adequate assessment of the BCS subgroup
1.1.2 Rationale for Use of Preoperative Radiotherapy	**Description of change:** -Addition of study conclusion **Brief rationale:** - Was accidentally missing
2. Objectives and Endpoints	Cfr. Synopsis – Outcomes. The text and changes in both sections are identical.
3.1 General Scheme of Study Design	**Description of change:** - Improved specifications - Remove 'immediate reconstruction' from the experimental arm description - Addition of a longer and more detailed explanation detailing the scheme of the study - Update of figure 1

	Brief rationale: - Clarity - Only immediate reconstructions will be performed in the experimental arm. - A more detailed description was added to avoid misunderstandings and improve the reader's understanding of how this trial is set up. For example detailing the rationale and pitfalls behind including the BCS subcategory, as well as the additional visit in the delayed reconstruction subgroup. - Update of figure 1, to reflect the changes made in this amendment
4.1 Definitions	**Description of change:** - Improved specifications - Changed email address **Brief rationale:** - Clarity - Changed email address due to organisational changes
4.3 Subject Exclusion Criteria	**Description of change:** - Improved specifications - Addition to the clause regarding adjuvant chemotherapy based on pCR, that the decision of a centre to include/exclude these patients should be made before randomisation. **Brief rationale:** - Clarity - The decision of this clause should be made before randomisation to avoid bias and ITT analysis conflicts.
4.4 Study Restrictions	**Description of change:** - Improved specifications - Lifestyle study restriction 'smoking' and its definition **Brief rationale:** - Clarity - Was missing
4.5 Screen Failures	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
5.1 Study Procedures	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
5.1.1 Screening Period	**Description of change:** - Improved specifications

	- More detailed description of ICF procedure - Changed email address **Brief rationale:** - Clarity - Clarity and explicit regulation adherence - Changed email address due to organisational changes
5.1.2 Treatment period	**Description of change:** - Improved specifications - Specification of intermediary follow-up in the delayed reconstruction subgroup - Addition of systemic treatment and p/ypTNM registration **Brief rationale:** - Clarity - Rationale and clarity, as well as detailing the assessments during this extra study visit. - Important medical information for subgroup/regression analysis
5.1.3 Follow-up Period	**Description of change:** - Improved specifications - at 3M FU: addition of EQ5D5L assessment; Checking of treatment characteristics registration - Addition of BCT module for BCS patients - Digital photographs from 3 to 4 photographs **Brief rationale:** - Clarity - Improved follow-up of QoL and assuring correct and final treatment registration - To represent changes as discussed earlier - To reflect changes as discussed in later chapter
5.2 Discontinuation or Withdrawal	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
5.4.3 Clinical Assessment	**Description of change:** - Addition of concurrent medication use description **Brief rationale:** - Was missing, registered at screening
5.4.4 BREAST-Q questionnaire	**Description of change:** - Elaboration on the use of the BREAST-Q questionnaires and in which setting they will be used. **Brief rationale:** - Clarity, addition of the BCT module

5.4.5 European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L) questionnaire	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
5.4.6 Digital Photographs of the Breasts	**Description of change:** - Improved specifications - Changed from 3 to 4 photographs, including detailed description of how to take them **Brief rationale:** - Clarity - Improved assessment and reproducibility
5.4.7 Assessment of Surgical Complications	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
5.4.8 Assessment of Pathological Tumour Response and pathology TNM	**Description of change:** - Addition of 'No preoperative therapy' option for pCR assessment - Addition of p/ypTNM reporting **Brief rationale:** - Not all patients will receive preoperative therapy, in these patients pCR assessment is not applicable - p/ypTNM assessment is SoC and important oncological information
5.4.9 Collection of Data on Tumour Recurrence Rates	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
6.1 Radiation Therapy	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
6.2 Oncological breast Surgery	**Description of change:** - Improved specifications - Description and positioning of BCS in this trial **Brief rationale:** - Clarity - Making clear why BCS is included and how it will be handled
6.3 Breast Reconstruction surgery	**Description of change:** - Improved specifications

	- Removing the delayed reconstruction from the experimental group **Brief rationale:** - Clarity - Only immediate reconstruction in the experimental group
6.4.2 Stratification	**Description of change:** - Decision to only stratify for treatment centre at randomisation **Brief rationale:** - 1 stratification parameter implies less danger for treatment group allocation imbalances
6.4.3 Randomisation	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
6.5 Treatment Compliance and Adherence	**Description of change:** - Improved specifications - Addition of 6.5.3 Systemic treatment characteristics **Brief rationale:** - Clarity - Provide succinct description of how these character
7.8 Method of Detecting Adverse and Serious Adverse Events	**Description of change:** - Improved specifications **Brief rationale:** - Clarity
7.11 Regulatory Reporting Requirements for Serious Adverse Events	**Description of change:** - Email address of GZA was changed to ZAS, reflection the changes due to GZA-ZNA hospital network fusion. **Brief rationale:** Update to reflect changed reality.
8.1 Justification of Sample Size	**Description of change:** - Improved specifications - Removal of statement on exploratory subgroup analysis **Brief rationale:** - Clarity - To be discussed in another section, not sample size calculation.
8.2 Analysis Populations	**Description of change:** - Addition of per-protocol-analysis

	Brief rationale: - This will be used to assess outcomes without subject who've undergone BCS, as these didn't undergo breast reconstruction, but needed to be included in ITT analysis.
8.3.1 Primary Endpoint	**Description of change:** - Improved specifications - Breast reconstruction as subgroup analysis was removed, baseline characteristics was added - Linear regression analysis was moved to represent the first line of statistical analysis. **Brief rationale:** - Clarity - As advised by statistician - As advised by statistician
8.3.2 Secondary Endpoints	**Description of change:** - Improved specifications - BREAST-Q score as a secondary outcome was added **Brief rationale:** - Clarity - Was not yet included here, only as primary outcome.
9.4.5.2 Source Documentation	**Description of change:** - Re-definition of possible source documentation storage location **Brief rationale:** - The initial definition was too narrow and may not reflect the situation at all study sites.
References	**Description of change:** - 1 references was added, Nr. 40 **Brief rationale:** - Used in Appendix 4
Appendix 2 BREAST-Q questionnaire	**Description of change:** - Improved specifications - Addition of the 'Satisfaction with Breasts' scale, from the 'Breast Conserving Therapy' module. (Not yet included) - English and French versions were added where available, for each BREASTQ questionnaire **Brief rationale:** - Clarity - To reflect the subjects undergoing BCS. Not yet included due to the fact that this questionnaire is not readily available in Dutch. The Dutch version does exist and is requested through the BREAST-Q organisation, yet is not yet available to us.

	At this moment the English and French version is included. The Dutch version will be added and supplied to the EC as soon as possible. - To be able to provide the questionnaire in the language of choosing
Appendix 4 Assessment of Cosmetic Outcome	**Description of change:** - Elaboration on the process of digital photograph evaluation - The aesthetic items scale was added as a tool to assess the cosmetic outcome, as an expert panel, based on digital photographs. **Brief rationale:** - Clarity - Added as a tool to assess the cosmetic outcome, as an expert panel, based on digital photographs.
Appendix 6 Amendment history	**Description of change:** - This appendix was added **Brief rationale:** - In order to track the history of changes per amendment.
Appendix 7 Study overview (detailed)	**Description of change:** - This appendix was added **Brief rationale:** - To add figures for more detailed information on the clinical pathways of subjects in this study.

<u>Protocol v3.0, amendment 2 17-JUN-2025</u>

Purpose of this amendment:

1. Exclusion criterium 'MRI contra indications' was removed. Contrary to what was initially intended, there will be no use of MRI imaging.
2. During the IMFU visit photographs will also be taken.
3. Improved, more detailed description of the data collected, and statistical methods.
4. Overhaul of texts throughout the protocol to be more precise and less redundant.
5. Implementation of the SPIRIT statement 2013

Summarised list of key changes:

Section Number and Name	**Description of change and Brief Rationale**
Cover page + Sponsor's Approval + Investigator Agreement + Administrative Structure	**Description of change:** - The abbreviated title was changed from PRADA II to PRADA IIBE - The ClinicalTrials.Gov ID was added

	- Protocol version and date were updated (to V3.0) - Update cancertrials email. **Brief rationale:** - Updating to changed reality.
Statement of compliance	**Description of change:** - Changed the WMA Declaration of Helsinki from 2013 to 2024 **Brief rationale:** - Since the previous amendment, this has become the most recent version.
New headings: 'Roles and responsibilities' & 'Funding'	**Description of change:** - These headings were added, reporting all actors and their roles within this trial **Brief rationale:** - In compliance with the SPIRIT statement 2013 items 4 and 5, Increasing transaprancy
Table of contents	**Description of change:** - Updated **Brief rationale:** - cfr. Other changes
Removed heading: 'Administrative structure'	**Description of change:** - Merging of contents in new headings 'Roles and responsibilities' & 'Funding' **Brief rationale:** - This improves SPIRIT statement compliance and clarity
Amendments	**Description of change:** - The 'History of the protocol and its amendments' table was updated. - The list of amendments in V2 was moved to - Appendix 6 'Amendment history', and a new list for V3 was formed. **Brief rationale:** - Updates in accordance with the current amendment history
List of Abbreviations	**Description of change:** - 'MRI' was removed - 'IBR'; 'DBR'; 'TE'; 'SoC'; Were added **Brief rationale:** - No longer included in the text - Adopted in the text

Synopsis – General	**Description of change:** - Changed from PRADA II BE to PRADAIIBE - Minor layout changes - Addition of "Disease under study" **Brief rationale:** - Improved readability - In compliance with the WHO trial registration data set and SPIRIT statement 2013.
Synopsis – Objectives/Endpoints	**Description of change:** - Each outcome variable was rewritten to improve clarity. No major changes were made to which data/variables will be recorded/used. The new text is in compliance with the SPIRIT 2013 statement. - Included the BREAST-Q 'BCT' module by name. **Brief rationale:** - Improved understanding - The 'BCT' module is used for the rare (is not expected) case that BCS is performed. - Improved clarity and uniform reporting/naming
Synopsis – Study Design	**Description of change:** - Skin-sparing mastectomy (SSM) → Skin/nipple sparing mastectomy (SSM/NSM) - 'Number of patients' → 'Sample size' **Brief rationale:** - More correct naming
Synopsis - Eligibility criteria	**Description of change:** - Inclusion criterium 1: added '/NSM'; changed 'adjuvant radiation therapy' to 'postoperative radiotherapy'. - Exclusion criterium 1 changed to: "A previous history of breast cancer or irradiation of the chest wall for any other indication." - Exclusion criterium 3 "Subject is not pregnant or breastfeeding" is moved from inclusion criteria to exclusion criteria - Exclusion criterium concerning MRI contraindications was removed - Exclusion criterium 7 → Added 'Metastatic disease', changed wording of 'SSM not possible' to ''SSM/NSM not indicated' **Brief rationale:** - Exclusion criteria better reflects the eligibility implications - MRI contraindications is no longer relevant - Metastatic disease as an exclusion criterium was already implied by 'SSM not possible/indicated', this is now explicitly stated

Synopsis - Length of participation	**Description of change:** - Added mentioning of 3M FU **Brief rationale:** - Improved accuracy
Synopsis - Intervention	**Description of change:** - Preoperative radiotherapy must be planned to commence as quickly as reasonably possible after randomization, at the discretion of the Investigator, or no longer than 6 weeks after the last dose of neoadjuvant chemotherapy (if applicable) or randomization. → Added "or randomization" **Brief rationale:** - In the initial text there was no hard deadline for planning preoperative radiotherapy. This is now defined as =<6 weeks.
Schedule of events	**Description of change:** - Table 1B SoE for patients in the experimental treatment arm. Timing of pre-op RT scheduling was changed from "At the discretion of the physician of ≤6w after last dose of NACT (if applicable)", to within 6 weeks of Rz or NACT - Indicated that treatment characteristics will also be collected/checked at the 3 months after final treatment follow-up visit. - footnote 'g' → Addition that the participant wil be asked to return for a termination visit. - During IMFU visit photos will also be taken. - Complete overhaul of both tables **Brief rationale:** - Changed to reflect the change described under 'Synopsis – Intervention' - To assure complete and correct registration of all treatment characteristics. - Participants cannot be forced to return for a termination visit. - Photos during the IMFU visit will help assess the effect on cosmesis between mastectomy and reconstruction. Which might be a confounder for the primary outcome. - The overhaul of SoE tables are intended to make the tables more readable and shorter. No further content changes were made, the changed content is listed above.
1. Introduction	**Description of change:** - The text was rewritten and the scientific literature references were updated.

	Brief rationale: - Improved readability, improved scientific accuracy
2. Objectives and Endpoints	Table 2 was copy-pasted from the same section in the 'Synopsis' section. Cfr. This section for adaptations.
3. Overall Study Design – 3.1 General Scheme of Study Design	**Description of change:** - PRADA II trial → PRADAIIBE study - Skin sparing; SSM→ Skin/Nipple sparing; SSM/NSM - Adjuvant → Preoperative - Clarification that systemic therapies are not study related treatments but ill be recorded. - Explicit mentioning of the AIS evaluation during IMFU visit. - Correction of IMFU taking place 3 months after oncological surgery → To 3M after last RT treatment - Changed Figure 1, same content/info, less text - Other minor changes in word choice and grammatic **Brief rationale:** - Improved clarity
3. Overall Study Design – 3.2 Study Duration, Enrolment and Number of Sites	**Description of change:** - Improved description of the duration of study participation, explicitly stating that treatment duration is variable and that the 10 years of follow-up start from the moment of treatment conclusion. - Projection of 10 study sites. - Other minor changes in word choice and grammatic **Brief rationale:** - Improved clarity
4.1 Definitions	**Description of change:** - **Brief rationale:** -
4. Population – 4.2 + 4.3 (In- and exclusion criteria)	This section was copy-pasted from the same section in the 'Synopsis' section. Cfr. This section for adaptations.
4.4 Study restrictions	**Description of change:** - "…, as per standard of care. The study is not responsible for contraceptive measures or pregnancy testing" Was added on the end of the sentence describing contraceptive requirements.

	- The main text regarding concomitant medication registration is moved tot 5.4.3.3 **Brief rationale:** - Improved clarity, the study is not responsible for the follow-up of potential/accidental pregnancies during the study as this is part of the SoC. The study merely emphasizes this aspect of the SoC therapy. - This section is better suited for registering this information.
5. Study conduct – 5.1	**Description of change:** - Changed from PRADA II BE to PRADAIIBE - Added "Assessment of baseline breast cancer disease characteristics" to the list of screening evaluations - Changed email address: "cancertrials@zas.be" - Minor layout/word choice changes - Added the taking of photographs to the IMFU visit, as an assessment. - Addition that an unscheduled visit can also be initiated by the participant. - Addition of section "5.1.1 Recruitment" **Brief rationale:** - Improved clarity - This was not explicitly mentioned before but is an important factor in post hoc analyses. - New email address (old will be kept operational) - These photographs at IMFU visit may offer important insight in the experience of patients at this stage. - Included a section on recruitment, in accordance with the SPIRIT statement.
5. Study conduct – 5.2	**Description of change:** - Added: "This is documented by registering an 'Unscheduled visit' in the eCRF." **Brief rationale:** - Improved clarity on how withdrawal of consent needs to be handled.
5. Study conduct – 5.4	**Description of change:** - Added: "Patients will be questioned regarding concomitant medication use only at the screening visit. The patient will be asked to report all the medication they currently use, especially those medications which are taken on a regular basis (chronic use). The substance, route of administration, dose and start/stop date (if known) will be recorded. All prior and concomitant systemic therapy (including neoadjuvant systemic chemotherapy,

	adjuvant systemic therapy, endocrine therapy, immune therapy, or any other forms of systemic therapy) for breast cancer must be recorded in the eCRF, as discussed in Section 6.5.3." - Changed the wording of what the BREAST-Q is measuring/asking - Changed wording of how the results from the BREAST-Q are handled from raw score to the BREAST-Q score. - Added that photographs will also be taken during the IMFU visit. - Clarification of how surgical complications will be collected/registered. - Added section 5.4.7 (and change of subsequent sections and their references) – Disease baseline characteristics - Redefining of surgical (S)AEs in section 5.4.8. - 5.4.10 – addition of data concerning overall survival - 5.4.11 Treatment pathway times was added - Minor layout/word choice changes **Brief rationale:** - The indication of the medication will not be recorded as this information will be too unstructured to be used for analysis, while offering minimal added value. The recording of 'substance' is added for improved clarity. - This summation is more precise and correct than the previous summation. - This description of BREAST-Q results handling is more correct. - Photographs will also be taken during the IMFU visit. - All (S)AEs will be collected, surgical complications will be extracted from this registry. - The data regarding disease characteristics was not clearly defined as a separate topic, this is now rectified. - This description better reflects what constitutes surgical (S)AEs. - Overall survival is important in assessing oncological safety. - A description of how the treatment pathway times will be recorded and operationalized was added as this was not yet explicitly described. - Improved clarity
6. Study Intervention – 6.1	**Description of change:** - NACT was changed to preoperative radiotherapy - Preop-RT planning within 6w of randomization **Brief rationale:** - To improve uniformity - No max time interval was yet defined for Rz to

	Preop-RT - Improved clarity
6. Study Intervention – 6.2	**Description of change:** - Minor changes in wording and grammatic. **Brief rationale:** - Improved clarity
6. Study Intervention – 6.3	**Description of change:** - Minor changes in wording and grammatic. **Brief rationale:** - Improved clarity
6. Study Intervention – 6.4	**Description of change:** - Change 5 to 6-digit ID - Expand the description of how randomization is performed and handled. - Addition of "6.4.4 blinding" - Minor changes in wording and grammatic. **Brief rationale:** - This was changed in Castor software - Improved clarity
6. Study Intervention – 6.5	**Description of change:** - Re-phrasing of data collected for all treatment modalities **Brief rationale:** - More detailed overview of the recorded data.
7. Safety monitoring – 7.5	**Description of change:** - An update changed the ID size - The description of the randomization process indicates that there is no way of 1) manipulating Rz outcomes, 2) no way of gaining insight into block sizes. - This subtopic describes the decision of NOT using blinding in this trial. Adding that the expert panel will be blinded. - Minor changes in wording and grammatic. **Brief rationale:** - Improved clarity
7. Safety monitoring – 7.6	**Description of change:** - Minor changes in wording and grammatic. **Brief rationale:** - Improved clarity
7. Safety monitoring – 7.7	**Description of change:** - Minor changes in wording and grammatic.

	Brief rationale: - Improved clarity
7. Safety monitoring – 7.8	**Description of change:** - Minor changes in wording and grammatic. - Added phrase on (S)-AEs reported by physicians **Brief rationale:** - Improved clarity - This was previously not described but is also a possible route of reporting.
7. Safety monitoring – 7.9	**Description of change:** - Minor changes in wording and grammatic. **Brief rationale:** - Improved clarity
7. Safety monitoring – 7.10	**Description of change:** - Changed ”pharmacovigilance” to “sponsor representatives” **Brief rationale:** - This is not a pharmacological study.
7. Safety monitoring – 7.11	**Description of change:** - Removed paragraph on reporting to the EMA - Changed EMA to IER/IRB **Brief rationale:** - This is not a pharmacological study, therefore the EMA is not involved.
8. Statistical concerns – 8.1	**Description of change:** - Minor changes in wording and grammatic. - Further elaboration on how the detection of a minimally important difference was selected. **Brief rationale:** - Improved clarity - More accurate representation of the decisions made in sample size calculation.
8. Statistical concerns – 8.3	**Description of change:** - Addition of the ‘Breast conserving therapy’ module concerning the BREAST-Q questionnaire and improved definition of the primary endpoint - Additional explanation concerning the AIS and the operationalization of the cosmetic outcome secondary endpoint. - Added the secondary endpoints ‘surgical AEs’, ‘pathological response’, ‘Treatment pathway duration time’, and ‘Oncological events/survival’ - For each endpoint the statistical analyses are

	summarized and the SAP is referenced for more detailed information. **Brief rationale:** - Improved clarity and more precise description of the primary endpoint - Improved clarity and more precise description of the cosmetic outcome secondary endpoint - These secondary endpoints were not yet explicitly defined under section 8.3 - The SAP contains a more complete description of the statistical methods, avoiding redundancy in the protocol.
8. Statistical concerns – 8.4	**Description of change:** - Redefining of the interim analyses **Brief rationale:** - These newly defined timepoints offer improved safety monitoring, balanced against feasibility of the efforts involved of an interim analysis.
9. Study management	**Description of change:** - Minor changes in wording and grammatic. - Addition of section “9.5 Data management plan” and renaming of “Study termination or study closure” to 9.6 - 9.4.3 protocol amendments: addition of how the changes will be communicated to study personnel - 9.2 Informed consent: expansion on additional provisions. **Brief rationale:** - Improved clarity - Discussion of the DMP was not yet included, this is in accordance with the SPIRIT statement. - Change communication plan is in accordance with the SPIRIT statement. - ICF additional provisions statements is in accordance with the SPIRIT statement.
Appendix 2	**Description of change:** - Added the BCT Dutch postoperative version. - Added a note on the BCT French postoperative version **Brief rationale:** - This was not yet available to us at the previous protocol amendment, now it is. - This translation doesn’t yet exist, we will translate it and provide it to the EC once available.
Appendix 4	**Description of change:** - Improve description of how the expert panel evaluation will be organized and performed.

	Brief rationale: - Improved clarity
Appendix 6 Amendment history	**Description of change:** - The overview table was updated and the amendment history of V2 was moved here. **Brief rationale:** - Keeping track of the amendment history.

Protocol v4.0, amendment 3 24-DEC-2025

Purpose of this amendment: Please refer to section 'Amendments'

Summarised list of key changes:

Section Number and Name	**Description of change and Brief Rationale**
Cover page + Sponsor's Approval + Investigator Agreement + Administrative Structure	**Description of change:** - Update of version and date - Change date of first registration CTG - Update of the trial steering committee members - Minor changes in wording **Brief rationale:** - Update according to amendment - The previously mentioned date was the date of final approval. The new date is the date of first registration as found on the public CTG page. - Update of TSC members - Improve clarity and correctness
Statement of compliance	**Description of change:** - GCP E6 R3 instead of R2 **Brief rationale:** - New current GCP guidelines
New headings: 'Roles and responsibilities' & 'Funding'	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
"Sponsor's Approval" & "Investigator Agreement"	**Description of change:** - Update of version and date **Brief rationale:** - Update according to amendment
Table of contents	**Description of change:** - Updating of contents according to changes

	Brief rationale: - Update
"List of tables and figures" & "List of attachments" & "List of abbreviations"	**Description of change:** **-** Update according to other changes in this protocol **Brief rationale:** **-** Update
Amendments	**Description of change:** - Addition of this new amendment **Brief rationale:** - Tracking of amendments
Synopsis – Objectives/Endpoints	**Description of change:** - BREAT-Q: Addition of the Mastectomy module questionnaire, improved details on how the outcome will be reported. - EQ-5D-5L: Index score transformation to the 0-1 scale - AEs (general and surgical): Improved description of tabulation and dichotomous/proportion outcomes - pCR: Re-defining this outcome to only include patients that received preoperative systemic therapy, instead of also including patients that only received preop-RT + Improved description of tabulation and dichotomous/proportion outcomes - Improved definition and overhaul of the tertiary outcomes section regarding oncological survival and TTE data, according to the DATECAN 2015 consensus. - Minor changes in wording **Brief rationale:** - Updating of outcome reporting according to what was discussed during the development of the SAP - By re-defining the pathological response outcome we avoid a large level of bias against the experimental arm, as it is improbable that the pathological response based on preop-RT alone is comparable to preop-chemotherapy. We don't expect that RT by itself (monotherapy in preop setting) will have any significant influence on the pathological response category at the study interval of 2-6 weeks. - Improve clarity and correctness
Synopsis – Study Design	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness

Synopsis – Eligibility criteria	**Description of change:** - The first exclusion criterium was specified to only concern ipsilateral previous treatment **Brief rationale:** - Improve clarity and avoid confusion concerning eligibility.
Synopsis – Length of participation	**Description of change:** - Changed the title to "Length of study participation and study visits" - Added the IMFU visit - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
Synopsis - Intervention	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
Synopsis - Statistical methods	**Description of change:** - Addition of the mastectomy module - Addition of the estimands framework instead of PP-analysis - Rectification of SZ number (no impact on actual SZ) - Minor changes in wording **Brief rationale:** - New questionnaire module - Improved statistical methods (estimands framework) - Small error in the reported results from the SZ-calculation, which doesn't change the eventual SZ of n=180 due to the same conclusion after correcting for dropout. - Improve clarity and correctness
Schedule of events	**Description of change:** - Addition of the mastectomy module in the IMFU visit - Minor changes in wording **Brief rationale:** - New questionnaire module - Improve clarity and correctness
1. Introduction	**Description of change:** - Rewriting of the introduction section, focused on presenting the results in a more concise manner and avoiding repetition

	Brief rationale: - This rewriting has led to both a shorter introduction section, as well as the addition of some important/relevant studies.
2. Objectives and Endpoints	**Description of change:** - Copy-paste from the equivalent section in the synopsis **Brief rationale:** - Update according to the changes mentioned in the synopsis section
3. Overall Study Design – 3.1 General Scheme of Study Design	**Description of change:** - **Brief rationale:** -
3. Overall Study Design – 3.2 Study Duration, Enrolment and Number of Sites	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
4.1 Definitions	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
4.4 Study restrictions	**Description of change:** - Clarification of the smoking cessation limitations/eligibility - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
5. Study conduct – 5.1	**Description of change:** - Improved and more detailed description of the recruitment process - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
5. Study conduct – 5.2	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
5. Study conduct – 5.3	**Description of change:** - Minor changes in wording

	Brief rationale: - Improve clarity and correctness
5. Study conduct – 5.4	**Description of change:** - Addition of the BREAST-Q 'Mastectomy' module - Addition of the EQ-5D-5L index score transformation - The pathological response options were changed to fit the Pinder classification, and outcome redefenition for patients with Preop-RT without Preop Systemic therapy was added. - Minor changes in wording **Brief rationale:** - New questionnaire - Improved interpretability of the Index score - Improve clarity and correctness
6. Study Intervention – 6.1	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
6. Study Intervention – 6.2	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
6. Study Intervention – 6.3	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
6. Study Intervention – 6.4	**Description of change:** - This subsection was moved to section 5 **Brief rationale:** - More appropriate location within the document
6. Study Intervention – 6.5	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
7. Safety monitoring – 7.1	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
7. Safety monitoring – 7.4	**Description of change:** - Minor changes in wording

	Brief rationale: - Improve clarity and correctness
7. Safety monitoring – 7.6	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
7. Safety monitoring – 7.9	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
7. Safety monitoring – 7.10	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
7. Safety monitoring – 7.11	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
8. Statistical concerns – 8.1	**Description of change:** - Minor changes in wording - Correction of calculated sample size (cfr. Synopsis, no impact on eventual sample size) - Addition of SZ-PWR graph **Brief rationale:** - Improve clarity and correctness - Rectification - This graph improves the interpretability of the impact of changes in sample size or effect size, on the power
8. Statistical concerns – 8.2	**Description of change:** - Addition of the estimands framework approach instead of PP-analysis **Brief rationale:** - Improved handling of intercurrent events
8. Statistical concerns – 8.3	**Description of change:** - Addition of the BREAST-Q Mastectomy module - The pathological response options were changed to fit the Pinder classification - Update of the analyses according to what was discussed in the development of the SAP - Minor changes in wording

	Brief rationale: - New questionnaire - Update according to SAP - Improve clarity and correctness
8. Statistical concerns – 8.4	**Description of change:** - Removal of the 100% mark **Brief rationale:** - This is superfluous, as it would almost coincide with completion of accrual
9. Study management	**Description of change:** - Minor changes in wording **Brief rationale:** - Improve clarity and correctness
Appendix 2	**Description of change:** - Addition of the BREAST-Q Mastectomy module - Addition of subheadings **Brief rationale:** - New questionnaire - Improving navigation
Appendix 3	**Description of change:** - Addition of the NL and FR translations - Addition of subheadings **Brief rationale:** - Improved reporting - Improving navigation
Appendix 4	**Description of change:** - Removal of mentioning the software tool **Brief rationale:** - There are currently no active plans to include a software-based evaluation
Appendix 6 Amendment history	**Description of change:** - Update concerning this amendment **Brief rationale:** - Update
Appendix 7	**Description of change:** - Addition of the mastectomy module in the IMFU visit **Brief rationale:** - New questionnaire module

Appendix 7: Study overview (detailed)

Detailed SOE

			Inclusion				
			Baseline data	BQ1	EQ5D5L	Photographs	Randomisation
Control	Immediate reconstruction	Tissue expander / Prosthesis	X	X	X	X	X
		(Prosthesis)	X	X	X	X	X
		(Autologous)	X	X	X	X	X
		(Autologous+TE / Pro)	X	X	X	X	X
		(Autologous+Pro)	X	X	X	X	X
	Delayed reconstruction	Tissue expander / Prosthesis	X	X	X	X	X
		Prosthesis	X	X	X	X	X
		Autologous	X	X	X	X	X
		Autologous+TE / Pro	X	X	X	X	X
		Autologous+Pro	X	X	X	X	X
Intervention	Immediate reconstruction	Tissue expander / Prosthesis	X	X	X	X	X
		Prosthesis	X	X	X	X	X
		Autologous	X	X	X	X	X
		Autologous+TE / Pro	X	X	X	X	X
		Autologous+Pro	X	X	X	X	X
	(BCS)	No reconstruction	X	X	X	X	X

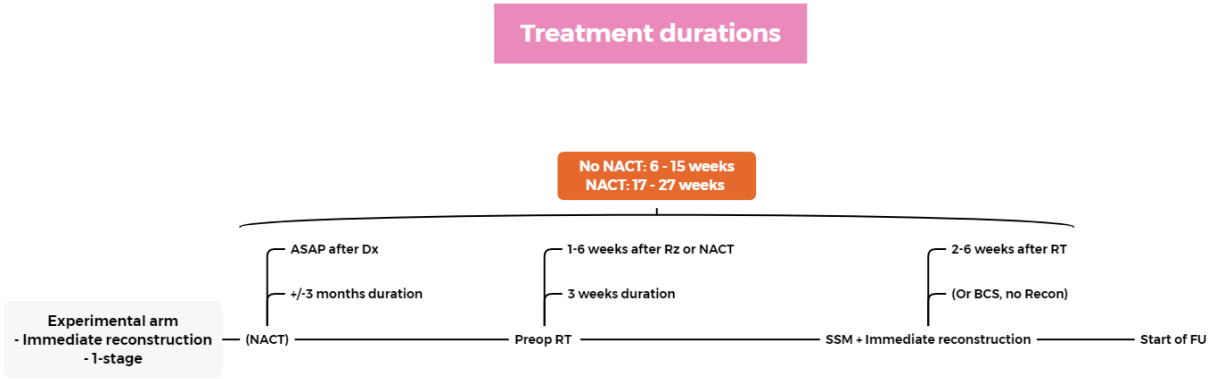
Treatment period (R/)												
Pre-operative treatment		Operative treatment			Post-operative treatment							
Preop-ChT	Pre-operative RT	SSM/NSM	BCS	Immediate reconstruction	Post-operative RT	Postop-ChT	IF Delayed Recon: Follow-up visit at last RT +3M				Delayed reconstruction	Definitive prosthesis
							BQ IMFU	EQ5D5L	Photographs	AE's		
+/-		X		X	X	+/-						X
+/-		X		X	X	+/-						
+/-		X		X	X	+/-						
+/-		X		X	X	+/-						+/-
+/-		X		X	X	+/-						
+/-		X			X	+/-	X	X	X	X	X	X
+/-		X			X	+/-	X	X	X	X	X	
+/-		X			X	+/-	X	X	X	X	X	
+/-		X			X	+/-	X	X	X	X	X	+/-
+/-		X			X	+/-	X	X	X	X	X	
+/-	X	X		X		+/-						X
+/-	X	X		X		+/-						
+/-	X	X		X		+/-						
+/-	X	X		X		+/-						+/-
+/-	X	X		X		+/-						
+/-	X		X			+/-						

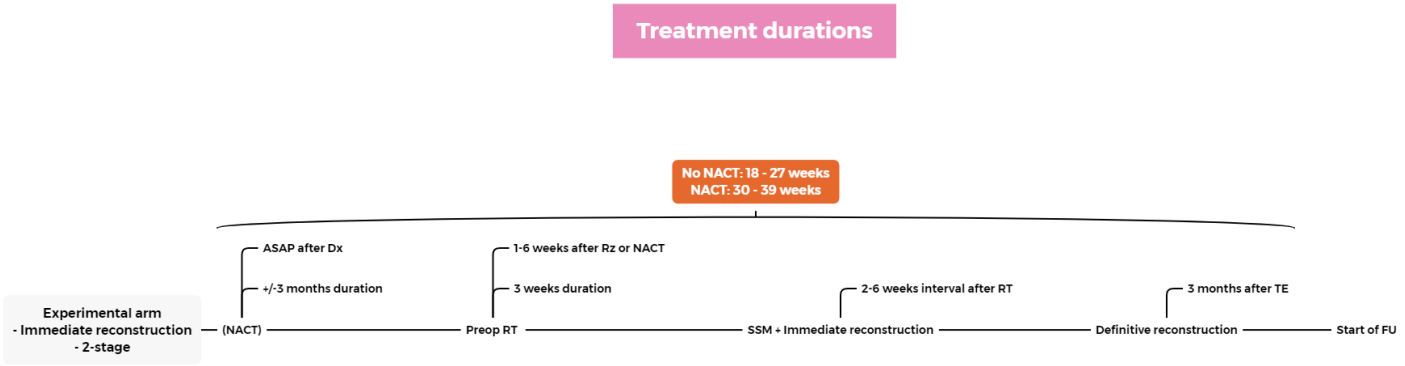
Follow-up period																		
R/+3M					R/+1Y							R/+2Y						
BQ2	BQ3	EQ5D5L	Photographs	AE's	BQ2	BQ3	EQ5D5L	Survival	Photographs	Onco PM	AE's	BQ2	BQ3	EQ5D5L	Survival	Photographs	Onco PM	AE's
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X

R/+5Y							R/+10Y						
BQ2	BQ3	EQ5D5L	Survival	Photographs	Onco PM	AE's	BQ2	BQ3	EQ5D5L	Survival	Photographs	Onco PM	AE's
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
X		X	X	X	X	X	X		X	X	X	X	X
	X	X	X	X	X	X		X	X	X	X	X	X

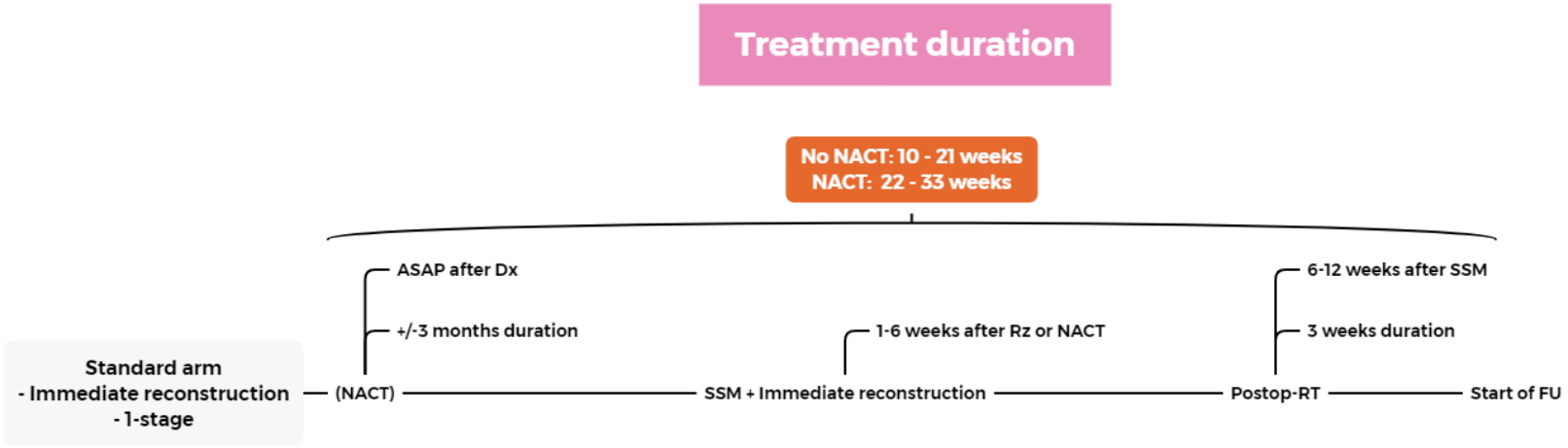
BQ1	Pre-operative questionnaire of the 'Satisfaction with breasts' scale. Which is the same for the 'BCT', 'Mastectomy' and 'Reconstruction' modules of the BREAST-Q v2.
BQ IMFU	Post-operative questionnaire of the 'Satisfaction with breasts' scale from the 'Mastectomy' module of the BREAST-Q v2.
BQ2	Post-operative questionnaire of the 'Satisfaction with breasts' scale, for the 'Reconstruction' module of the BREAST-Q v2.
BQ3	Post-operative questionnaire of the 'Satisfaction with breasts' scale, for the 'BCT' module of the
+/-	This may or may not be included
(...)	Clinical pathways marked with '(...)' are deemed to be less likely, yet are included as a possibility to

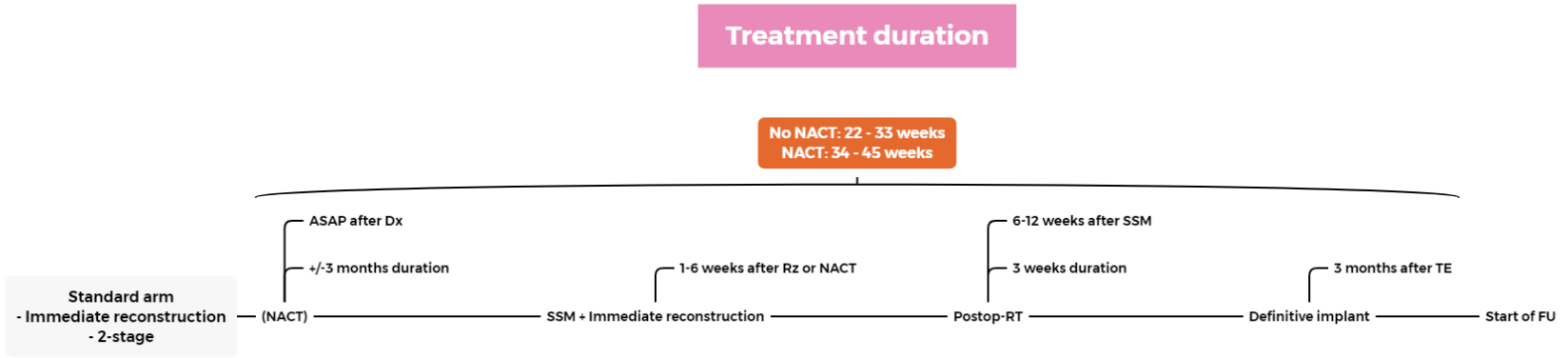
Timelines per treatment arm and subgroups – Experimental arm

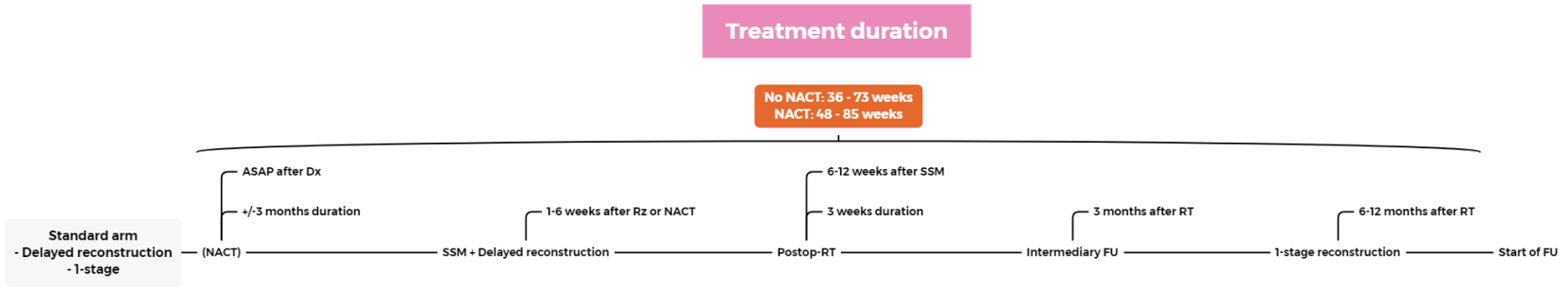


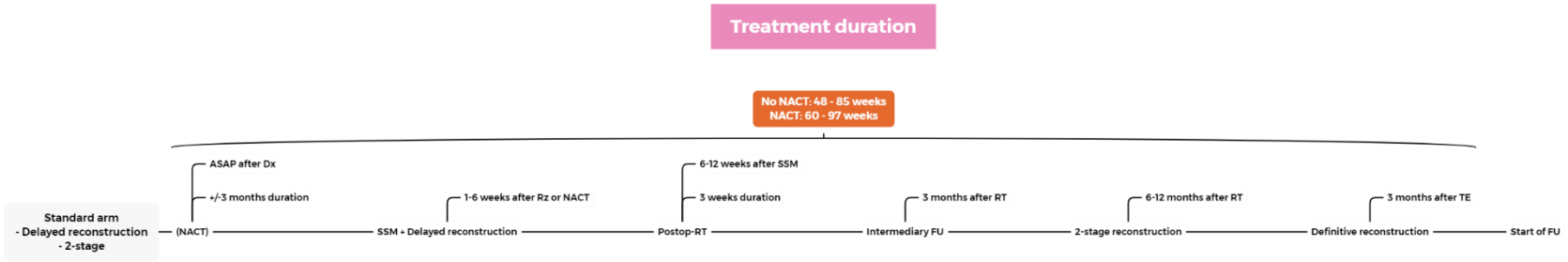


Timelines per treatment arm and subgroups – Treatment arm




Treatment duration
No NACT: 22 - 33 weeks
NACT: 34 - 45 weeks
Standard arm
- Immediate reconstruction
- 2-stage
(NACT)
ASAP after Dx
+/-3 months duration
SSM + Immediate reconstruction
1-6 weeks after Rz or NACT
Postop-RT
6-12 weeks after SSM
3 weeks duration
Definitive implant
3 months after TE
Start of FU


Treatment duration
No NACT: 36 - 73 weeks
NACT: 48 - 85 weeks
Standard arm
- Delayed reconstruction
- 1-stage
(NACT)
ASAP after Dx
+/-3 months duration
SSM + Delayed reconstruction
1-6 weeks after Rz or NACT
Postop-RT
6-12 weeks after SSM
3 weeks duration
Intermediary FU
3 months after RT
1-stage reconstruction
6-12 months after RT
Start of FU


Treatment duration
No NACT: 48 - 85 weeks
NACT: 60 - 97 weeks
Standard arm
- Delayed reconstruction
- 2-stage
(NACT)
ASAP after Dx
+/-3 months duration
SSM + Delayed reconstruction
1-6 weeks after Rz or NACT
Postop-RT
6-12 weeks after SSM
3 weeks duration
Intermediary FU
3 months after RT
2-stage reconstruction
6-12 months after RT
Definitive reconstruction
3 months after TE
Start of FU