Statistical Analysis Plan for PROTECT Randomized Controlled Trial

Resources

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.

Section 1: Administrative Information

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Revision Control

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SAP Version Number being approved: Version 1.0 (1 March 2026).

Role	**Name**	**Date**	**Signature**
Trial Principal Investigator	Bolette Skjødt Rafn	March 1st, 2026	

Abbreviations and Definitions

BCRL	Breast cancer-related lymphedema
PS	Prospective surveillance (model), (intervention group)
BIS	Bioimpedance Spectroscopy
UC	Usual care (control group)
LR	Low-risk (cohort)
NRS	Numeric Rating Scale
L-DEX	Lymphedema Index
CDT	Complex Decongestive Therapy
EQ-5D	EuroQol 5-Domaine Questionnaire
HRQoL	Health-Related Quality of Life measured by the EQ-5D
QuickDASH	Quick Disabilities of Arm, Shoulder & Hand
NACT	Neoadjuvant Chemotherapy
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30
REDCap	Research Electronic Data Capture
BMI	Body Mass Index

Section 2: Introduction

Background and rationale

Breast cancer-related lymphedema (BCRL) is a progressive condition caused by damage to the lymphatic system(1) and affects one in three patients following axillary lymph node dissection.(2)

Clinical guidelines (3–7) recognize the importance of early detection and management of BCRL to allow simpler treatment and better clinical outcomes and highlight the need for research into development and testing of programs that enable surveillance of survivors at-risk.(6–8)

Prospective surveillance and early management (PS) programs are suggested to improve early detection and treatment of BCRL and prevent progression of the condition.(9)

Hospital-based PS programs afforded by therapists present with barriers related to patient access and participation and barriers related to program implementation costs (e.g., trained healthcare professionals, sophisticated measurement tools to identify BCRL, and the associated cost of long-term surveillance for a large at-risk population).

Self-management PS using patient reported at home arm circumference measurements demonstrated to be feasible, reliable, and valid. Self-management PS supplementary to hospital-based PS has the potential to increase the reach and equity of access to surveillance programs.

Objectives

This trial examines if a self-managed PS program (intervention) reduces the prevalence of chronic BCRL (outcome) compared to usual care (comparator).

Section 3: Study Methods

Trial design

This trial is:

a) Multicenter (Copenhagen University Hospital-Rigshospitalet, Herlev-Gentofte Hospital, Zealand's University Hospital-Roskilde, Odense University Hospital, and Aarhus University Hospital),
b) Single-blinded (blinded 24M follow-up assessor),
c) Two-arm randomized controlled superiority trial (PS intervention groups vs. US control group)
d) 24-month follow up (outcome, chronic BCRL prevalence)

Randomization

Randomization occurred approximately one month after baseline data collection and primary breast cancer surgery, upon publication of pathology results showing the number of lymph nodes removed.

We used computer-based randomization (REDCap) and stratified by hospital. Participants with ≥6 axillary lymph nodes removed were randomized 1:1 to either PS-group or US-group.

Participants with <6 axillary lymph nodes removed are allocated to the low-risk (LR) cohort.

Sample size

Sample size calculations were targeted to have 80% statistical power in a prospective analysis followed by a log-rank test with 5% significance level. We hypothesize that PS would reduce the prevalence of chronic BCRL by 50% compared to UC.(9) A prevalence of BCRL of 30% in the UC group is anticipated,(2) and 15% loss to follow-up. On this basis, 250 randomized participants are needed.

Superiority will be claimed upon a statistically significant relative risk reduction of BCRL in the PS group compared to the UC group.

Statistical interim analysis and stopping guidance

No interim analyses are planned. This study does not have early stopping rules.

Timing of final analysis

Final analysis will be performed after all participants have reached the 24-months timepoint and completed final assessments.

Timing of outcome assessments

Table 1 details the timing of outcome assessments. The primary outcome is assessed at 24-months. Throughout the trial period secondary and explorative outcomes are collected at baseline, at 3-months intervals for PS-group (i.e., baseline, 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-months), and at 6-months intervals for the UC-group and LR-cohort (i.e., baseline, 6-, 12-, 18-, and 24-months).

Table 1. Timing of outcome assessments

Assessments	Baseline	Post-NACT*	3M			6M			9M			12M			15M			18M			21M			24M (Primary Outcome Endpoint)		
			PS	UC	LR	PS	UC	LR	PS	UC	LR	PS	UC	LR	PS	UC	LR	PS	UC	LR	PS	UC	LR	PS	UC	LR
L-Dex	X	X																						X	X	X
BCRL diagnosis/treatment[1]			X			X	X	X	X			X	X	X	X			X	X	X	X			X	X	X
HRQoL[2]	X					X	X	X				X	X	X				X	X	X				X	X	X
Arm function[3]	X					X	X	X				X	X	X				X	X	X				X	X	X
Emotional functioning[4]	X					X	X	X				X	X	X				X	X	X				X	X	X
Body composition (BIS)	X	X																						X	X	X

Abbreviations: PS = Prospective surveillance and early management group. UC = Usual Care. LR = Low-risk cohort. BIS = Bioimpedance Spectroscopy. BCRL = Breast Cancer-Related Lymphedema. NACT = Neoadjuvant Chemotherapy. HRQoL = Health-Related Quality Of Life Measured

[1]Self-reported if BCRL has occurred and time of initiation of treatment.

[2]HRQoL measured by the EQ-5D.

[3]Arm function measured by the QuickDASH.

[4]Emotional functioning measured by the subscale from the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) using items Q21, Q22, Q23, Q24.

***** This is offered only to participants who receive NACT (6-9 months).

Section 4: Statistical Principals

Confidence intervals and P values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

All confidence intervals will be 95% confidence intervals.

Adherence and protocol deviations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally assigned, regardless of their adherence to their assigned treatments.

No adherence thresholds will be specified for PS-intervention. Table 2 presents how this information will be reported.

Table 2. Adherence to intervention

PS Component	Description	Adherence Threshold	Other indicators
Home-based self-reported bilateral arm circumference measurements	Complete home-based self-reported bilateral arm circumference measurements at 3-months intervals (3-, 6-, 9-, 12-, 15-, 18-, and 21-months, excluding baseline and 24-months measurements which are hospital-based), a total of 7 arm circumference measurements.	No	The proportions (number and percentage) of PS-group participants completing the (self-reported) arm circumference measurements will be reported as mean and standard deviation (of the 7 measurements periods).
Off-the-Shelf BCRL treatment	Wear an off-the-shelf compression sleeve for a prescribed number of hours per day, for a period of 4 weeks or until their follow up appointment	No	The proportions (number and percentage) of PS-group participants (a) referred to lymphedema specialist (BIS≥7 points), (b) diagnosed by lymphedema therapist, (c) treated for BCRL by off-the shelf BCRL compression sleeve, (d) use of prescribed compression garment, and (e) adverse events related to use of compression garment.

A protocol deviation is an unplanned action or process that departs for the approved study protocol. A deviation is usually identified retrospectively (after the event occurred). Study team was tasked to keep a log of all deviations to record, assess, and develop corrective actions that occur during the conduct of the research study. Deviations are/were assessed in the context of the protocol.

Major deviations for protocol may constitute serious noncompliance that may adversely affect (1) the rights of the participants, (2) the welfare of participants, or (2) the scientific integrity of the study.

Any protocol deviations (if they occur), including errors applying inclusion/exclusion criteria and/or administration of the wrong intervention will be summarized in a separate document. Randomization errors resulting from these errors will be handled according to recommendations.(10)

Analysis populations

The primary analysis will be based on the principle of intention-to-treat (ITT), whereby participants are included in the groups to which they were originally randomized, regardless of their adherence to their assigned treatments (regardless of missing data, lost to follow-up, or adherence to the intervention).

Section 5: Trial Population

Screening data

Data pertaining to participant screening and eligibility assessment will be collected and summarized. A CONSORT flow diagram will be used.(11) The following summaries will be presented in text and/or flow diagram: time frame for recruitment, the number of patients screened, the number of patients recruited, the number of screened patients not recruited, and the reasons for non-recruitment.

Eligibility

Trial inclusion and exclusion criteria are described in the study protocol as follows:

Inclusion criteria:

a) 18 years;
b) planned surgery for breast cancer;
c) understands Danish.

Exclusion criteria:

a) previous surgery for breast cancer;
b) preexisting lymphedema;
c) pacemaker;
d) pregnancy;
e) conditions known to cause swelling (i.e. thrombosis in the arms).

Reasons for exclusion will be summarized in the CONSORT flow diagram.(11)

Recruitment

A CONSORT flow diagram (11) will be used to describe the number of people enrolled, randomized, allocated to each treatment group, lost to follow up (including reasons) and analyzed.

Withdrawal/follow-up

Losses to follow-up (including reasons) will be summarized in the CONSORT flow diagram (11) by treatment group.

Feasibility will be evaluated using the following:

1. Recruitment rate

We define recruitment rate as

b. proportion of eligible participants who agreed to take part in the study (eligible, invited, written consent)/number of eligible participants (eligible and invited)).(12)

2. Attrition rate (overall and each separate treatment group)

We define attrition rate as the proportion of participants at defined study points who discontinued the intervention (voluntary withdrawal), were lost to follow-up (no 24 month data), or participant death calculated as the total number of participants that withdrew (numerator)/number of participants randomized (denominator)) (12)

If a participant withdraws from the study, the nature, timing of, and reasons for withdrawal will be described (provided the participant responds to contact made by the research team).

Any data provided up to the point of withdrawal will be analyzed in accordance with intention-to-treat analyses.

Baseline patient characteristics

Baseline characteristics will be summarized by treatment group (PS-group and UC-group) and presented in Table 1: Baseline characteristics.

These include:

- Demographics: gender, age, height, weight, BMI, BMI classification,
- Socioeconomics: education, income, living situation, employment
- Comorbidities: smoking status, chronic illness, selected comorbidities (1-14)
- Cancer-related variables: stage, side of operation, type of surgery, lymphatic system surgery, lymph nodes removed, lymph nodes positive, chemotherapy, radiation therapy, endocrine therapy

Baseline characteristics will be summarized as appropriate (means and standard deviations for continuous variables that appear to be distributed approximately symmetrically, medians and interquartile ranges for other continuous variables, counts and percentages for categorical variables) in Table: Baseline characteristics. Tests of statistical significance will not be reported for comparing baseline characteristics of treatment groups; rather the clinical importance of any imbalance will be noted.

Table: Baseline characteristics

	Group	
	PS-group	UC-group
	Mean (SD), Median (IQR), n (%)	Mean (SD), Median (IQR), n (%)
Demographics **Female** **Age** **BMI** **BMI classification** **Underweight** **Normal Weight** **Overweight** **Obese**		
Socioeconomic **Education** **Income** **Living Situation** **Employment**		
Health Literacy		
Comorbidities **Smoking Status** **Chronic Illness** **Selected Comorbidities**		
Cancer Stage & Treatment **Stage** **Side of Operation** **Type of Surgery** **Lymphatic System Surgery** **Lymph Nodes Removed** **Lymph Nodes Positive** **Chemotherapy** **Radiation Therapy** **Endocrine Therapy**		

Outcome variables will be presented in a separate table. Table: Outcomes will provide summaries of baseline levels of primary and secondary outcomes and 24-months follow-up and compare these characteristics between two groups. T-tests will be used to compare continuous characteristics between these groups, and chi-squared tests will be used to compare categorical characteristics.

Table: Outcomes

	PS-group (n=)			**UC-group (n=)**			
	Mean (SD), Median (IQR), n (%)		p-value*	Mean (SD), Median (IQR), n (%)		p-value*	p-value**
	Baseline	24M		Baseline	24M		
Primary Outcome **Lymphedema (yes)**							
Secondary Outcomes **Time to diagnosis (days/months)** **Time to treatment (days/months)** **HRQoL (EQ-VAS, 0-100)** **Arm Function (QuickDASH, 0-100)**							
* Within Group Comparison ** Between Group Comparison							

A descriptive table (Table: Lymphedema assessment for at-risk arm) including the variable below will made available as supplementary material.

- L-Dex baseline, L-Dex 24-months
- Arm volume baseline, arm volume 24-months
- BCRL symptoms 24-months
- BCRL diagnosis self-reported (UC group)
- BCRL assessment and treatment (PS group)

Table: Lymphedema Assessments for at-risk arm

	PS-group (n=)			**UC-group (n=)**			
	Mean (SD), Median (IQR), n (%)		p-value*	Mean (SD), Median (IQR), n (%)		p-value*	p-value**
	Baseline	24M		Baseline	24M		
L-Dex **Arm volume (ml)** **BCRL symptoms (0-10)** **BCRL diagnosis** **BCRL treatment**							
* Within Group Comparison ** Between Group Comparison							

A descriptive table (Table: Exploratory outcomes) including exploratory variable will be made available as supplementary material.

Table: Explonatory outcomes

	PS-group (n=)			**UC-group (n=)**			
	Mean (SD), Median (IQR), n (%)		p-value*	Mean (SD), Median (IQR), n (%)		p-value*	p-value**
	Baseline	24M		Baseline	24M		
Body Composition **Fat Mass (kg, %)** **Skeletal Muscle Mass (kg, %)** **Emotional Functioning** **Raw Score** **EF Score** **Item score** **Q21. Did you feel tense?** **Q22. Did you worry?** **Q23. Did you feel irritable?** **Q24. Did you feel depressed?**							
* Within Group Comparison ** Between Group Comparison							

Section 6: Analysis

Outcome definitions

Primary outcome

The primary outcome is the prevalence of chronic BCRL at 24M, a binary variable (yes/no), The primary outcome variable is not available in the existing data set in REDCap. This primary variable will be created using to existing variable: [BIS change] from baseline to 24-months (BIS 24-months minus BIS baseline) and [BIS 24-months] (BIS at 24-month) as follows:

- The value of "yes" will be assigned when the value of at least one of the two BIS variables is over a predefined cut-off (threshold), i.e., [BIS change] ≥ +10 points OR [BIS 24-months] ≥ +10 points, which is outside of manufacturer's specified the normal range ±10, and indicates lymphedema.
- The value "no" will be assigned when both primary outcomes are below the predefined cut-off, e.g., [BIS change] <+10 points AND [BIS 24-months] within the normal range ±10 (-10 to +10) points.

Secondary outcome

1. Time-To-Treatment

- Time-to-treatment is a time-to-event outcome and denotes time from primary surgery to BCRL treatment initiation.
- For PS-group, this will be calculated as the time from surgery using the variable "date of primary surgery" ([dato_for_operation]) to first elevated L-DEX which triggers immediate treatment using the variables "date of lymphedema assessment" and "compression garment delivered" or "compression garment ordered" ([dato_bcrl_assessment] AND ([compression_garment] OR [order_sleeve])
- For UC-group and LR-cohort, this will be calculated as the time from surgery using the variable "date of primary surgery" ([dato_for_operation]) to BCRL diagnosis using the variables "date of lymphedema assessment" and "date of lymphedema" ([date_bcrl_dx_con_mXX]) and [date_bcrl_tx_con_mXX])
- Time-to-treatment assumes that BCRL diagnosis triggers same day BCRL treatment initiation. If BCRL diagnosis and treatment occur on distinct dates, i.e., treatment is delayed by ≥30 days from diagnosis, a separate time-to-diagnosis outcome will also be calculated, analyzed, and reported.

2. Health-Related Quality of Life (HRQoL)

- Health-Related Quality of Life is measured by the EuroQol 5-Domaine Questionnaire (13,14) at 6-, 12-, 18-, and 24-months.

- EQ-5D-5L
    - Domains: MOBILITY (walking about), LOOKING AFTER MYSELF, DOING USUAL ACTIVITIES (for example, going to school, hobbies, sports, playing, doing things with family or friends), HAVING PAIN OR DISCOMFORT, FEELING WORRIED, SAD OR UNHAPPY
    - Health status levels: LEVEL 1: indicating no problem, LEVEL 2: indicating a little bit of a problem, LEVEL 3: indicating some problems, LEVEL 4: indicating a lot of problems, LEVEL 5: indicating cannot/extreme problems.(15)
    - The EQ-5D-5L health states range from 11111 (corresponding to 'full health', i.e. no problem on any of the EQ-5D dimensions) to 55555 (corresponding to the worst health state, i.e. maximum problems on all the EQ-5D dimensions).(16)
    - requires a transformation in the data set to make profile variable
- EQ VAS a 0–100 scale on which the respondent is asked to indicate their current health. The bottom endpoint is labelled 0 (worst imaginable health state), and the top endpoint is labelled 100 (best imaginable health state).(16)

3. Arm Function

- Measured by the QuickDASH Questionnaire(17) at 6-, 12-, 18-, and 24-months. "The *Quick*DASH is a shortened version of the DASH Outcome Measure. [...] the *Quick*DASH uses 11 items [the disability/symptom section] to measure physical function and symptoms in people with any or multiple musculoskeletal disorders of the upper limb [scored 1-5]."(18) "At least 10 of the 11 items must be completed for a score to be calculated. The assigned values for all completed responses are simply summed and averaged, producing a score out of five. This value is then transformed to a score out of 100 by subtracting one and multiplying by 25. This transformation is done to make the score easier to compare to other measures scaled on a 0-100 scale. A higher score indicates greater disability."(19)
    - Requires a transformation in the data set

Explorative outcomes

Explorative outcomes are:

1. Body composition analysis:

- Skeletal Muscle Mass (SMM) is measured by BIS at baseline and 24-months. SMM is reported in kg (absolute value). The relative value (%) can be estimated using total body weight (kg) ((skeletal muscle mass / total body weight)*100).
- Fat Mass is measured by BIS at baseline and 24-months. FM is reported in kg (absolute value). The relative value (%) can be estimated using total body weight (kg) ((fat mass / total body weight)*100)
- Body composition analysis will include:
    a) baseline to post- neoadjuvant chemotherapy (NACT) for participants who receive NACT; and
    b) baseline to 24 months post-surgery for all participants.

2. Emotional Functioning (EF)

- Measured by the subscale from the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)(13) at baseline, 6-, 12-, 18-, and 24-months
    - It is scaled to range from 0 to 100, with a high score indicating high emotional functioning(20)
    - No Missing score (20)
        - RawScore = (Q21 + Q22 + Q223 + Q24)/4
        - EF score = {1-(RawScore-1)/3}*100
    - Missing score (20)
        - RawScore = (Q21 + NA + Q223 + Q24)/3
        - EF score = {1-(RawScore-1)/3}*100
- Requires a transformation in the data set

Analysis methods

For primary outcomes

The binary outcomes of chronic BCRL (yes/no) at 24-months will be compared between groups (PS-group vs UC-groups) using risk differences (attributable risk) and risk ratios calculated after fitting log-binomial regression models (unadjusted model) and adjusting for stratification variable (adjusted model). (Table 3)

Should the log-binomial regression models fail to converge, logistic regression models adjusting for the same variables will be fit, with results reported as odds ratios, risk ratios and risk differences, calculated from fitted logistic regression models.

For secondary outcomes

Continuous outcome variables will be assessed using linear regression modeling. Time-to-treatment of lymphedema outcomes will use the Kaplan-Meier method, use the log-rank test to compare time to event between groups, and fit a Cox proportional hazards regression model (crude/unadjusted) adjusting for stratification variables (adjusted model) and checking for proportional hazards assumption.(21)

Repeated measure outcomes (i.e., arm function, health-related quality of life) will be assessed using Generalized Linear Mixed-Effects Models (GLMM) (22) Both unadjusted model and adjusted for stratification variables will be reported. (Table 3)

As described above, analyses will be conducted adjusting the stratifying variable (hospital/site). If necessary, secondary analyses will additionally include baseline covariates that appear to be unbalanced between treatment groups (see sensitivity analyses below).

We will test and validate the underlying assumptions behind all statistical models.(23)

In 2023, following an *Urgent Field Safety Notice* by Impedimed® regarding the validity of L-Dex bilateral arm assessment, the bilateral assessment function was deactivated. (24) This instrumentation update subsequently impacted the assessment of the primary outcome in participants operated for bilateral breast cancer. To account for this measurement validity issue, we plan to do a sensitivity analysis excluding all participants operated for bilateral breast cancer across all sites.

No subgroups analyses are planned. (Table 3)

Table 3. Analysis methods

	Instrument of assessment	Timing of assessment	Analysis method
Primary			
Chronic BCRL (yes/no) binary	BIS (Sozo)	24-months	Log-binomial and logistic regression crude/unadjusted and adjusting for stratification
Secondary			
Time-to-treatment (days) (continuous)	Clinician reported	Continuously during the intervention period	Kaplan-Meier method, Cox proportional hazards model; crude/unadjusted and adjusting for stratification
HRQoL (VAS 0-100 (continuous)	PRO	Baseline, 6-, 12-, 18-, 24-month	Generalized Linear Mixed-effects Model (GLMM); crude/unadjusted and adjusting for stratification
Arm function (scale 0-100) (continuous)	PRO	Baseline, 6-, 12-, 18-, and 24-months	Generalized Linear Mixed-effects Model (GLMM); crude/unadjusted and adjusting for stratification
Exploratory			
Body composition	BIS	Baseline to post-NACT, Baseline to 24months	No statistical analysis planned; exploratory study protocol and/or SAP will be reported separately
Emotional functioning	PRO	Baseline, 6-, 12-, 18-, and 24-months	No statistical analysis planned; exploratory study protocol and/or SAP will be reported separately

Missing data

All participants will be followed from time of inclusion until death or end of follow-up, whichever comes first. The occurrence of BCRL will be treated as the main event of the analysis. Participants who die will be censored out of the outcome analysis, while multiple imputation will be used to obtain data for participants who discontinue the trial prior to final assessment.

If more than 5% of participants are missing the outcome data, we will assess missing data mechanisms, i.e., missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR), to identify if missingness is independent of the data (the unobserved missing value themselves). If data are MAR, we will use multiple imputation to handle the missing data. (21)

Multiple imputation will be performed using the Multivariate Imputation by chained Equations (MICE) method. This method predicts one variable's missing value (outcome) by using the other value of the same variable (predictors). The method is iterative as it moves to the next missing value and repeats the prediction algorithm.(21) We will utilize predictive mean matching for continuous variables, logistic regression for binary variables, multinomial (polytomous) logistic regression for unordered (nominal) categorical variables, and ordinal (proportional odds) logistic regression for ordered categorical variables.(21)

Additional analyses

A separate SAP will be completed prior to any additional exploratory data analysis.

Harms

Side effect from off-the-shelf compression sleeve provided to PS-group will be reported. Non-severe side effects may include itching, skin irritation, hand swelling, discomfort/tightness, pain, allergic reaction, and bacterial and fungal infection.(25,26) Severe side effects may include soft tissue damage or necrosis, nerve damage, arterial impairment, venous thromboembolism, and cardiac decompression.(25,26)

Data on potential harms from BCRL treatment delivered to UC participants as part of usual care was not collected.

Statistical software

Statistical analyses will be performed using RStudio statistical software.

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