Statistical analysis plan (SAP)

Official title: Prophylactic Treatment of Breast Implants With a Solution of Gentamicin, Vancomycin and Cefazolin Antibiotics for Women Undergoing Breast Reconstructive Surgery: a Randomized Controlled Trial (The BREAST-AB Trial)

NCT: NCT04731025

Document date: 30/01/2026

Version: 1.0

This document relates to the ClinicalTrials.gov study record above.

Rigshospitalet

Statistical Analysis Plan

The BREAST-AB trial

Prophylactic treatment of breast implants with a solution of gentamicin, vancomycin and cefazolin antibiotics for women undergoing breast reconstructive surgery: a randomised controlled trial

EudraCT number: 2020-002459-40

EU trial number: 2024-517672-38-(00)

ClinicalTrials.gov: NCT04731025

SAP version: 1.0 Date: January 30th, 2026. Initial SAP (v1.0) finalized before inclusion of last patient and before unblinding.

This SAP has been written based on information contained in the trial protocol version 3.0, dated November 20th, 2025.

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1.0 Background

The BREAST-AB trial is a multi-centre, investigator-initiated, double-blind, 2-arm, parallel, randomised, placebo-controlled trial.[1] The trial aims to evaluate whether intraoperative irrigation of breast implants and the surgical pocket with gentamicin, cefazolin, and vancomycin reduces the incidence of clinically significant infection leading to explantation of the implant, compared to placebo in patients undergoing implant-based breast reconstruction. Patients are randomised to implant and pocket irrigation with 80 mg gentamicin, 1 g cefazolin and 1 g vancomycin in 500 mL saline or placebo which is 500 mL saline in a 1:1 ratio. Patients undergoing unilateral breast reconstruction are randomised to either the triple antibiotic solution or placebo, whereas patients undergoing bilateral breast reconstruction act as their own control, with one breast randomised to the triple antibiotic solution and the contralateral breast to saline. The trial plans to include 1,003 patients, which will provide a power of 90% to detect an absolute risk reduction of 5% with an estimated incidence of the primary outcome in the control group of 10%.

1.1 Implant infection

Each year, approximately 5,000 Danish women are diagnosed with breast cancer, and many undergo implant-based reconstruction following mastectomy.[2,3] One of the most severe short-term complications is postoperative infection, affecting approximately 10% of patients and often require implant removal, and a subsequent reconstruction attempt is delayed or abandoned altogether. [4–8] Chronic bacterial contamination without clinical signs of infection is also suspected to cause capsular contracture, a severe foreign body reaction to the implant, leading to a hard and deformed breast affecting 10–20% of patients. [9,10]

To reduce bacterial contamination during surgery, many plastic surgeons irrigate the breast implant and pocket with antibiotics.[11] Adams et al. recommended an irrigation regimen of gentamicin, cefazolin and vancomycin, which has become widely adopted internationally. [12,13]Despite this common practice, the regimen has never been evaluated in a randomised trial.[14] The most common pathogens identified in breast implant infections include *Staphylococcus epidermidis*, *Cutibacterium acnes, Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, which are typically found on the skin and in breast ducts. [15,16]

The use of local antibiotics offers several advantages, including high tissue concentrations with minimal systemic exposure and potentially a lower risk of systemic side effects.[17] Observational studies and case series have reported mixed results of using antibiotic irrigation to prevent infection and capsular contracture, but these studies are limited by small sample sizes, non-randomised design, poorly defined outcomes and lack of blinding. In short, current evidence is insufficient to determine whether prophylactic antibiotic irrigation reduces implant-related complications. The BREAST-AB trial was therefore designed to provide a definitive, high-quality evidence of whether intraoperative antibiotic irrigation of implants reduces implant complications leading to explantation in women undergoing implant-based reconstruction.

1.2 Method of randomisation

The trial participants undergo stratified randomisation to minimize the risk of an imbalanced distribution between the placebo and intervention groups of key prognostic indicators that could confound the between-group comparison of outcomes. The randomisation strata were generated using the following factors:

- Trial site
- Unilateral or bilateral reconstruction
- Immediate or delayed reconstruction
- Previous radiotherapy and/or planned radiotherapy within the follow-up period (Y/N)

Further details of the randomisation method are described in the protocol.[1]

2.0 Purpose of this Statistical Analysis Plan

This Statistical Analysis Plan (SAP) describes the rationale and detailed methods for the statistical comparisons of the primary, secondary and tertiary outcomes of the BREAST-AB trial, and it has been developed according to the estimands framework[18] and the JAMA guidelines for the content of statistical analysis plans in clinical trials.[19] It will guide the analysis of efficacy and safety endpoints, and missing data. Operational data management procedures (data entry, query handling, cleaning, audit trail, and archiving in the trial master file) are described in the trial protocol and institutional SOPs and are outside the scope of this SAP. Moreover, the SAP outlines the general approach for future exploratory sub-analyses that may be conducted and reported in future publications, although these cannot be pre-specified in details. All statistical analysis will be performed by the independent BREAST-AB trial Data Assessment Committee consisting of Mathias Ørholt, MD, Sebastian Wiberg, MD, MSc, PhD, and Bruno R. da Costa, PhD.

3.0 Estimands framework

This SAP was developed in accordance with the estimand framework described in ICH E9(R1).[18] Estimands define the treatment effects of interest and prespecify how intercurrent events are handled.

3.1 Intercurrent events

The treatment of interest in the BREAST-AB trial is intraoperative irrigation of the breast implant and surgical pocket with a triple-antibiotic solution in sterile saline, compared with placebo (sterile saline). Therefore, possible intercurrent events will be divided into treatment-modifying events and truncating events that include:

3.1.1 Treatment-modifying events

- Non-receipt of trial treatment
    - Non-adherence by the surgeon, intentional or non-intentional
    - Logistic challenges

3.1.2 Truncating events

- Death within 180 days from administration of treatment
- Non-receipt of a breast implant
    - Intraoperative abandoning of implant-based breast reconstruction
    - Post-randomisation cancellation of breast reconstruction
- Removal of expander or implant that does not constitute a primary outcome according to the definition in **section 4.0**

3.2 Strategy for handling intercurrent events

For the primary estimand, treatment-modifying events will be handled using a treatment-policy strategy. This implies that outcomes are attributed to the randomised treatment assignment regardless of treatment adherence. Truncating events are handled through the endpoint definition (while-alive). Participants who die within 180 days without prior explantation will be classified as not having experienced explantation within 180 days. This is expected to be very rare, since breast reconstruction is generally not scheduled when the expected remaining life expectancy is less than 180 days. Likewise, patients with removal of an expander or implant within 180 days that does not constitute a primary outcome according to the definition in **section 4.0** will be classified as not having experienced explantation within 180 days. Participants who never receive an implant are classified as not having experienced explantation. This reflects the treatment strategy used in routine care where cancellation/abandonment is considered part of the routine care. A pre-specified sensitivity analysis described in **section 5.2.2** will test the robustness of results on a per protocol population.

3.3 Primary estimand

The primary estimand is the effect of assignment to triple antibiotic irrigation versus placebo of the breast implant and surgical pocket on the risk of all-cause explantation of the breast implant within 180 days after implant-based breast reconstruction ("day 0" defined as the first surgery where the allocated trial treatment is administered, see **section 4.0**), among all randomised breasts, regardless of treatment adherence or protocol deviations, estimated as a population-averaged effect. See Appendix A for a table summarising the estimands.

3.4 Key secondary estimands

3.4.1 Infection-specific revision surgery

A key secondary estimand is the effect of assignment to triple antibiotic irrigation versus placebo of the breast implant and surgical pocket on the risk of infection-specific revision surgery within 180 days after implant-based breast reconstruction ("day 0" defined as the first surgery where the allocated trial treatment is administered, see **section 4.0**), among all randomised breasts, regardless of treatment adherence or protocol deviations, estimated as a population-averaged effect.

3.4.2 Surgical site infection requiring antibiotic treatment

Another key secondary estimand is the effect of assignment to triple antibiotic irrigation versus placebo of the breast implant and surgical pocket on the risk of surgical site infection requiring antibiotic treatment within 180 days after implant-based breast reconstruction ("day 0" defined as the first surgery where the allocated trial treatment is administered, see **section 4.0**), among all randomised breasts, regardless of treatment adherence or protocol deviations, estimated as a population-averaged effect.

3.5 Relationship to sensitivity analyses

A prespecified sensitivity analysis will be performed to assess the extent to which the primary conclusions are sensitive to protocol deviations, primarily non-receipt of the allocated intraoperative trial treatment. This analysis re-estimates the treatment effect on the primary endpoint within 180 days in a per protocol population defined as randomised participants with valid informed consent who received the allocated treatment at the first surgery and who have not experienced prespecified major protocol deviations that preclude interpretation of treatment receipt (as defined prior to database lock and unblinding, see **section 5.1.2** and **5.2.2**). Outcome ascertainment will follow the same endpoint definition and assessment procedures as the primary analysis. In practice, this analysis requires ascertainment of the primary endpoint within 180 days. Participants with missing primary outcome data will not be considered as having 'complete outcome data' and will be handled according to **section 5.5**.

This analysis targets an adherence-related estimand: the effect of assignment to triple antibiotic irrigation versus placebo on the risk of all-cause explantation within 180 days among participants who adhered to the allocated intraoperative treatment (received the allocated irrigation). The effect measure will be presented using the same estimand summary measure as the primary analysis (adjusted odds ratio with 95% confidence interval). This analysis is supportive and is not intended to provide independent confirmatory evidence.

4.0 Primary outcome definition and adjudication

The primary outcome is all-cause explantation of the breast implant within 180 days after a breast reconstruction with implants. The primary analysis will be performed in a modified intention-to-treat population of all randomised participants to either triple antibiotic irrigation or placebo with a valid informed consent. Explantation is defined as the removal and discarding of the implant. Replacement of an expander with a permanent implant and replacement of a permanent breast implant with a new permanent breast implant (e.g., due to cosmetic revisions such as asymmetry) will not count as an explantation. Additionally, planned removal of an expander to reconstruct the breast with an autologous flap is not counted as an explantation.

In this trial, the breast reconstruction surgery that defines the start (day 0) of the 180 days follow-up is the first breast reconstruction surgery at which the allocated treatment was administered. For breasts with tissue expander reconstruction (two-stage reconstruction), "day 0" is the day of

the first surgery, where the tissue expander is implanted, and the participant receives the allocated treatment. The planned exchange of tissue expander to permanent implant does not redefine “day 0” and does not extend the 180-days primary outcome follow-up window nor does it count as an explantation. In participants where the tissue expander is exchanged within 180 days of “day 0” (expander implantation), the exchange to a permanent implant will not count as an event, but complications to this procedure happening within 180 days from the original “day 0” (expander implantation) will count as an event. For breasts with direct-to-implant (DTI) reconstruction, “day 0” is the day of the first (and only planned) surgery with implantation of the permanent implant where the implant receives the allocated treatment.

All potential primary outcome events will be assessed by trained outcome assessors who are blinded to treatment allocation. If an assessor is uncertain whether a case meets the outcome definition, the case will be submitted for adjudication. Adjudication will be carried out by a senior investigator who is blinded to the treatment allocation or, when needed, by a panel of investigators who are also blinded to treatment allocation. Disagreements will be resolved through discussion until a final classification is reached. All adjudication will be completed before any unblinded analysis is undertaken, and records of adjudication decisions will be stored for audit and transparency.

4.1 Secondary outcome

The secondary comparisons between all randomised participants to triple antibiotic irrigation versus placebo with a valid informed consent will be:

- Surgical site infection requiring antibiotic treatment within 180 days (Y/N)
- Infection-specific revision surgery: Revision surgery due to clinically suspected deep surgical site infection with surgical access to the breast implant pocket or clinical signs of an infection in the breast implant pocket found intraoperatively within 180 days after the breast reconstruction surgery (Y/N)
- Revision surgery with incision of the fibrous capsule within 180 days (Y/N)
- Exchange of permanent implant to expander within 180 days (Y/N)
- The number of days from the surgery where the trial treatment was allocated to explantation (censored at 180 days if no explant)
- All-cause explantation within 1 year (Y/N)

Secondary infection outcomes will be assessed by the same blinded outcome assessors and adjudication process as the primary outcome. Unless otherwise specified, time windows are calculated from “day 0” as defined in section 4.0 (e.g., “within 180 days after the breast reconstruction surgery”).

4.2 Tertiary outcomes

The tertiary comparisons will be performed among all randomised participants with a valid informed consent who underwent unilateral breast reconstruction:

- Time from the breast reconstruction surgery to discharge (days)
- Re-admission within 180 days after the breast reconstruction surgery (Y/N)
- Quality-of-life (BREAST-Q) 3 months postoperatively

See Appendix B for a table overview of all outcomes. Unless otherwise specified, time windows are calculated from "day 0" as defined in section 4.0 (e.g., "within 180 days after the breast reconstruction surgery").

4.3 Safety outcomes

The primary safety assessment will be carried out in a safety population defined as all participants with a valid informed consent who received any amount of the trial treatment, and will compare randomised patients allocated to the triple antibiotic solution or placebo on the first occurrence of any allergic or irritative reactions within 14 days of administration of the trial drug defined as:

- Systemic allergic reactions including anaphylactic shock, urticaria and erythema multiforme
- Local irritative reactions including skin irritation, delayed wound healing and itching

Definitions, collection procedures, and reporting of adverse events (AE), adverse reactions (AR), serious adverse events (SAE), serious adverse reactions (SAR), and suspected unexpected serious adverse reactions (SUSAR) follow the trial protocol, section 7 (Assessment of safety and harm), including severity grading and assessment of relatedness, protocol v3.0, sections 7.3.1–7.3.6.

Expected postoperative surgical complications are common in this patient population and are prespecified clinical outcomes in this trial. These events are not considered adverse reactions to the trial drugs unless assessed as such according to the protocol, protocol sections 7.1–7.2.

Some clinical events may satisfy both an efficacy outcome definition (e.g., revision surgery) and an AE/SAE definition. Such events will contribute to both endpoint analyses and harms summaries, and overlap will be noted in harms reporting (e.g., via footnotes stating that some SAEs correspond to prespecified trial endpoints). No hypothesis testing is planned for harms. For unilateral reconstruction, the composite safety endpoint is defined at patient level (any systemic allergic reaction and/or any local irritative reaction within 14 days). For bilateral reconstruction, local irritative reactions are summarised at breast level by allocated treatment, whereas systemic allergic reactions are summarised at patient level overall.

4.4 Exploratory long-term outcomes

The long-term efficacy assessment will be performed among the modified intention-to-treat population allocated to triple antibiotic irrigation versus placebo of the following outcomes at 1, 5, 10, and 15 years:

- All-cause incision of the fibrous capsule around the breast implant (Y/N)
- Capsular contracture defined as Baker grade[20] I/II (no) versus Baker grade III/IV (yes)
- Baker classification (I–IV)
- Quality-of-life (BREAST-Q)

The statistical methods for these long-term outcomes are described in Section **5.9** and all long-term analyses will be considered exploratory.

4.4.1 Exploratory post-tissue expander exchange to permanent implant outcomes in patients with two stage reconstruction

For breasts reconstructed using a two-stage approach with a temporary tissue expander followed by planned exchange to a permanent implant (stage 2), we will perform exploratory analyses of postoperative outcomes in the 180-day window after the expander-to-implant exchange surgery. These analyses are distinct from the primary and key secondary estimands, which use "day 0" defined as the first surgery where the allocated trial treatment is administered (see **section 4.0**), and the post-exchange analyses will not redefine "day 0" or extend the 180-day primary endpoint window.

In this exploratory post-exchange window, time origin is the date of the planned expander-to-permanent implant exchange surgery (stage 2). The planned exchange procedure itself is not an explantation event. All post-exchange outcomes will be assessed among breasts that underwent the planned expander exchange and will be analysed according to the original randomised allocation (the permanent implant receives the same allocated treatment as at stage 1).

The following exploratory outcomes will be assessed within 180 days after stage 2:

- All-cause explantation of the permanent implant within 180 days after stage 2
- Infection-specific revision surgery within 180 days after stage 2
- Surgical site infection requiring antibiotic treatment within 180 days after stage 2

5.0 Statistical methods (estimators)

Unless otherwise specified, the independent sample unit is breast for both patients undergoing unilateral and bilateral reconstruction, as patients undergoing bilateral reconstruction will have one breast allocated to the control group and the contralateral breast allocated to the intervention group. Pre-specified comparisons will involve modified intention-to-treat analyses between all randomised participants with a valid informed consent allocated to triple antibiotic solution or placebo. The primary analysis will be adjusted to account for the randomisation strata and clustering within patients. However, crude estimates will also be performed as a sensitivity analysis for transparency and potential descriptive comparison. All models will take clustering between the two breasts of the participant undergoing bilateral reconstruction into account.[21]

5.1 Analysis populations

5.1.1 Modified intention-to-treat (mITT)

Unless otherwise specified, all comparisons will be performed on a modified intention-to-treat population consistent with the treatment-policy strategy defined in **section 3.1**. This also includes participants who were randomised but did not receive the allocated treatment or did not undergo implant-based breast reconstruction as planned. However, it will not include participants who

withdrew their consent either before or after the treatment was administered as per Danish legislation.

5.1.2 Per protocol population

The per protocol population is defined as all randomised participants to either triple antibiotic irrigation or placebo with a valid informed consent who received the allocated treatment during surgery. As the trial treatment is an intraoperative one-time, blinded procedure, the primary anticipated reasons to be excluded from the per protocol population is non-adherence by the surgeon (intended or forgetting to use the trial treatment), intraoperative abandoning of implant-based breast reconstruction or logistic challenges. In addition, any other potential major protocol deviations that are identified will undergo blinded adjudication to classify whether it leads to exclusion from the per protocol population. The final classification of eligibility to the per protocol population will be completed before data lock and unblinding.

5.1.3 Safety population

The primary safety assessment will be carried out in a safety population defined as all participants with a valid informed consent who received any amount of the trial treatment. This safety population will be used for descriptive summaries of AEs (including SAEs), ARs (including SARs), and SUSARs occurring within 14 days after administration of trial treatment, in accordance with the trial protocol section 7 (Assessment of safety and harm).

5.2 Estimator for the primary estimand and all other binary outcomes

All efficacy binary outcomes including the primary estimand described in **section 3.3** will be analysed using multivariable logistic regression with a generalised estimating equation (GEE) with an exchangeable correlation structure. The primary model will include treatment group and the categorical stratification variables: site, unilateral vs bilateral, immediate vs delayed reconstruction, and radiotherapy status (yes/no). The primary comparison will be reported as event counts and proportions for the intervention and placebo groups separately. The contrast of the primary estimand will be presented as an adjusted odds ratio with 95% confidence intervals. The hypothesis test and corresponding p-value of the primary estimand will be calculated using a Wald-test comparing the multivariable logistic regression model with a generalised estimating equation with and without the treatment allocation term. Kaplan–Meier curves with dashed lines indicating the median time to event if estimable for each treatment group will be used descriptively to visualise the timing of the observed events. The descriptive Kaplan–Meier plots will be restricted to breasts that receive an implant.

The primary analysis will test the null hypothesis of no difference in the primary outcome between triple antibiotic irrigation versus placebo at a two-sided significance level of 0.05. Treatment effects will be estimated and reported with corresponding 95% confidence intervals. There will be no adjustment for multiple testing. Key secondary outcomes will be interpreted as supportive, and all other additional analyses will be interpreted as exploratory.

5.2.1 Rationale for choice of model

The multivariable logistic regression model is chosen as the primary outcome is binary at a fixed 180-day time window. The model can adjust for the randomization strata and other potential confounders to control for residual imbalances in the baseline parameters. Using a generalized estimating equation (GEE) is necessary to account for correlation between the two breasts nested within a patient undergoing bilateral reconstruction. An exchangeable correlation structure is chosen due to the maximal cluster size of two and as the clustered observations are not distributed over time. The GEE method models the population treatment effect which has a more appealing interpretation than random effects models which are subject specific/within subject interpretation. The GEE would likely gain more efficacy from the unilateral patients with no clustering whereas the random effects model could become unstable due to singularity and random effects variances near or equal to zero. We do not assume non-linearity of the adjustment covariates, as all randomization strata are categorical. See Appendix C for details regarding the simulation work used to assess model performance across different simulated scenarios.

5.2.2 Sensitivity analysis for the primary estimand

As a prespecified sensitivity analysis, the primary outcome will be re-estimated in the per-protocol population defined in **section 5.1.2**. This prespecified sensitivity analysis targets a different estimand than the primary treatment-policy estimand, and it is designed to assess the robustness of the main findings when accounting for protocol deviations. Together with the primary analysis, this prespecified per protocol analysis will inform the overall interpretation of the trial with respect to both presence and absence of a clinically relevant effect.

5.3 Estimators for secondary estimands

All binary secondary estimands will be estimated using the same multivariable logistic regression model with a generalised estimating equation (GEE) with an exchangeable correlation structure as the primary estimand. Time to explantation will be estimated using Cox proportional hazards models with robust standard errors using the sandwich estimator to account for clustering between two breasts within same patient in bilateral reconstructions. The assumptions of proportionality will be assessed visually using scaled Schoenfeld residuals and cumulative Martingale residuals.[22] In case of violation of the proportional hazards assumption, time-to-event outcomes will be modelled with a time horizon of 180 days using direct binomial regression models with robust standard errors as described by Blanche et. al.[23] The time-to-explantation analysis will be restricted to breasts that actually receive an implant, and the index time will be time of reconstruction censored at 180 days or death depending on what comes first. Time to discharge will be presented descriptively for each group using median, interquartile range (IQR) and range.

5.4 Subgroup analyses

Subgroup analyses will assess heterogeneity of the primary estimand across the following subgroups:

- Patients with unilateral reconstruction and bilateral reconstruction separately
- Immediate versus delayed reconstruction
- Radiotherapy versus no radiotherapy
- Direct-to-implant versus tissue expander reconstruction
- BMI (divided into WHO categories <18.5, 18.5–25, 25–30, and >30 kg/m^2)
- Active smokers versus non-active smokers
- Reconstruction with mesh versus without mesh

We will test for heterogeneity using a single global interaction test that evaluates whether the treatment effect differs across all subgroups collectively.[24] This test will be performed by including all subgroup variables and their interaction terms with treatment allocation in one model. The p-value will be estimated using a Wald test comparing the models with/without interaction terms.

If the global interaction test is not significant, the interpretation will be that there is no statistical evidence of heterogeneity, and the overall treatment effect applies consistently across all the examined subgroups.

If the global interaction test is significant, exploratory post hoc interaction Wald tests will be performed for each prespecified subgroup. These individual interaction p-values will be adjusted using a Bonferroni correction to account for multiple testing. The purpose of these analyses is to identify potential groups with differential treatment response, while recognising that they are exploratory and not powered for confirmatory inference.

The results will be presented in forest plots with point estimates, confidence intervals and interaction p-values. No claims of differential efficacy will be based solely on subgroup findings.

5.5 Missing data

We expect a low risk of missing data for the primary outcome, as emigration within 180 days from the breast reconstruction is expected to be the main reason for missingness.

In case of missingness greater than 5% for the primary outcome, we will apply multiple imputations by chained equations using the MICE package in R, assuming that data is missing at random. The missing outcome will be imputed using multivariable logistic regression using the covariates age, BMI, unilateral/bilateral reconstruction, immediate/delayed reconstruction, radiotherapy and the additional axillary variables chemotherapy, direct-to-implant/tissue expander reconstruction, smoking, site, comorbidity, therapeutic/risk reducing mastectomy, implant plane, and mesh. Continuous variables will be categorized into deciles for age and <18.5, 18.5–25, 25–30, and >30 kg/m^2 for BMI. The multiple imputation procedure will burn the first three imputations and subsequently impute ten times. Convergence will be checked for

pathological convergence by visualizing the changes in imputed estimate and SE across the imputation iterations.[25] The iterated datasets will be analysed separately as described in the primary analysis and pooled using Rubin's rules. The analysis of the multiple imputed datasets will be regarded as a sensitivity analysis, as stated in the trial protocol.

For the secondary binary outcomes, we will perform complete-case analyses as the primary approach. If unexpectedly missingness exceed 5% for important secondary outcomes, we will use multiple imputations using the same strategy as outlined above for the primary outcome. For BREAST-Q responses, missingness will be handled according to the BREAST-Q portfolio guidelines. Long-term outcomes will be analysed using a complete case strategy and will be interpreted as exploratory.

5.6 Adjustment for multiple testing

No formal statistical adjustment for multiple hypothesis testing will be applied to the primary outcome, which will be interpreted at the conventional two-sided significance level of $P < 0.05$. Secondary and tertiary outcomes will not be adjusted for multiple testing and should be interpreted as supportive and exploratory.

5.7 Timing of database lock, unblinding and primary analysis

Follow-up for the primary endpoint is complete when the last included breast has reached 180 days after the first breast reconstruction surgery ("day 0"), defined as the reconstructive surgery at which the allocated trial treatment was first administered (see **section 4.0**). The primary analysis will be conducted after completion of this follow-up period for all included breasts.

Prior to database lock, all outcomes within the 180-day window (primary and key secondary outcomes) will be ascertained and, where applicable, adjudicated under blinded conditions. All outstanding data queries will be resolved, and derived variables required for the prespecified analyses will be finalised. The database will then be locked.

Unblinding of the analysis dataset will occur only after database lock. The primary analysis will be executed thereafter using the prespecified analysis code, table shells, and procedures described in this SAP. Any changes to analysis code after database lock will be restricted to correction of programming errors that prevent execution or cause demonstrable inaccuracies. Any such changes will be documented in an analysis log prior to dissemination of results.

All statistical analysis code and table shells for the main publication have been developed and finalised before unblinding, using only simulated or masked datasets. Dummy tables and figures have been generated with masked treatment labels to verify model specification and layout.

Exploratory post-exchange analyses in two-stage reconstructions described in **section 4.4.1** will be performed subsequently once 180-day follow-up after stage 2 is available. These analyses will not affect the timing of database lock, unblinding, or the primary analysis.

5.8 Interim analysis and stopping rules

No interim analysis will be performed during the trial. Safety will be monitored continuously throughout the trial but no formal rules for trial termination have been made. Instead, the Trial Steering Committee will evaluate whether termination of the trial should be recommended based on the adverse events reporting. This is since both the control and intervention arm are widely used treatments with no reports of harmful effects.

5.9 Details of analyses for long-term outcomes

Binary outcomes at the long-term follow-up timepoints will be analysed using the same statistical framework for binary outcomes used for the primary analysis.

Continuous outcomes will be analysed using multivariable linear regression with GEE with exchangeable correlation structure adjusted for the randomization strata. Comparisons will be presented as means and a mean difference with 95% confidence intervals with the p-value derived from Wald tests. The data will be transformed in case of violation of the assumption of normality.

Repeated continuous outcomes will be analysed using linear regression with GEE. The model will include treatment allocation and time as an interaction term and will be adjusted for the randomization strata. For repeated patient-level BREAST-Q, clustering is at patient level, and the correlation structure will be a first order autoregressive structure under the assumption that the correlation is higher between adjacent measurements in time.

All categorical outcomes, including Baker grade, will be analysed using ordinal regression if ordered and multinomial regression if not ordered. All outcomes will be modelled with GEE and adjusted for the randomization strata. The comparisons from both models will be presented as adjusted odds ratios, 95% confidence intervals and p-values derived from a Wald test.

5.9.1 Details of analysis of exploratory post-tissue expander exchange to permanent implant

Exploratory post-exchange outcomes defined in **section 4.4.1** will be analysed among breasts that underwent the planned expander-to-permanent implant exchange (stage 2). For these outcomes, time origin is the date of stage 2 exchange surgery, and the analysis window is 180 days thereafter. Outcomes will be analysed according to the originally allocated treatment (as randomised at stage 1 as the same allocated treatment is used for the stage 2 exchange surgery as described in the trial protocol v3.0).

Binary post-exchange outcomes will be summarised as counts and percentages by treatment group and analysed using the same statistical framework as other binary efficacy outcomes, that is multivariable logistic regression with a generalised estimating equation (GEE) and exchangeable correlation structure to account for clustering within participants in bilateral reconstructions.

Models will be adjusted for the randomisation strata (site, unilateral vs bilateral, immediate vs delayed reconstruction, and radiotherapy status). Results will be presented as adjusted odds ratios with 95% confidence intervals and p-values. These analyses will be considered exploratory.

6.0 Pre-specified table shells and planned figures

The main article will report summary statistics describing the trial population and baseline characteristics per breast by treatment group. Binary variables will be presented as counts and proportions. Continuous outcomes will be presented as means and standard deviations for normally distributed outcomes and median and interquartile ranges for non-normal distributed outcomes. Distributions will be assessed with histograms, QQ-plot and Shapiro-Wilks test.[26] The patient demographics table will be split into two tables. One table with per patient characteristics (i.e., age, BMI etc.), and the table will be stratified based on control/intervention group and unilateral or bilateral reconstruction in whom a patient receive placebo in one breast and intervention in the contralateral breast. The second demographics will be used to present the randomisation balance and will be per breast stratified into a control group and intervention. The baseline parameters will not be hypothesis tested. Table shells can be found below.

Patient demographics

	Unilateral Placebo (N=130)	Unilateral Intervention (N=131)	Bilateral Placebo / Intervention (N=742)
Patient Age, Yr			
Median (Q1, Q3)	50.0 (43.2, 56.2)	50.5 (43.6, 58.2)	49.7 (42.5, 56.4)
Range	25.3 - 75.1	20.0 - 76.1	17.6 - 81.9
BMI, kg/m2			
<18	44 (34%)	34 (26%)	190 (26%)
18-25	30 (23%)	23 (18%)	188 (25%)
25-30	26 (20%)	39 (30%)	183 (25%)
>30	30 (23%)	35 (27%)	181 (24%)
Trial Site			
1	28 (22%)	32 (24%)	134 (18%)
2	22 (17%)	18 (14%)	110 (15%)
3	15 (12%)	22 (17%)	131 (18%)
4	20 (15%)	24 (18%)	129 (17%)
5	21 (16%)	21 (16%)	118 (16%)
6	24 (18%)	14 (11%)	120 (16%)
Chemotherapy			
No	108 (83%)	110 (84%)	594 (80%)

	Unilateral Placebo (N=130)	Unilateral Intervention (N=131)	Bilateral Placebo / Intervention (N=742)
Yes	22 (17%)	21 (16%)	148 (20%)
Smoking Status			
Never Smoker	45 (35%)	36 (28%)	233 (31%)
Former Smoker	40 (31%)	53 (40%)	264 (36%)
Active Smoker	45 (35%)	42 (32%)	245 (33%)
ASA Class			
1	57 (44%)	63 (48%)	322 (43%)
2	62 (48%)	60 (46%)	382 (52%)
3	11 (8.5%)	8 (6.1%)	38 (5.1%)

All values in the table shells are placeholders for layout only and do not reflect trial data.

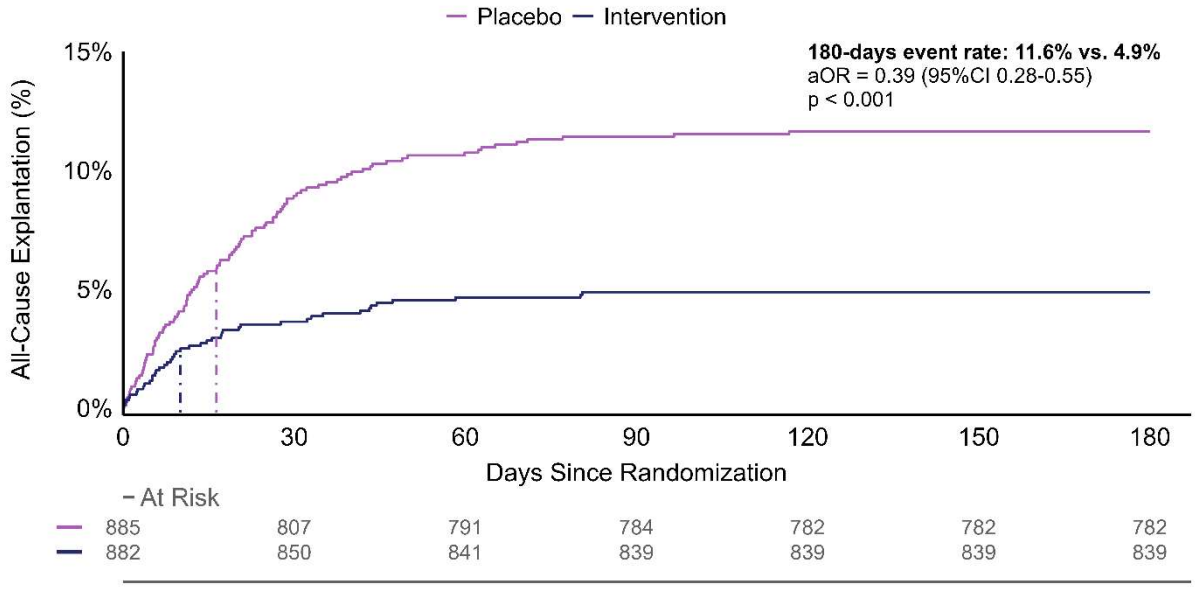
Per breast demographics and randomization balance

	Placebo (N=872)	Intervention (N=873)
Trial Site		
1	162 (19%)	166 (19%)
2	132 (15%)	128 (15%)
3	146 (17%)	153 (18%)
4	149 (17%)	153 (18%)
5	139 (16%)	139 (16%)
6	144 (16%)	134 (15%)
Unilateral/Bilateral Reconstruction		
Bilateral	742 (85%)	742 (85%)
Unilateral	130 (15%)	131 (15%)
Timing of Reconstruction		
Immediate	733 (84%)	760 (87%)
Delayed	139 (16%)	113 (13%)
Radiotherapy		
No	498 (57%)	500 (57%)

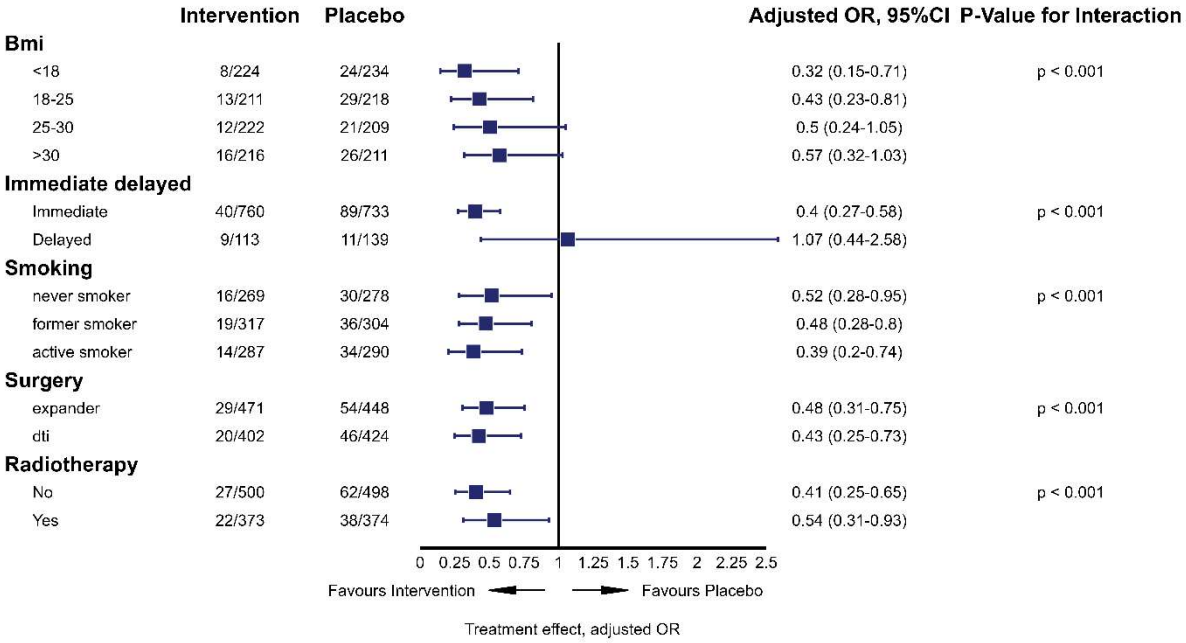
	Placebo (N=872)	Intervention (N=873)
Yes	374 (43%)	373 (43%)
Laterality		
Left	446 (51%)	434 (50%)
Right	426 (49%)	439 (50%)
Type of Reconstruction		
Immediate Dti	349 (40%)	353 (40%)
Immediate Expander	384 (44%)	407 (47%)
Delayed Dti	75 (8.6%)	49 (5.6%)
Delayed Expander	64 (7.3%)	64 (7.3%)
Indication for Mastectomy		
Therapeutic	306 (35%)	279 (32%)
Risk Reducing	288 (33%)	293 (34%)
Other	278 (32%)	301 (34%)
Implant Plane		
Subpectoral	277 (32%)	304 (35%)
Prepectoral	289 (33%)	287 (33%)
Other	306 (35%)	282 (32%)
Mesh		
No	449 (52%)	425 (49%)
Yes	423 (48%)	448 (51%)

All values in the table shells are placeholders for layout only and do not reflect trial data.

The primary outcome assessing the treatment effect of antibiotics versus placebo will be presented as counts and proportions with adjusted odds ratios (aOR) with 95% confidence intervals. The results will be visualized with Kaplan-Meier curves with dashed lines indicating the median time to event for each treatment group for descriptive purposes if estimable.



If the global test of heterogeneous treatment effects is significant, the interaction analysis will be visualized using a forest plot displaying the levels of the subgroup, adjusted odds ratios, 95% confidence intervals and the p-value for the interaction term.



6.1 Code and software

All code for the main analyses and figures has been developed and tested on simulated datasets and is provided in Appendix D (BREAST-AB Functions.R), Appendix E (BREAST-AB Simulation.R) and Appendix F (BREAST-AB Table shells.R). These scripts will be used, without substantive

modification, to generate the final results once the database has been locked and unblinded. All code for data management, simulations and analyses have been performed in R version 4.5.1 with a saved session info file (Appendix G).

7.0 Publication plan

The main publication will report the primary endpoint together with the two prespecified secondary endpoints most directly linked to the hypothesised effect of antibiotic irrigation: infection-related revision surgery and surgical site infection requiring antibiotic treatment within 180 days. The remaining prespecified secondary outcomes, tertiary outcomes, and long-term follow-up will be analysed and disseminated in subsequent peer-reviewed publications. All outcomes, including neutral and inconclusive results, will be reported in accordance with the protocol and shared through international journals, scientific meetings, and public communication channels.

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Appendix A: Estimands

The primary- and key secondary estimands are described in detail in **section 3.3-3.4**. Below is an overview of the primary estimand. Estimands for the key secondary outcomes (infection-specific revision surgery and surgical site infection requiring antibiotic treatment within 180 days) are the same as the primary estimand except for the endpoints.

Attribute	**Definition**
Population	Women scheduled for implant-based breast reconstruction with valid informed consent
Treatment conditions	**Intervention** – irrigation of breast implant and surgical pocket with 80mg gentamicin, 1000mg vancomycin, and 1000mg cefazolin dissolved in 500mL sterile saline. **Placebo** – irrigation of breast implant and surgical pocket with sterile saline.
Endpoint	All-cause explantation of the breast implant within 180 days after a breast reconstruction with implants ("day 0" defined as the first surgery where the allocated trial treatment is administered, see **section 4.0**)
Summary Measure	Odds ratio
Intercurrent events	**Strategy**
Treatment-modifying events: Non-receipt of trial treatment - Non-adherence by the surgeon, intentional or non-intentional - Logistic challenges	Treatment policy
Truncating events: Death within 180 days from administration of treatment Non-receipt of a breast implant - Intraoperative abandoning of implant-based breast reconstruction - Post-randomization cancellation of breast reconstruction Removal of expander or implant that does not constitute a primary outcome according to the definition in **section 4.0**	Endpoint definition: death within 180 days without explantation counted as non-event Endpoint definition: no-implant (including cancellation/abandoning) counted as non-event (see **section 3.2**) Endpoint definition: removal but not primary outcome within 180 days counted as non-event

Appendix B: Outcomes table

Outcome	Outcome type	Timepoint[#]	Unit	Confirmatory vs exploratory	Estimator
All-cause explantation	Binary	180 days	Breast	Confirmatory	Multivariable logistic regression with GEE
Infection-specific revision surgery	Binary	180 days	Breast	Prespecified secondary (supportive)*	Multivariable logistic regression with GEE
Surgical site infection requiring AB	Binary	180 days	Breast	Prespecified secondary (supportive)*	Multivariable logistic regression with GEE
Revision surgery with incision of the fibrous capsule	Binary	180 days	Breast	Exploratory	Multivariable logistic regression with GEE
Exchange of permanent implant to expander	Binary	180 days	Breast	Exploratory	Multivariable logistic regression with GEE
Time-to-explantation	Time-to-event	Day 0 (first surgery with allocated treatment), censored at 180 days or death	Breast	Exploratory	Cox proportional hazards model with robust SE
All-cause explantation	Binary	1 year	Breast	Exploratory	Multivariable logistic regression with GEE
Time from the breast reconstruction	Continuous	Day 0 (first surgery with	Patient	Exploratory	Median (IQR, range)

surgery to discharge		allocated treatment)			
Re-admission	Binary	180 days	Patient	Exploratory	Multivariable logistic regression
All-cause explantation of permanent implant (post-expander exchange, two-stage only)	Binary	180 days¤ after expander exchange (stage 2)	Breast	Exploratory	Multivariable logistic regression with GEE
Infection-specific revision surgery (post-expander exchange, two-stage only)	Binary	180 days¤ after expander exchange (stage 2)	Breast	Exploratory	Multivariable logistic regression with GEE
Surgical site infection requiring AB (post-expander exchange, two-stage only)	Binary	180 days¤ after expander exchange (stage 2)	Breast	Exploratory	Multivariable logistic regression with GEE
Quality-of-life (BREAST-Q)	Continuous	3 months-, 1-, 5-, 10-, and 15 years post-op	Patient	Exploratory	Linear regression
Safety Allergic or irritative reactions	Binary	14 days	Patient (unilateral reconstruction and breast for local events in patients with	Descriptive	Counts and percentages (no hypothesis testing)

			bilateral reconstruction)		

[#]Timepoints that reference surgery (e.g., 180 days, time-to-event, discharge) are calculated from "day 0", defined as the day of the first surgery where the allocated trial treatment is administered (see **section 4.0**). For two-stage tissue expander reconstruction, "day 0" is expander implantation (stage 1).

*The key secondary outcomes Infection-specific revision surgery and surgical site infection requiring antibiotic treatment will not be adjusted for multiple testing and should be interpreted as supportive and exploratory.

[¤]For exploratory post-exchange outcomes in two-stage reconstruction (**section 4.4.1**), the time origin is the date of expander-to-permanent implant exchange surgery (stage 2).

Appendix C: Simulations and rationale for choice of model

C1.0 Simulation

To assess the model performances, we conducted a simulation with 10.000 replicated analyses. The simulated dataset consisted of 1003 patients / 1274 breasts (according to sample size estimation) with the covariates: treatment allocation (intervention/placebo), site (1-6), laterality (unilateral/bilateral), timing of surgery (immediate/delayed) and radiotherapy (y/n). The proportion of bilateral patients was assumed to be 27%. For all simulations we assumed a baseline event probability of 10%, a correlation between the two breasts of 15% and a relative treatment effect of 50% (corresponding to OR = 0.5 / log(OR) = -0.7). We assumed that the odds ratio of 0.5 approximates the corresponding risk ratio under the rare disease assumption. All assessed models were adjusted for trial site, immediate/delayed reconstruction, unilateral or bilateral reconstruction and radiotherapy Y/N.

We tested the performance of five potential multivariable models that take clustering between the two breasts in patients with bilateral reconstruction into account. The main candidate frameworks were:

Multivariable logistic regression with robust standard errors using sandwich estimation

- glm.cluster(), miceadds version 3.18.36 (“GLM_robust”)

Multivariable logistic regression with a generalised estimating equation using an “exchangeable” correlation structure

- geeglm(), geepack version 1.3.13 (“GEE”)

Random effects multivariable logistic regression models with each patient as a random intercept (RE) with different estimation methods.

- GLMMadaptive() (adaptive Gaussian quadrature approximation), GLMMadaptive version 0.9.7 (“GLMM_adaptive”)
- glmmTMB() (Laplace approximation), glmmTMB version 1.1.14 (“GLMM_TMB”) with the optimizer “BFGS”
- glmmPQL() (penalized quasi-likelihood), MASS version 7.3.65 (“GLMM_PQL”) with the controls maxIter = 100, msMaxIter = 100 and niterEM = 50
- glmer(), (Laplace approximation), lme4 version 1.1.38 (“GLMER”) with the optimizer “bobyqa” and controls maxfun = 10000.

The models were evaluated based on:

1) the mean log(OR)
2) bias - calulcated as mean(log(OR)) – true(log(OR))
3) Empirical standard error calculated as the SD(log(OR)) / sqrt(number of simulations)

4) Type-I error rate calculated as the number of significant p-values / number of simulations, when the true treatment effect = 0.
5) Monte Carlo Standard Error of the type-I error rate calculated as sqrt((type-I error*(1-type-I error))/number of simulations
6) Power calculated as the number of significant p-values / number of simulations, when the true treatment effect was > 0.

The full R-script for the simulation is found in the Appendix D and E.

C1.2 Model performances

The best performing candidate models were GEE and GLM. Both models were close to the true log(OR) treatment effect (Bias: GEE= -1.262 and GLM = -1.264) with narrow standard errors (GEE = 0.0022, GLM = 0.0022). The type-I error rates were <5% (GEE = 4.8%, GLM = 4.1%) and the power >90% (GEE = 94.6%, GLM 94.5%). The random effects models showed much more biased estimates on the log(OR) scale, with wider standard errors and increased type-I error rates. Furthermore, the convergence failure was only seen in the random effects models.

type	Number of Simulations	True Treatment Effect	Mean Log(OR)	Bias	Empirical Standard Error	Type-I error rate	Type-I Monte Carlo SE	Power
GEE	10,000	0%	0.0015	0.0015	0.0018	0.0483	0.0021	
GEE	10,000	10%	-0.1194	-0.2194	0.0018			0.0944
GEE	10,000	25%	-0.3213	-0.5713	0.0019			0.3886
GEE	10,000	50%	-0.7617	-1.2617	0.0022			0.9457
GLM_robust	10,000	0%	0.0013	0.0013	0.0018	0.0479	0.0021	
GLM_robust	10,000	10%	-0.1199	-0.2199	0.0019			0.0972
GLM_robust	10,000	25%	-0.3221	-0.5721	0.0020			0.3832
GLM_robust	10,000	50%	-0.7635	-1.2635	0.0022			0.9447
GLMM_Adaptive	9,998	0%	0.0018	0.0018	0.0024	0.0413	0.0020	
GLMM_Adaptive	9,992	10%	-0.1546	-0.2546	0.0024			0.0846
GLMM_Adaptive	9,975	25%	-0.4058	-0.6558	0.0025			0.3591
GLMM_Adaptive	9,899	50%	-0.9259	-1.4259	0.0029			0.9334

type	Number of Simulations	True Treatment Effect	Mean Log(OR)	Bias	Empirical Standard Error	Type-I error rate	Type-I Monte Carlo SE	Power
GLMM_TMB	9,990	0%	0.0076	0.0076	0.0104	0.1801	0.0038	
GLMM_TMB	9,988	10%	-0.4459	-0.5459	0.0110			0.2391
GLMM_TMB	9,971	25%	-1.2787	-1.5287	0.0157			0.4903
GLMM_TMB	9,719	50%	-4.1040	-4.6040	0.1099			0.9119
GLMER_LME4	10,000	0%	0.0031	0.0031	0.0085	0.3141	0.0046	
GLMER_LME4	10,000	10%	-0.4364	-0.5364	0.0089			0.3845
GLMER_LME4	10,000	25%	-1.1953	-1.4453	0.0107			0.6028
GLMER_LME4	9,998	50%	-3.1337	-3.6337	0.0178			0.9432
GLMM_PQL	10,000	0%	-37,861,376,365.0560	-37,861,376,365.0560	37,861,376,365.0634	0.5842	0.0049	
GLMM_PQL	9,999	10%	-219,694,870,112.2050	-219,694,870,112.3051	246,883,520,833.4882			0.6448
GLMM_PQL	9,997	25%	-217,217,028,112.9108	-217,217,028,113.1608	167,041,401,018.0466			0.8081
GLMM_PQL	9,995	50%	-846,999,185,914.5013	-846,999,185,915.0013	503,376,658,771.7057			0.9831

C1.3 Final model choice

Overall, the two final candidate models (GEE and GLM_robust) performed comparably in terms of bias, error, type-I error and power. The GEE model had a slightly superior performance compared with GLM with sandwich estimation based on slightly less biased results and lower SE. GEE has the lowest bias and standard error across varying treatment effects compared with the other candidate models. Furthermore, GEE is more flexible as the correlation structure can be specified.

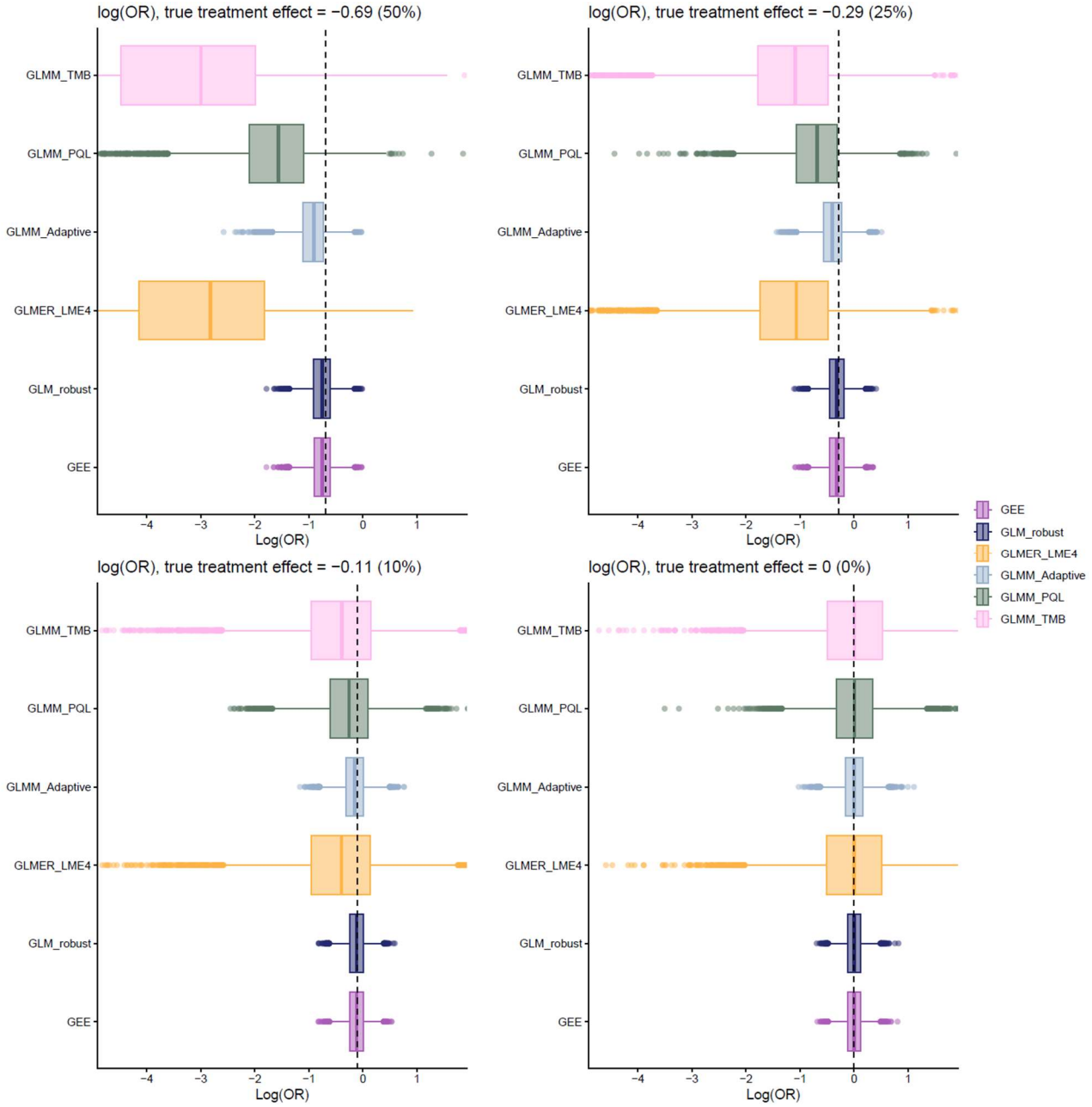

Figure 1. Boxplots of the log(OR) estimates across the six tested models under the true treatment effects 0%, 10%, 25% and 50%.

Appendix D: BREAST-AB Functions.R

```
library(geepack)
library(lme4)
library(colorspace)
library(GLMMadaptive)
library(glmmTMB)
library(MASS)
library(miceadds)
library(data.table)
library(tidyverse)


sim_events <- function(data,
                       bilat_prob,
                       corr_prob,
                       event_prob,
                       treat_prob,
                       seed = 1){

   set.seed(seed)

  data_out <-
     rbindlist(lapply(unique(data$record_id), function(i){

        data[data$record_id == i,] %>%
          #distribute random events with probability = event_prob minus
correlation effect
         mutate(event = rbinom(n(), 1, prob=(event_prob-
(corr_prob*bilat_prob*event_prob))),
                #induce correlation. Breasts with event = 0 and
contralateral event = 1 changes event to 1 with the probability = corr_prob
                event = ifelse(event == 0 & 1 %in%event, rbinom(1, 1,
corr_prob), event),
                #induce treatment effect. Breast with allocation =
"Intervention" changes event from 1 to 0 with the probability = 1-treat_prob
                event = ifelse(allocation == "Intervention" & event == 1,
rbinom(1, 1, 1-treat_prob), event))

     }))%>%as.data.frame()

  list(data=data_out,
       info = lst(seed,
                  event_prob,
                  corr_prob,
                  treat_prob))

}

sim_extract <- function(data, models = c("GEE", "GLM", "GLMM_adaptive",
"GLMM_TMB", "GLMM_PQL", "GLMER")){

   df <- data$data
    info <- data$info

     output_list <- list()
```

```
      if("GEE" %in%models){

         geeuni <- geeglm(event ~allocation +site +immediate_delayed
+uni_bilat +radiotherapy, data=df, id=record_id, family="binomial",
corstr="exchangeable")

         output_list[["GEE"]] <-
             data.frame(or = as.numeric(geeuni$coefficients[2]),
                        cid = (1.96*summary(geeuni)$coefficients[2,2])*2,
                        se = summary(geeuni)$coefficients[2,2],
                        pval = summary(geeuni)$coefficients[2,4],
                        type = "GEE")

      }


      if("GLMM_adaptive" %in%models){

         #GLMMadaptive
         reuni1 <- GLMMadaptive::mixed_model(event~allocation +site
+immediate_delayed +uni_bilat +radiotherapy,
                                             random = ~1 | record_id,
                                             data = df,
                                             family = "binomial",
                                             #iter_EM = 0,
                                             max_coef_value = 100)
          output_list[["GLMM_Adaptive"]] <-
             data.frame(or = as.numeric(summary(reuni1)$coef_table[2,1]),
                        cid = (1.96*summary(reuni1)$coef_table[2,2])*2,
                        se = summary(reuni1)$coef_table[2,2],
                        pval = summary(reuni1)$coef_table[2,4],
                        type = "GLMM_Adaptive")

      }

      if("GLMM_TMB" %in%models){
         #glmmTMB
        output_list[["GLMM_TMB"]] <-
          tryCatch(
            {
         reuni2 <- glmmTMB::glmmTMB(event~allocation +site
+immediate_delayed +uni_bilat +radiotherapy +(1|record_id),
family="binomial", data=df,
                                    control =
glmmTMBControl(optimizer=optim,
                                                           optArgs =
list(method = "BFGS")))



             data.frame(or =
as.numeric(summary(reuni2)$coefficients$cond[2,1]),
                        cid =
(1.96*summary(reuni2)$coefficients$cond[2,2])*2,
                        se = summary(reuni2)$coefficients$cond[2,2],
```

```
                          pval = summary(reuni2)$coefficients$cond[2,4],
                          type = "GLMM_TMB")
       },
     error = function(e) {

       data.frame(type = "GLMM_TMB")

     })


      }

      if("GLMM_PQL" %in%models){
        output_list[["GLMM_PQL"]] <-
          tryCatch(
          {
         reuni3 <- MASS::glmmPQL(event~allocation +site +immediate_delayed
+uni_bilat +radiotherapy,
                                  random = ~1 | record_id,
                                  family="binomial", data=df,
                                 control = nlme::lmeControl(
                                   maxIter = 100,
                                   msMaxIter = 100,
                                   niterEM = 50
                                 ))

                         data.frame(or =
as.numeric(summary(reuni3)$tTable[2,1]),
                          cid = (1.96*summary(reuni3)$tTable[2,2])*2,
                          se = summary(reuni3)$tTable[2,2],
                          pval = summary(reuni3)$tTable[2,5],
                          type = "GLMM_PQL")

      },
     error = function(e) {

       data.frame(type = "GLMM_PQL")

     })
      }


      if("GLMER" %in%models){
         #LME4 package
        output_list[["RE_All_LME4"]] <-
          tryCatch(
          {
         reuni <- glmer(event~allocation +site +immediate_delayed +uni_bilat
+radiotherapy +(1|record_id), family="binomial", data=df,
                         control = glmerControl(optimizer = "bobyqa",
                                                optCtrl = list(maxfun =
10000)))

                          data.frame(or =
as.numeric(summary(reuni)$coefficients[2]),
                          cid = (1.96*summary(reuni)$coefficients[2,2])*2,
```

```
                          se = summary(reuni)$coefficients[2,2],
                          pval = summary(reuni)$coefficients[2,4],
                          type = "GLMER_LME4")

          },
         error = function(e) {

           data.frame(type = "GLMER_LME4")

         })


      }

      if("GLM" %in%models){

         glm_uni <- miceadds::glm.cluster(data=df, formula=event ~allocation
+site +immediate_delayed +uni_bilat +radiotherapy,
                                          cluster="record_id",
family="binomial")
          s <- summary(glm_uni)

           output_list[["GLM_robust"]] <-
              data.frame(or = s[2,1],
                          cid = abs(s[2,1] - (1.96*s[2,2]))+abs(s[2,1]
+(1.96*s[2,2])),
                          se = s[2,2],
                          pval = s[2,4],
                          type = "GLM_robust")

      }


     rbindlist(output_list, fill=TRUE)%>%
       mutate(
          event_prob = info$event_prob,
           corr_prob = info$corr_prob,
           treat_prob = info$treat_prob,
           grp = paste0(type,
                        ", event_prob = ", info$event_prob,
                        ", corr_prob = ", info$corr_prob,
                        ", treat_prob = ", info$treat_prob))%>%
        as.data.frame()

}

plotf <- function(frame,
                  estimate,
                  modifier,
                  intercept = 0,
                  title,
                  label = "",
                  xlab,
                  breaks,
                  limits,
                  bw=0.05, lt=rep("solid", length(cept))){
```

```
   estimate_c <- frame %>%select({{estimate}})%>%names
    modifier_c <- frame %>%select({{modifier}})%>%names



     tab <-
        frame %>%
        mutate(sig = ifelse(pval < 0.05, 1, 0),
               delta = or - log(1-treat_prob))%>%
        group_by(!!!syms(c("type", modifier_c)))%>%
        summarise(q1_or = quantile(or, 0.25),
                  median_or = median(or),
                  mean_or = mean(or),
                  q3_or = quantile(or, 0.75),
                  median_se = median(se, na.rm=T),
                  sd_or = sd(or),
                  mean_delta = mean(delta),
                  sd_delta = sd(delta),
                  pval = median(pval, na.rm=T),
                  power = sum(sig, na.rm=T)/1000
                  )%>%
        mutate(cv = sd_or / (mean_or+5),
               across(c(q1_or:cv), ~round(.,2)))

      if(missing(modifier)){

         plot <-
            ggplot(base %>%filter(str_detect(type, "GLM|GEE")),
aes(x={{estimate}}, y=type, fill = type, color = type))+
            geom_boxplot(alpha = 0.5)+
            geom_vline(xintercept = intercept, linetype = "dashed")+
            theme_classic()+
            labs(title = title, x = xlab, y=ylab)+
            scale_x_continuous(breaks = breaks)+
            scale_fill_manual(values=cancR_palette)+
            scale_color_manual(values=cancR_palette)

          savR(plot, paste0("Overall_", estimate_c), height = 80, formats =
c("svg", "pdf"))


           tab %>%flextable()%>%savR("Table_overall", table.width = 0.6)

            return(lst(tab, plot))

      }
      else {

         plots <-
            lapply(seq_along(unique(frame[[modifier_c]])), function(i){

               vals <- unique(frame[[modifier_c]])

                frame %>%filter(treat_prob == vals[i])%>%
```

```
                    ggplot(aes(x={{estimate}}, y=type, fill = type, color =
type))+
                    geom_boxplot(alpha = 0.5)+
                    geom_vline(xintercept = intercept[i], linetype =
"dashed")+
                    theme_classic()+
                    labs(title = title[i], x = xlab, y=ylab)+
                    scale_x_continuous(breaks = breaks, limits = limits)+
                    scale_fill_manual(values=cancR_palette)+
                    scale_color_manual(values=cancR_palette)

            })%>%
            collectR(ncol = 1, nrow = 4)

          tab %>%arrange(treat_prob)%>%flextable()%>%savR("Table_treatprob",
table.width = 0.6)

           savR(plots, paste0(estimate_c, "_treat_probs"), formats =
c("svg", "pdf"))

            return(lst(tab, plots))

      }


}
```

Appendix E: BREAST-AB Simulation.R

```
library(geepack)
library(lme4)
library(colorspace)
library(GLMMadaptive)
library(glmmTMB)
library(MASS)
library(miceadds)
library(flextable)
library(parallel)
library(doParallel)
library(foreach)
library(data.table)
library(tidyverse)
library(ggpubr)

source("sim_functions.r")

`%nin%` = Negate(`%in%`)

#Proportion of bilateral cases
bilat_prob = 0.27
#No patients
n = 1003

#Simulate dataframe
set.seed(1)
data <- bind_rows(lapply(1:n, function(i){

   #Laterality
   lat <- sample(c(1, 2), size = 1, replace=F, prob=c((1-bilat_prob),
bilat_prob))

    #Simulate covariates
    df <- data.frame(record_id = i)%>%
       slice(rep(1,lat))%>%
       mutate(site = as.character(sample(c(1:6), 1)),
              allocation = sample(c("Intervention", "Placebo"), size = lat,
replace=FALSE),
              right_left = sample(c("Right", "Left"), size = lat,
replace=FALSE),
              uni_bilat = ifelse(lat == 1, "Unilateral", "Bilateral"),
              immediate_delayed = sample(c("Immediate", "Delayed"), size =
lat, replace=TRUE, prob = c(0.85, 0.15)),
              age = rnorm(1, 50,10),
              bmi = sample(c("<18", "18-25", "25-30", ">30"), 1,
replace=FALSE),
              surgery = sample(c("expander", "dti"), lat, replace=TRUE),
              asa = as.character(sample(1:3, 1, replace=F, prob =
c(0.45,0.5,0.05))),
              indication = sample(c("therapeutic", "risk reducing",
"other"), lat, replace=T),
              plane = sample(c("subpectoral", "prepectoral", "dual plane",
"other"), lat, replace=T),
              bq_baseline = ifelse(allocation == "Intervention",
round(runif(1, 0,30),0), round(runif(1, 10,70),0)),
```

```
              bq_po1 = ifelse(allocation == "Intervention", round(runif(1,
10,50),0), round(runif(1, 10,60),0)),
              bq_po2 = ifelse(allocation == "Intervention", round(runif(1,
30,100),0), round(runif(1, 10,50),0)))

     #Simulate yes/no covariates with probabilites
     probs <- c(0.01, 0.10, 0.2, 0.5)
      vars <- c("radiotherapy", "smoking", "chemo", "mesh")

       for(v in seq_along(vars)){

          df <- df %>%
             mutate(!!sym(vars[v]):= sample(c("Yes", "No"), size = lat,
replace=FALSE, prob = c(probs[v], 1-probs[v])))

       }

       df
}))%>%
   factR(
      vars = c(allocation, right_left, uni_bilat, immediate_delayed, chemo,
smoking, surgery, indication, plane, mesh),
       num.vars = c(site, bmi,asa),
       reference = list("radiotherapy" = "No",
                        "smoking" = "No",
                        "chemo" = "No",
                        "mesh" = "No",
                        "allocation" = "Placebo"))

#Setup clusters
cl <- makeCluster(10)
doParallel::registerDoParallel(cl)
nsim = 14*4
tickR()
base <- rbindlist(foreach(i = seq(1364,1366),#seq(1,nsim),
        .packages = c("tidyverse", "data.table", "foreach", "geepack",
"lme4", "GLMMadaptive", "glmmTMB", "MASS", "miceadds")
        ) %do% {

  sim <- sim_events(
    data = data,
    bilat_prob = bilat_prob,
    event_prob = 0.10,
    corr_prob = 0.15,
    treat_prob = 0.5,
    seed = i)

  sim_extract(sim, models = c("GEE", "GLM", "GLMM_adaptive", "GLMM_TMB",
"GLMM_PQL"))%>%
    mutate(nsim = nsim)

        }) %>% arrange(type)

stopCluster(cl)

tockR()
```

```
savR(base, "base_df2", format = "rds")


#Run simulations on varying treatment effects
cl <- makeCluster(14)
doParallel::registerDoParallel(cl)
nsim = 10000
treatments <- c(0.5, 0.25, 0.1, 0)
tickR()

treatments_res <- rbindlist(foreach(s = seq_along(treatments)) %do% {

   cat(paste0("Current treatment: ", treatments[s], ", time: ", tickR()))

   res <- rbindlist(
     foreach(i = seq(1,nsim),
                                              .packages = c("tidyverse",
                                                            "data.table",
                                                            "foreach",
                                                            "geepack",
                                                            "lme4",
                                                            "GLMMadaptive",
                                                            "glmmTMB",
                                                            "MASS",
                                                            "miceadds"))
%dopar% {

                                                sim <- sim_events(
                                                  data = data,
                                                  bilat_prob = bilat_prob,
                                                  event_prob = 0.10,
                                                  corr_prob = 0.15,
                                                  treat_prob = treatments[s],
                                                  seed = i)

                                                  sim_extract(sim)%>%
                                                  mutate(nsim = nsim)

                                              }) %>% arrange(type)


    res

})
stopCluster(cl)

tockR()

#savR(treatments_res, "treatment_results", format = "rds")

#base <- readR("base_df.rds")
treatments_res <- readR("treatment_results.rds")

treatments_res <- treatments_res %>%
  mutate(type = ifelse(type == "GLMER", "GLMER_LME4", type))
```

```
treatments_res %>%
  filter(is.na(se)) %>%
  group_by(type) %>%
  count

tframe <-
  treatments_res %>%
  filter(!is.na(se)) %>%
  group_by(type, treat_prob) %>%
  mutate(nsim = n()) %>%
    ungroup()


#Treatment effect 50%
sim_results <-
  tframe %>%
  group_by(type, treat_prob) %>%
  summarise(or_mean = mean(or),
            or_sd = sd(or),
            psig = sum(pval < 0.05),
            nsim = first(nsim)) %>%
  mutate(bias = or_mean - treat_prob,
         emp_se = or_sd / sqrt(nsim),
         type1 = ifelse(treat_prob == 0, psig/nsim, NA),
         type1_MCSE = ifelse(treat_prob == 0, sqrt((type1*(1-type1))/nsim),
NA),
         type2 = ifelse(treat_prob != 0, psig/nsim, NA)) %>%
    ungroup() %>%
  select(type, nsim, treat_prob, or_mean, bias, emp_se, type1, type1_MCSE,
type2) %>%
    mutate(across(c(or_mean:type2), ~ round(.,4)),
           treat_prob = paste0(treat_prob*100, "%"),
           type = factor(type, levels = c("GEE", "GLM_robust",
"GLMM_Adaptive", "GLMM_TMB", "GLMER_LME4", "GLMM_PQL"),
                         )) %>%
    arrange(as.integer(type)) %>%
  flextable()



#plots
(plot <- ggarrange(plotlist=
lapply(seq_along(treatments), function(t) {

  tframe %>% filter(treat_prob == treatments[t]) %>%
    ggplot(aes(x=or, y=type, fill=type, color = type)) +
    geom_boxplot(alpha = 0.5) +
    coord_cartesian(xlim=c(log(0.01),log(5))) +
    scale_x_continuous(breaks = seq(-4,1)) +
    theme_classic() +
    geom_vline(xintercept = log(1-treatments[t]), linetype = "dashed") +
    scale_fill_manual(values = cancR_palette) +
    scale_color_manual(values = cancR_palette) +
    labs(title = paste0("log(OR), true treatment effect = ", round(log(1-
treatments[t]),2), " (", paste0(treatments[t]*100, "%"), ")"),
```

```
          x="Log(OR)",
          y="",
          color = "",
          fill = "")


}), common.legend = T, legend="right"))

savR(sim_results)


savR(plot,
     "sim_plot",
     formats = c("pdf", "jpg"))


writeLines(capture.output(sessionInfo()), "Tables and
Figures/sessionInfo.txt")









#Results
plotf(base,
```

```
       or,
       intercept = log(0.5),
       title = paste0("log(OR), true treatment effect = ",
round(log(0.5),2)),
       breaks = seq(0,-10,-0.5),
       xlab = "log(OR)")

plotf(base,
       se,
       intercept = 0,
       title = "Standard Errors",
       breaks = seq(0,3,0.25),
       xlab = "SE")


plotf(treatments_res,
       estimate = or,
       modifier = treat_prob,
       breaks = seq(0,-10,-0.5),
       limits = c(-1,1),
       intercept = log(1-treatments),
       xlab = "log(OR)",
       title = paste0("log(OR), true treatment effect = ", round(log(1-
treatments),2)))

plotf(treatments_res,
       estimate = se,
       modifier = treat_prob,
       breaks = seq(0,0.5, 0.1),
       limits = c(0,0.5),
       intercept = rep(0,4),
       xlab = "log(SE)",
       title = paste0("Standard Error, true treatment effect = ",
round(log(1-treatments),2)))

treatments_res %>%
   filter(treat_prob == 0)%>%
   mutate(fp = ifelse(pval<0.05, 1, 0))%>%
   group_by(type)%>%
   summarise(fp = sum(fp),
             n = n())%>%
   mutate(alpha = fp/n,
          mcse = sqrt((alpha*(1-alpha))/n))

treatments_res %>%
   filter(treat_prob == 0)%>%
   mutate(delta = or - log(1-treat_prob))%>%
   group_by(type)%>%
   summarise(mean = abs(mean(delta)),
             sd = sd(delta),
             n = n())%>%
   mutate(mcse = sd / sqrt(n))

#Power
treatments_res %>%
   filter(treat_prob > 0)%>%
```

```
mutate(ns = ifelse(pval > 0.05, 1, 0))%>%
group_by(type, treat_prob)%>%
summarise(type_2 = sum(ns, na.rm=T),
          total = n())%>%
mutate(power = 1-(type_2/total))
```

Appendix F: BREAST-AB Table shells.R

```
library(geepack)
library(lme4)
library(colorspace)
library(GLMMadaptive)
library(glmmTMB)
library(MASS)
library(geeasy)
library(cancR)

source("sim_functions.r")

#Proportion of bilateral cases
bilat_prob = 0.27
#No patients
n = 1003

#Simulate dataframe
set.seed(1)
data <- bind_rows(lapply(1:n, function(i) {

  #Laterality
  lat <- sample(c(1, 2), size = 1, replace=F, prob=c(bilat_prob,(1-
bilat_prob)))

  #Simulate covariates
df <- data.frame(record_id = i) %>%
    slice(rep(1,lat)) %>%
    mutate(site = as.character(sample(c(1:6), 1)),
           allocation = sample(c("Intervention", "Placebo"), size = lat,
replace=FALSE),
           right_left = sample(c("Right", "Left"), size = lat,
replace=FALSE),
           uni_bilat = ifelse(lat == 1, "Unilateral", "Bilateral"),
           immediate_delayed = sample(c("Immediate", "Delayed"), size = lat,
replace=TRUE, prob = c(0.85, 0.15)),
           age = rnorm(1, 50,10),
           bmi = sample(c("<18", "18-25", "25-30", ">30"), 1,
replace=FALSE),
           surgery = sample(c("expander", "dti"), lat, replace=TRUE),
           asa = as.character(sample(1:3, 1, replace=F, prob =
c(0.45,0.5,0.05))),
           indication = sample(c("therapeutic", "risk reducing", "other"),
lat, replace=T),
           plane = sample(c("subpectoral", "prepectoral", "other"), lat,
replace=T),
           bq_baseline = ifelse(allocation == "Intervention", round(runif(1,
0,30),0), round(runif(1, 10,70),0)),
           bq_po1 = ifelse(allocation == "Intervention", round(runif(1,
10,50),0), round(runif(1, 10,60),0)),
           bq_po2 = ifelse(allocation == "Intervention", round(runif(1,
30,100),0), round(runif(1, 10,50),0)))

#Simulate yes/no covariates with probabilites
probs <- c(0.01, 0.10, 0.2, 0.5)
vars <- c("radiotherapy", "smoking", "chemo", "mesh")
```

```
for(v in seq_along(vars)) {

      df <- df %>%
        mutate(!!sym(vars[v]) := sample(c("Yes", "No"), size = lat,
replace=FALSE, prob = c(probs[v], 1-probs[v])))

    }

  df
})) %>%
  factR(
    vars = c(allocation, right_left, uni_bilat, immediate_delayed, chemo,
smoking, surgery, indication, plane, mesh),
    num.vars = c(site, bmi,asa),
    reference = list("radiotherapy" = "No",
                     "smoking" = "No",
                     "chemo" = "No",
                     "mesh" = "No",
                     "allocation" = "Placebo"))


#Simulate events and add random event times with an exponential distribution
df <- sim_events(
  data = data,
  bilat_prob = bilat_prob,
  event_prob = 0.10,
  corr_prob = 0.15,
  treat_prob = 0.5,
  seed = 1)$data %>%
  mutate(t_event = round(rexp(n(), 0.05),2),
         t_event = ifelse(event == 1, t_event, 180))


t1p <-
  df %>%
  mutate(demographic = case_when(uni_bilat == "Unilateral" & allocation ==
"Placebo" ~ "Unilateral Placebo",
                                 uni_bilat == "Unilateral" & allocation ==
"Intervention" ~ "Unilateral Intervention",
                                 T ~ "Bilateral Placebo / Intervention"))
%>%
  group_by(record_id, demographic) %>%
  slice(1) %>%
  ungroup() %>%
  factR(demographic, levels = c("Unilateral Placebo",
                                "Unilateral Intervention",
                                "Bilateral Placebo / Intervention")) %>%

tablR(group = demographic,
      vars = c(age, bmi, site, chemo, smoking, asa),
      num.vars = c(site, bmi, asa),
      test = F,
      print=T,
      flextable=T,
      labs.headings = list("Patient Age, Yr" = "age",
```

```
                              "BMI, kg/m2" = "bmi",
                              "Trial Site" = "site",
                              "Chemotherapy" = "chemo",
                              "Smoking Status" = "smoking",
                              "ASA Class" = "asa"))

t1p %>% mutate(across(everything(), ~ ifelse(str_detect(., "%"),

ifelse(as.numeric(str_extract(., "\\d+\\.\\d+(?=(%))")) > 10,
                                                    str_replace(.,
"\\d{2,}\\.\\d*(?=(%))", as.character(round(as.numeric(str_extract(.,
"\\d{2,}\\.\\d*(?=(%))")),0))),
                                                    .)

                                                , .)))

savR(t1p, "Table1_Patient_Demographics",
     table.width = 1.8)

t1b <-
  df %>%
  mutate(recon_type = case_when(immediate_delayed == "Immediate" & surgery
== "dti" ~ "Immediate DTI",
                                immediate_delayed == "Immediate" & surgery
== "expander" ~ "Delayed Expander",
                                immediate_delayed == "Delayed" & surgery ==
"dti" ~ "Delayed DTI",
                                immediate_delayed == "Delayed" & surgery ==
"expander" ~ "Delayed Expander")) %>%
  tablR(group = allocation,
      vars = c(site, uni_bilat, radiotherapy, right_left, immediate_delayed,
recon_type, indication, plane, mesh),
      num.vars = site,
      print = T,
      flextable = T,
      levels = list("mesh" = c("No", "Yes"),
                    "plane" = c("subpectoral", "prepectoral", "other")))

savR(t1b,
     "Table1_Breast_Demographics",
     table.width = 1.5)

#Check for missing data
missR(df)

#Crude risks
risks <-
  df %>% group_by(allocation) %>%
    count(event) %>%
    pivot_wider(names_from = c(event), values_from = n) %>%
    rename(total = `0`,
           events = `1`) %>%
       mutate(risk = events/(events + total) * 100)

#Model for primary outcome
```

```
geeuni <- geeglm(event ~ allocation + site + immediate_delayed + uni_bilat +
radiotherapy, data=df, id=record_id, family="binomial",
corstr="exchangeable")
summary(geeuni)
exp(confint.default(geeuni))
#Model with treatment allocation omitted
gee_lrt <- geeglm(event ~ site + immediate_delayed + uni_bilat +
radiotherapy, data=df, id=record_id, family="binomial",
corstr="exchangeable")

exp_res <-
  paste0("adjusted OR = ",
         round(exp(summary(geeuni)$coefficients[2,1]),2),
         " (95%CI ",
         round(exp(confint.default(geeuni))[2,1],2),
         "-",
         round(exp(confint.default(geeuni))[2,2],2),
         "), ",
         pvertR(summary(geeuni)$coefficients[2,4]))

#Cumulative incidens plot
cuminc <- incidencR(df,
          t_event,
          event,
          group = allocation,
          time = 180,
          breaks = 30)

(cumincplot <- plotR(cuminc,
      time.unit = "days",
      contrast = "none",
      risk.col = F,
      print.est = F,
      linewidth = 0.8,
      y=15,
      se=F,
      x.title = "Days Since Randomization",
      y.title = "All-Cause Explantation (%)",
      table = "risk") +
  # annotate("text", x = 90, y=c(0.15,0.17), label =
paste0(as.character(cuminc$time_to_event$allocation),
  #                                                          " ",
  #
cuminc$time_to_event$quantile,
  #                                                          " (IQR ",
  #
cuminc$time_to_event$lower,
  #                                                          " - ",
  #
cuminc$time_to_event$upper,
  #                                                         ")"),
  #          hjust = "left",
  #          size = 5) +
  annotate("text", x=120, y=0.14, label = paste0("180-days event rate: ",
                                                 round(risks$risk[1],1),
                                                 "% vs. ",
```

```
                                                    round(risks$risk[2],1),
                                                    "%"),


                                                    hjust = "left", size = 5,
fontface = 2) +
  annotate("text", x=120, y=0.13, label = paste0("a",str_extract(exp_res,
"OR.*\\)")), hjust = "left", size = 5) +
  annotate("text", x=120, y=0.12, label = str_extract(exp_res, "p.*"), hjust
= "left", size = 5) +
  annotate("segment",
           x=cuminc$time_to_event$quantile,
           xend=cuminc$time_to_event$quantile,
           y=-0.002,
           yend=cuminc$plot_data$est[cuminc$plot_data$time %in%
cuminc$time_to_event$quantile][c(2,3)],
           linewidth = 0.8,
           linetype = "dotdash",
           color = cancR_palette[1:2]))


savR(cumincplot)



#Global interaction test
gee_interaction <- geeglm(event ~ allocation * (site + immediate_delayed +
uni_bilat + radiotherapy), data=df, id=record_id, family="binomial",
corstr="exchangeable")
gee_none <- geeglm(event ~ allocation + site + immediate_delayed + uni_bilat
+ radiotherapy, data=df, id=record_id, family="binomial",
corstr="exchangeable")

#Significance using Wald test comparing models with/without interaction
anova(gee_interaction, gee_none)

#Proceed only if global interaction test is p < 0.05
sg_vars <- c("bmi", "immediate_delayed", "smoking", "surgery",
"radiotherapy")
adj_vars <- c("site", "immediate_delayed", "uni_bilat", "radiotherapy")


#Sequential Wald tests comparing: y ~ var + allocation + covariates versus y
~ var + var:allocation + covariates
mods <- lapply(sg_vars, function(i) {

  form_interaction <- as.formula(paste0("event ~ ", i, " + ", paste0(i,
":allocation + ", collapse=""), paste0(adj_vars[adj_vars != i], collapse = "
+ ")))

  form_none <- as.formula(paste0("event ~ ", i, " + ",
paste0(adj_vars[adj_vars != i], collapse = " + ")))

  #mods[[i]]$model
  model_interaction <- geeglm(form_interaction, data=df, id=record_id,
family="binomial", corstr="exchangeable")
```

```
  model_none <- geeglm(form_none, data=df, id=record_id, family="binomial",
corstr="exchangeable")

  wald <- anova(model_interaction, model_none)


  lst(model = model_interaction, forms = c(form_interaction, form_none),
pval = wald[[3]])




}) %>% set_names(sg_vars)

#Extraction of results
subgroup <-
  lapply(seq_along(mods), function(m) {

  mod <- mods[[m]]$model
  nm <- names(mods[m])

  sum <- summary(mod)$coefficients

  indices <- which(str_detect(row.names(sum), ":allocation"))

  sum[indices,] %>%
    mutate(est = exp(sum[indices,1]),
           lower = exp(confint.default(mod))[indices, 1],
           upper = exp(confint.default(mod))[indices, 2],
           p.adj = `Pr(>|W|)`,
           pval = pvertR(`Pr(>|W|)`),
           opval = pvertR(mods[[m]]$pval),
           var = nm) %>%
    select(var, est, lower, upper, opval, pval, p.adj)




}) %>% bind_rows() %>%
    tibble::rownames_to_column("comp") %>%
    mutate(comp = str_remove_all(comp, ":allo.*"),
           comp = str_remove_all(comp, paste0(sg_vars, collapse="|")),
           order = row_number(),
           order_sep = case_when(var != lag(var) ~ 1,
                                 T ~ 0),
           order_sep = cumsum(order_sep),
           order = order + order_sep,
           order = 17-order,
           p.adj = pvertR(p.adj * n())) %>%
  group_by(var) %>%
  mutate(opval = ifelse(row_number() != 1, NA, opval))

#Headers
  labels <-
    subgroup %>% distinct(var, .keep_all=TRUE) %>% select(var, order) %>%
mutate(var = str_replace_all(str_to_title(var), "_", " "))
```

```
#Counting events for all subgroups stratified on allocation
  event.counts <-
    bind_rows(lapply(unique(subgroup$var), function(v) {
  df %>% group_by(allocation, !!sym(v)) %>% summarise(events = sum(event),
                                                      n = n()) %>%
      mutate(count = paste0(events, "/", n)) %>%
      select(allocation, !!sym(v), count) %>%
     pivot_wider(names_from=allocation,
      values_from = count) %>%
      mutate(var = v) %>%
      rename(comp = !!sym(v))



  }))

  #Final plot data
  plot_data <- left_join(subgroup, event.counts, by = c("var", "comp"))

p2 <-
  ggplot(plot_data, aes(x=est, y = order)) +
  geom_errorbar(aes(xmin=lower, xmax=upper), color = cancR_palette[2], width
= 0.2, linewidth = 0.8) +
  geom_point(size = 5, shape = 22, fill = cancR_palette[2], color = "white")
+
  annotate("text", x=-2.8, y = plot_data$order, label = plot_data$comp,
hjust="left") +
  annotate("text", x=-3, y=labels$order+1, label = labels$var, size = 5,
hjust="left", fontface = 2) +
    annotate("text", x=-0.4, y=plot_data$order, label =
plot_data$Intervention) +
    annotate("text", x=-1.3, y=plot_data$order, label = plot_data$Placebo) +
    annotate("text", x=c(-0.4, -1.3), y=max(plot_data$order)+2, label =
c("Intervention", "Placebo"), size = 5, fontface = 2) +
  annotate("text", x=2.5, y=plot_data$order, label =
paste0(round(plot_data$est,2),
                                                          " (",

round(plot_data$lower,2),
                                                          "-",

round(plot_data$upper,2),
                                                          ")"), hjust =
"center") +
  annotate("text", x=2.5, y=max(plot_data$order) +2, label = "Adjusted OR,
95%CI", fontface = 2, size = 5, hjust="center") +
    annotate("text", x=4.2, y=max(plot_data$order) + 2, label = "P-Value for
Interaction", fontface = 2, size = 5, hjust="center") +
    annotate("text", x=4.2, y=plot_data$order, label = plot_data$opval) +
  coord_cartesian(xlim=c(-3,5)) +
  scale_x_continuous(breaks = seq(0,2,0.25)) +
  theme_classic() +
  theme(axis.line = element_blank(),
        axis.text.y = element_blank(),
        axis.ticks = element_blank(),
```

```
        axis.text.x = element_text(vjust = 7)) +
  annotate("segment", x=1, xend=1, y=0, yend=max(plot_data$order)+1,
linewidth = 1) +
  annotate("segment", x=0, xend=2, y=0, yend=0, linewidth = 1) +
  labs(x="Treatment effect, adjusted OR", y="")

savR(p2, height = 80, format = "pdf")
```

Appendix G: BREAST-AB R session info

```
R version 4.4.3 (2025-02-28 ucrt)
Platform: x86_64-w64-mingw32/x64
Running under: Windows Server 2022 x64 (build 20348)

Matrix products: default


locale:
[1] LC_COLLATE=Danish_Denmark.utf8  LC_CTYPE=Danish_Denmark.utf8
LC_MONETARY=Danish_Denmark.utf8 LC_NUMERIC=C
[5] LC_TIME=Danish_Denmark.utf8

time zone: Europe/Copenhagen
tzcode source: internal

attached base packages:
[1] parallel  stats     graphics  grDevices utils     datasets  methods
base

other attached packages:
 [1] ggpubr_0.6.2       lubridate_1.9.4    forcats_1.0.1      stringr_1.6.0
dplyr_1.1.4        purrr_1.2.1
 [7] readr_2.1.6        tidyr_1.3.2        tibble_3.3.1       ggplot2_4.0.1
tidyverse_2.0.0    data.table_1.18.0
[13] doParallel_1.0.17  iterators_1.0.14   foreach_1.5.2
flextable_0.9.10   miceadds_3.18-36   mice_3.19.0
[19] MASS_7.3-65        glmmTMB_1.1.14     GLMMadaptive_0.9-7
colorspace_2.1-2   lme4_1.1-38        Matrix_1.7-4
[25] geepack_1.3.13

loaded via a namespace (and not attached):
 [1] Rdpack_2.6.4            DBI_1.2.3               gridExtra_2.3
sandwich_3.1-1          rlang_1.1.7
 [6] magrittr_2.0.4          multcomp_1.4-29         otel_0.2.0
matrixStats_1.5.0       compiler_4.4.3
[11] mgcv_1.9-4              systemfonts_1.3.1       vctrs_0.6.5
pkgconfig_2.0.3         shape_1.4.6.1
[16] fastmap_1.2.0           backports_1.5.0         labeling_0.4.3
utf8_1.2.6              rmarkdown_2.30
[21] tzdb_0.5.0              nloptr_2.2.1            ragg_1.5.0
xfun_0.55               glmnet_4.1-10
[26] jomo_2.7-6              uuid_1.2-1              pan_1.9
broom_1.0.11            R6_2.6.1
[31] stringi_1.8.7           RColorBrewer_1.1-3      car_3.1-3
boot_1.3-32             rpart_4.1.24
[36] numDeriv_2016.8-1.1     estimability_1.5.1      Rcpp_1.1.1
knitr_1.51              zoo_1.8-15
[41] timechange_0.3.0        splines_4.4.3           nnet_7.3-20
tidyselect_1.2.1        abind_1.4-8
[46] rstudioapi_0.17.1       effects_4.2-4           TMB_1.9.19
codetools_0.2-20        lattice_0.22-7
[51] withr_3.0.2             S7_0.2.1                askpass_1.2.1
coda_0.19-4.1           evaluate_1.0.5
[56] survival_3.8-3          survey_4.4-8            zip_2.3.3
xml2_1.5.1              pillar_1.11.1
```

```
[61] carData_3.0-5          rsconnect_1.7.0        reformulas_0.4.3.1
insight_1.4.4           generics_0.1.4
[66] hms_1.1.4              scales_1.4.0           minqa_1.2.8
xtable_1.8-4            glue_1.8.0
[71] gdtools_0.4.4          emmeans_2.0.1          tools_4.4.3
ggsignif_0.6.4          mvtnorm_1.3-3
[76] cowplot_1.2.0          grid_4.4.3             mitools_2.4
rbibutils_2.4           nlme_3.1-168
[81] Formula_1.2-5          cli_3.6.5              textshaping_1.0.4
officer_0.7.2           fontBitstreamVera_0.1.1
[86] gtable_0.3.6           rstatix_0.7.3          digest_0.6.39
fontquiver_0.2.1        TH.data_1.1-5
[91] farver_2.1.2           htmltools_0.5.9        lifecycle_1.0.5
mitml_0.4-5             fontLiberation_0.1.0
[96] openssl_2.3.4
```