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Impact of a compression garment, on top of the usual care, in breast cancer patients with early disturbance of the lymphatic transport: protocol of a randomized controlled trial.

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ABSTRACT

Introduction

Breast-cancer related lymphedema (BCRL) is a common phenomenon. When lymphedema is diagnosed late, options for treatment are diminished. Therefore, early diagnosis and treatment are very important to alter the potential deleterious evolution. Lymphofluoroscopy visualizes the superficial lymphatic architecture in detail, giving the opportunity to detect a disturbance in the lymphatic transport (i.e. dermal backflow) before the lymphedema is clinically visible.

The main objective is to investigate if there is an additional effect of a compression garment on top of the usual care (i.e. information and exercises) in patients with early disturbance of the lymphatic transport after breast cancer treatment. Development of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy is investigated.

Methodology

All patients scheduled for breast cancer surgery with unilateral axillary lymph node dissection or sentinel node biopsy in the Multidisciplinary Breast Clinic of the University Hospitals Leuven are being considered. Patients are assessed before surgery and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively. At each visit a clinical assessment is performed determining the volume difference between both arms and hands (through circumference measurements and water displacement), the water content, the extracellular fluid, the pitting status and the skinfold thickness. Quality of life questionnaires are filled in. At each visit a lymphofluoroscopy is performed as well. When a disturbance of the lymphatic transport is seen on lymphofluoroscopy, without the presence of clinical lymphedema, the patient is randomized in either a control group receiving usual care or a preventive treatment group receiving usual care and a compression garment (whether or not combined with a glove).

Conclusion

The investigators hypothesize that development of clinical BCRL can be prevented and/or the dermal backflow can be stabilized or improved, if a preventive treatment with compression garment is started in the early phase of disturbance.

SUMMARY

Early diagnosis and treatment is very important to alter the normal evolution of BCRL.

Lymphofluoroscopy and clinical measurements are performed at regular times after the surgery for breast cancer.

Lymphofluoroscopy gives the opportunity to detect a disturbance in the lymphatic transport before the lymphedema is clinically visible.

When an early disturbance is seen, patients are randomized into two groups.

The investigators hypothesize that development of clinical BCRL can be prevented and/or the dermal backflow can be stabilized or improved, if a preventive treatment with compression garment is started in the early phase of disturbance.

Key words: Lymphedema, clinical measurements, ICG lymphofluoroscopy, near-infrared fluorescence, diagnostic imaging, early detection

INTRODUCTION

Lymphedema is a chronic and debilitating disease caused by imbalance between lymph production and lymph transport. It reduces patient's quality of life by limb enlargement but also by other physical and psychosocial problems, e.g. decreased mobility, recurrent infections, stress and decreased ability to perform occupational activities.[1,2]

Breast cancer-related lymphedema (BCRL) is a secondary lymphedema of the upper limb that can occur after treatment for breast cancer. Incidence of BCRL vary in literature, especially since the introduction of less invasive techniques such as sentinel node procedures and radiotherapy. According to a review of DiSipio et al., the incidence of arm lymphedema was about four times higher in women who had an axillary lymph node dissection (19.9%) than after sentinel lymph node biopsy (5.6%).[4,5] A study by Rockson et al. suggested that in almost 75% of the cases, lymphedema is established within the first year after breast cancer treatment.[6] A volume difference between both limbs of 5 to 10% is normally used to define clinical lymphedema [4,7]

Lymphedema can progress from a soft pitting edema to a hard fibrotic or soft fatty and non-pitting edema because of lipogenesis, fibrosis, inflammation, lymphangiogenesis and immunosuppression. [8,9] There is no consensus concerning the best measuring tool to detect the development of BCRL.[10,11] Volume increase of the limb can be assessed with circumference measurements[12] or with the water displacement method.[13,14] A relative volume change between both arms is used, comparing preoperative measurements between the affected arm and the healthy arm, to the postoperative measurements.[7] In addition, the increase of water content in the edematous limb can be assessed by the pitting test,[15] by measuring the extracellular fluid (bioelectrical impedance spectroscopy)[16] or by measuring the water content of the skin (tissue dielectric constant).[17,18] Measurement of the skinfold thickness (Stemmer sign) can be performed, which is the typical sign for lymphedema.[19]

Historically lymphangiography has been the technique to image the lymphatic system. This technique is difficult to perform and has become obsolete.[20] Lymphoscintigraphy has replaced lymphangiography and became the new standard for imaging the lymphatic system. With lymphoscintigraphy a radionuclide (^{99m}Tc-labeled tracer) is injected and followed by sequential gamma imaging.[21,22] This technique not only provides dynamic imaging of the lymphatics and the lymph nodes, but also provides semi-quantitative data of radionuclide transport and lymph node absorption. Near-infrared fluorescence imaging or lymphofluoroscopy is another minimally invasive technique. The injection of indocyanine green (ICG) intradermally allows to visualize lymphatics in the upper 2 cm of the skin using an infrared camera system, capturing the fluorescence.[23,24] It provides real-time relatively high-resolution images and detailed information about the superficial lymphatic transport.[27,28] The images themselves are classified in different patterns: a normal linear lymph transport pattern and three

dysfunctional dermal backflow (DB) patterns. The first dysfunctional pattern is the splash pattern, representing a dispersed tracer in tortuous lymphatic channels. The second is the stardust pattern, which demonstrates spotted fluorescent signals, representing the effusion of lymph fluid into the interstitium. The last type is the diffuse pattern wherein the tracer is widely distributed without identifiable spots. In this pattern, besides accumulation in the lymphatic capillaries and lymph precollectors, lymph stagnates in the interstitium.[25,26] Different studies have demonstrated that lymphofluoroscopy is a valid imaging technique to evaluate superficial lymphatic transport in patients with BCRL[27,28] and can be used for early detection of BCRL.[29]

To prevent further evolution to fibrous and fatty tissue, early start of BCRL treatment is recommended.[30,31] Previous studies demonstrated that early detection of BCRL with clinical measurement tools such as bioelectrical impedance spectroscopy and volume measurements and subsequently early start of manual lymph drainage and exercise, reduces the rate of clinical lymphedema.[32,33] Encouraging participation in regular exercise and maintaining healthy body weight as well as giving information such as avoiding infection, heat and tight clothing are guidelines to prevent lymphedema.[3] The additional effect of a compression stocking, in combination with exercise and information, has never been investigated in patients with early disturbance of lymphatic transport visualized with lymphofluoroscopy.

Therefore, the aim of this study is to investigate the additional effect of wearing a compression garment on top of the usual care (i.e. exercise and information), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy, in patients developing early disturbance after treatment for breast cancer.

METHODOLOGY

Trial design

This study is a prospective randomised controlled trial. Figure 1 gives an overview of the participant flow in the trial. All participants are assessed at the Department of Vascular Surgery of the University Hospitals Leuven.

The trial has been approved by the Ethical Committee of the University Hospitals Leuven (CME reference S60382, EudraCT Number 2017-002306-12). The study has been registered in clinicaltrials.gov (NCT 03210311).

Patient and public involvement

The protocol was discussed extensively with the oncologists of the Multidisciplinary Breast Clinic. Patients with BCRL were involved in the trial design and the methods of assessing the lymphedema. They were informed through information sessions at the center for lymphedema. The results of the study will be communicated in a symposium organized for patients recruited in the study and the patients whom were involved in the trial design.

Participants

All patients scheduled for breast surgery combined with either unilateral axillary lymph node dissection (ALND) or sentinel node biopsy (SNB) in the Multidisciplinary Breast Clinic Center at the University Hospitals Leuven are screened for participation in the study.

Recruitment started in November 2017. Inclusion criteria were 1) Age ≥18y, 2) women/men with breast cancer and scheduled for unilateral ALND or SNB, 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) age <18y, 2) edema of the upper limb from other causes, 3) cannot participate during the entire study period, 4) mentally or physically unable to participate in the study, 5) contra-indication for the use of ICG: allergy to ICG, iodine, hyperthyroidism, 6) metastatic disease.

All patients receives written as well as oral information. All included patients sign an informed consent document prior to the start of the study.

Assessments

Figure 1 gives an overview of the different assessments and their timing in the trial. All assessments are performed at baseline and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively.

Near-infrared fluorescence imaging of the lymphatic system or lymphofluoroscopy

All lymphofluoroscopic assessments are performed by one person (ST) who is blinded to the participant's data as well as to the assigned group if relevant.

During lymphofluoroscopy, ICG is injected intradermally in the first and fourth webspace of the hand on the affected side. An infrared camera system (PDE, Hamamatsu®) captures the fluorescence. The procedure consists of three consecutive phases (table 1): an early phase, a break and a late phase. All information about the lymphatic transport is documented in a standard evaluation document and in case of disturbance, this information is drawn on a body diagram according to the legend (Figure 2).

Clinical assessments

The clinical assessments are performed by one assessor. In order to ensure blinding of the assessor, participants are asked not to share any information concerning their treatment (e.g. wearing compression garment or not) neither to wear their compression material during evaluations. In addition, the assessor is blinded to previous measurement data in order to avoid being influenced by previous results.
Table 2 and 3 provides a detailed overview of the clinical evaluation methods and procedures performed.

Randomization and allocation sequence generation

After visualization of an early disturbance of the lymphatic transport, without the presence of clinical lymphedema, patients are randomized in either the control group or the preventive treatment group. Randomization is performed according to 'www.randomization.com'. This generator randomizes each subject to a single treatment by using the method of randomly permuted blocks. Assessments are performed by a person blinded to the treatment allocation groups.

Interventions

During hospitalization all participants receive information about the prevention of lymphedema. They are advised to avoid lifting heavy objects, but to use the affected arm as normally as possible. Limb constriction and extremes of temperatures should be avoided. In case of heaviness the arm should be elevated. Skin care is recommended, and gain in body weight should be avoided to prevent lymphedema. Patients receive a brochure which outlines these guidelines.
Participants are prescribed exercise therapy, which is started during hospitalization with low level mobilizing exercises for the hand, elbow and shoulder. After hospitalization, these exercises are continued. Patients who underwent ALND are going to a physical therapist nearby to continue physical

therapy such as passive mobilization of the shoulder, stretching and transverse strain of the breast muscles, scar tissue massage and active mobilizing and stabilizing exercises. This starts twice a week and frequency is gradually diminished. Exercises are continued until a full range of motion is reached. When a seroma is present intensity of exercises is diminished. Patients who underwent SNB are not routinely seen by a physical therapist after discharge. If functional shoulder problems are seen at discharge or at follow-up consultation, physical therapy is prescribed. Patients are encouraged to do exercises at home twice a day until full range of motion is reached.

If early disturbance is seen on lymphofluoroscopy at a control visit, the patient is randomized in either the preventive treatment group or the control group. In the control group, the usual care is continued consisting of preventive measures and exercises as described above. The participants in the preventive treatment group receive the usual care and a compression garment whether or not combined with a glove on top. The compression garment is measured by an experienced compression specialist. The first choice is a round knitted custom-made compression garment, compression class 2 (23 -32 mmHg), Juzo®. If patients are not comfortable with this garment, a flat-knitted garment (Juzo®) is ordered. If the hand shows swelling after wearing the garment, a glove is measured. Patients need to wear the garment/glove at daytime during the remaining follow-up time of the trial. Written instructions for washing and maintenance of the garment and glove are given. Patients receive a new garment/glove every 6 months. A compression questionnaire is filled in at every visit to assess adherence and adverse events of the compression material.

If clinical lymphedema is established the patient receives the normal standard of care treatment for lymphedema with decongestive lymphatic therapy. Patients are referred to a specialized physical therapist or to the UZ Leuven center for lymphedema.

Primary outcomes

The primary outcomes are the incidence of clinical lymphedema of the arm/hand measured by circumference measurements and volume displacement defined as 5% volume increase compared to the contralateral side (first primary outcome) and the proportion of subjects with deterioration of the dermal backflow measured by lymphofluoroscopy (second primary outcome) (see table 2).

Secondary outcome

Secondary outcome measures are: the incidence of clinical lymphedema of the arm/hand based on the extracellular fluid content, based on the water content, based on thickening of the skinfold, the

relative change of arm volume, the change in functional problems related to the lymphedema and the change in health-related quality of life (see table 3).

Sample size calculation

For both hypotheses a sample size calculation is performed.

For the hypothesis that the incidence rate of clinical lymphedema will be lower in the preventive treatment group than in the control group, we estimate that 50% of the patients in the control group will develop clinical lymphedema in the first year after the randomization compared to 5% in the preventive treatment group (wearing a compression garment). The 5% is based on previous studies.[30-32] A study of Stout[30] treated patients, diagnosed with subclinical lymphedema, defined as a volume difference between both limbs of ≥ 3%, with a compression garment. The incidence of lymphedema (stage I/II) at 5 year was 5.6%. Another trial showed that the same type of treatment reduced the incidence of lymphedema to 4.4%.[31] The 50% incidence of clinical lymphedema in the control group is based on expert opinion.

The sample size calculation is based on the formula in Diggle for a longitudinal study for showing a time-averaged treatment effect for a binary outcome. Four time points per patient are foreseen (12m, 18m, 24m, 36m). Conservatively a high correlation of 0.90 between repeated measurements is assumed (higher correlation means larger sample size). Based on a power of 80% and 2.5% significance level (with a Bonferroni correction for multiple testing given that we test two outcomes, and keeping a family-wise alpha of 5%), we need a sample size of 14 patients per group. Taking into account a drop-out rate of 10%, 16 patient per group or a total of 32 randomized patients are needed.

For the hypothesis that patients in the preventive treatment group will have less deterioration of dermal backflow visualized by lymphofluoroscopy, we estimate that a deterioration of the dermal backflow can be expected in 40% of the cases in the preventive treatment group in contrast to 90% in the control group. There is one publication studying early detection with lymphofluoroscopy and the changes of the dermal backflow pattern in case of early treatment. Therapy consists of exercise, skin care, elevation and the use of a compression garment. This trial shows that only three out of 35 patients with dermal backflow deteriorate during the follow-up.[29] Deterioration was described as a change in severity of the dermal backflow pattern. In our study also the area of dermal backflow is taken into account, therefore we estimate a higher rate of deterioration. The 90% deterioration in the control group is based on expert opinion. The analysis is performed on a binary response (worsening versus stable condition/ improvement). Sample size calculation is completely analogous to the first outcome, leading to a total sample size of 30 patients after taking into account 10% of drop-out.

To calculate the total amount of patients to be included in the present trial two prospective observational studies about the incidence of subclinical lymphedema where considered [30-32] and one study about lymphofluoroscopic observations.[29] In the study by Akita, 196 patients are included in a 1-year follow-up study with lymphofluoroscopy. Twenty-five percent of the patients developed a dermal backflow pattern on lymphofluoroscopy.[29] The largest of both sample sizes, i.e. 32 patients, is adopted. We estimate that in 25% of the patients an early disturbance will be seen, hence 128 patients are included in the trial.

Statistical methods

Logistic regression analysis will be used for both primary endpoints, studying the difference between the preventive treatment and control group over the follow-up period. Generalized estimating equations (GEE) are used to account for repeated measurement. Model covariates include time and treatment group. The main effect of the preventive treatment group is estimated and presented by odds ratios with 95% confidence intervals. Both analyses are tested at the 2.5% significance level.
All data is analyzed according the intention to treat principle.
A 5% level of significance is applied for all secondary analyses.

Monitoring

There are no indications for setting up a data monitoring committee.
No adverse events (AE) are expected. AE will be reported during the entire trial period, i.e. 36 months. It will be specified that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case files).

DISCUSSION

This is the first randomized controlled clinical trial investigating the additional effect of wearing a compression garment, to the usual care (i.e. information and exercises), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by near infrared fluorescence imaging, in patients with early disturbance of the lymphatic transport (i.e. dermal backflow) after

treatment for breast cancer. If treatment can start in this early phase of disturbance, further evolution to clinical lymphedema can perhaps be prevented.

ETHICS AND DISSEMINATION

The trial is conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents has been approved by the Ethical Committee of the University Hospitals Leuven (CME reference S60382, EudraCT Number 2017-002306-12). The study has been registered in clinicaltrials.gov (NCT 03210311).

The study can and will be conducted only on the basis of prior informed consent by the participants, or their legal representatives, to participate in the study. The investigator will obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the study in compliance with all applicable laws, regulations and the approval of the Ethics Committee. The investigator will retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.
The investigator will treat all information and data relating to the study disclosed as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).
Data are anonymous if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.
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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The results of the study will be send for publication to a peer-review journal. Participants and healthcare providers will be invited for a symposium to communicate the trial results.

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CONTRIBUTERSHIP STATEMENT

All authors state that they contributed substantially to the design of the trial, revised it critically, gave their final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Protocol near-infrared fluorescence imaging

Step		description	reporting
Preparation	0.1 Dilution of ICG	Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml	
	0.2 Camera	Camera is held perpendicular to the observed skin at distance of 15 cm (best focus)	
	0.3 Injection of ICG	Intradermal injection in 1st (ulnar injection point) and 4th web space (radial injection point) dorsally in the hand 0.2 ml of the diluted solution is injected in each injection point	Time of injection
Early phase	1.1 Rest: 1 min	Hand in resting position on table	Linear transport starting from ulnar injection point: Yes / No (if "yes", after …… sec) Linear transport starting from radial injection point: Yes / No (if "yes", after …… sec)
	1.2 Stimulation: 3 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors is stimulated by the assessor	
	1.3 Scan with camera and measuring	1) of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region, 2) of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the contralateral axilla, 3) of the scapular region: from the ipsilateral to the contralateral axilla, 4) of the pectoral region: from the ipsilateral to the contralateral axilla	After scan, reporting on an assessment form: - Number of lymph collectors - Of each lymph collector: length (measured with tapeline in cm), location and normal versus dilated situation - Presence of splash, stardust and diffuse pattern and location (fingers, hand, proximal/ distal and ventral/ dorsal lower or upper arm, breast and trunk) - Number of lymph nodes (cubital, humeral, axillary, retroclavicular)

Break	30 min		
Late phase	3.1 Scan with camera and measuring	See step 1.3	See step 1.3
	3.2 Drawing on skin and body diagram	If disturbance is seen lymph collectors and dermal backflow (splash, stardust and diffuse) are designed on a body diagram (see figure 2)	Design on body diagram if disturbance is seen

Table 2. Overview of measurement method and calculation of the primary outcomes

Outcome parameter	Measurement time, method, material	Calculation
Cumulative incidence of clinical lymphedema defined as: ≥5% increase of relative arm volume difference compared to pre-surgical value	Before surgery, at 12M, 18M, 24M and 36M. With perimeter Circumferences at olecranon and 4, 8, 12, 16 and 20cm above and under olecranon of arm at affected and healthy side[12] With volumeter, weighing balance and recipient Water displacement method hand[13,14]	0 = No clinical lymphedema 1 = Clinical lymphedema Relative arm volume difference compared to pre-surgical value = relative arm volume difference at assessment – relative arm volume difference at baseline Relative arm volume difference = (absolute arm volume difference/ arm volume healthy side) x 100 Absolute arm volume difference = arm volume affected side – arm volume healthy side Arm volume = sum of volume of different arm segments determined by circumference measurements + hand volume

		Arm segment = $4 \times (C_1^2+C_1C_2+C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment (formula of the truncated cone)[12] Hand volume = volume measured with volumeter
Proportion of subjects with deterioration of the dermal backflow	At 12M, 18M, 24M and 36M. With lymphofluoroscopy: injecting ICG in the hand of the affected arm[26], protocol see table 1	0 = Stabilization or improvement 1 = Deterioration Stabilization: stable area of dermal backflow OR stable dermal backflow pattern Improvement: diminished area of dermal backflow OR diminished severity of dermal backflow pattern Deterioration: increased area of dermal backflow OR increased severity of dermal backflow pattern

Table 3. Overview of measurement method and calculation of the secondary outcomes

Outcome parameter	Measurement time, method, material	Calculation
Incidence of lymphedema based on pitting status	At 12M, 18M, 24M and 36M. The therapist gives a vertical pressure with the thumb for 5 seconds at the 7 reference points (see figure 3)[15]	0 = The skin immediately returns to starting position 1 = Pitting is present
Incidence of lymphedema based on skinfold thickness	At 12M, 18M, 24M and 36M. The examiner picks up the skinfolds between thumb and index finger at the 7 reference points (see figure 3).[19] The skinfold thickness of the edematous side is compared to the non-edematous side (Stemmer sign).	0 = No increase in skinfold thickness 1 = An increase in skinfold thickness
Incidence of lymphedema based on the amount of extracellular fluid	Before surgery, at 12M, 18M, 24M and 36M. Impedimed L-dex U400[16] Reference points On each hand, one double electrode is placed on the dorsum of the hand On the right foot, one double	0= Patients with a score of <10 L-Dex units or with an increase of < 10 units from baseline 1 = Patients with a score of >10 L-Dex units or with an increase of ≥ 10 units from baseline[31]

	electrode is placed on the dorsum of the foot.	
Incidence of lymphedema based on the water content	At 12M, 18M, 24M and 36M. MoistureMeter D Compact (Delfin Technologies) measured at the 7 reference points (see figure 3)[18]	Ratio PWC = PWC healthy side / PWC affected side 0 = ratio PWC < 1.2 1 = ratio PWC ≥ 1.2
Relative change of arm volume difference (in %)	Before surgery, at 12M, 18M, 24M and 36M.	Relative arm volume difference = relative volume difference at assessment – relative volume difference at baseline See table 2 for further explanation.
Problems in functioning related to development of lymphedema (score 0-100)	At 12M, 18M, 24M and 36M. Using Lymf-ICF questionnaire[35] Filled out by patient	Total score and physical function score, mental function score, household activities score, mobility activities score and life and social activities score A lower score indicates less problems in functioning
Health related quality of life	At 12M, 18M, 24M and 36M. Using Mc Gill questionnaire[36] (Dutch version) Filled out by patient	A lower score indicates a lower Quality of Life

Figure 1. Flow of participants

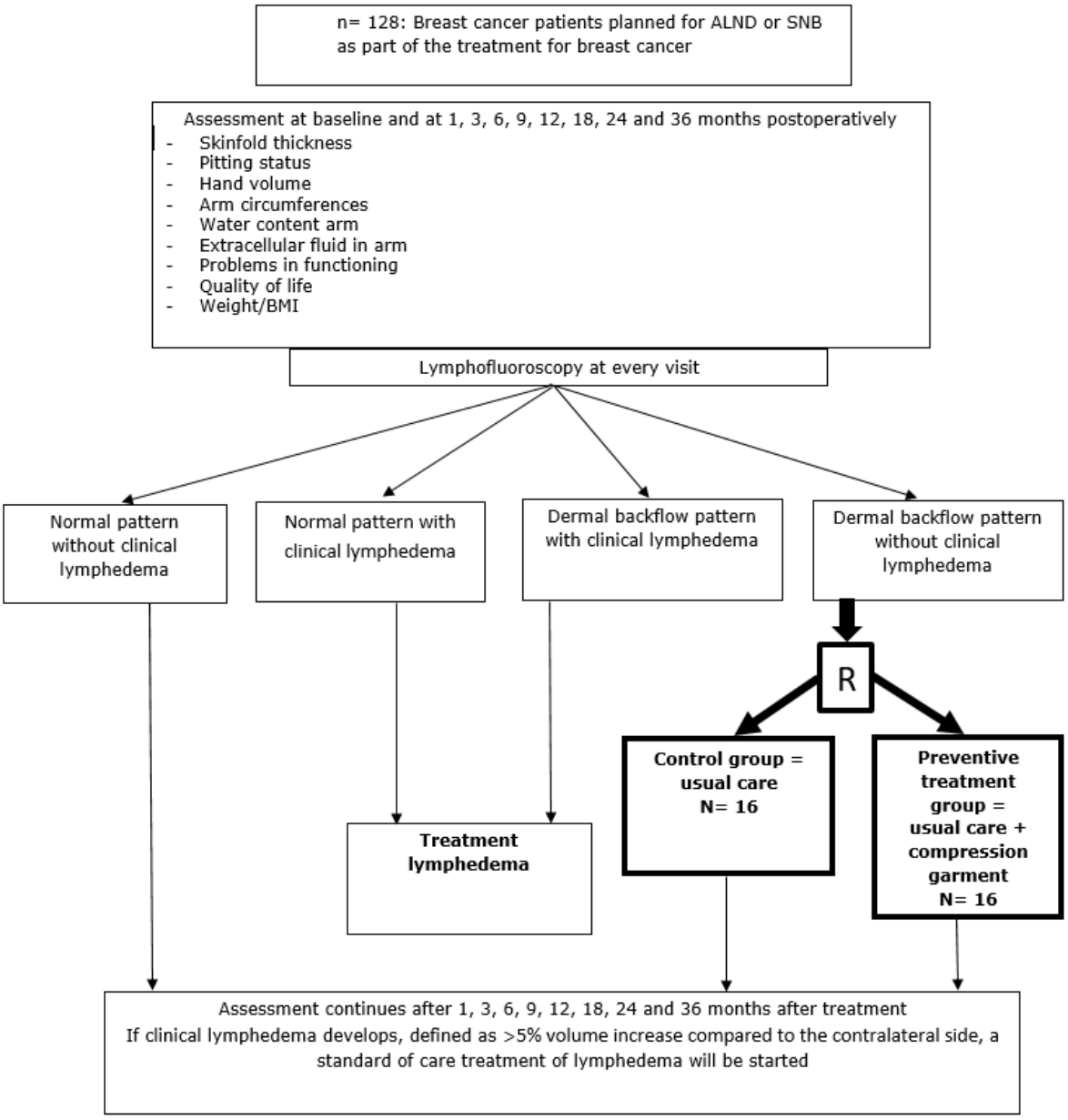


Figure 2. Example of body diagram

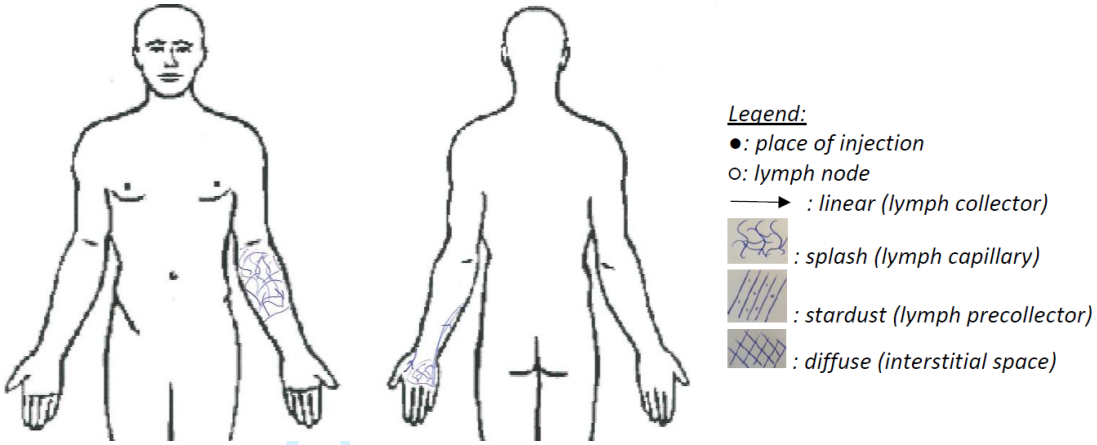
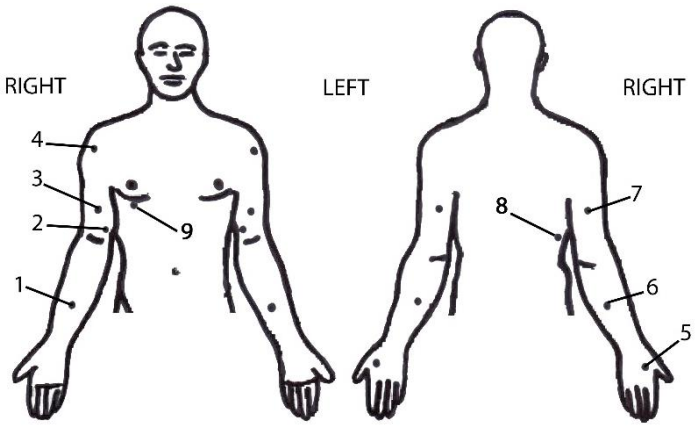


Figure 3: Description of the reference points needed for the local clinical assessments



1. **Ventral side forearm:**
   15cm distally of the elbow crease
2. **Medial side upper arm:**
   3cm proximally of the medial epicondyle of the humerus
3. **Ventral side upper arm:**
   7cm proximally of the elbow crease
4. **Shoulder:**
   5cm distally of the lateral border of the acromion
   in the direction of the lateral epicondyle of the humerus
5. **Hand:**
   Central point between dorsal side thumb and index finger
6. **Dorsal side forearm:**
   10cm distally of the proximal border of the olecranon
7. **Dorsal side upper arm:**
   7cm proximally of the proximal border of the olecranon
8. **Trunk:**
   5cm distally of the dorsal axillary fold
9. **Breast:**
   Lumpectomy: 3cm distally of the nipple (in case of mastectomy: 3cm distally from the middle of the scar)

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

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

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

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

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

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

Appendices

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

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

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Impact of a compression garment, on top of the usual care, in breast cancer patients with early disturbance of the lymphatic transport: protocol of a randomized controlled trial.

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Impact of a compression garment, on top of the usual care, in breast cancer patients with early disturbance of the lymphatic transport: protocol of a randomized controlled trial.

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ABSTRACT

Introduction

Breast-cancer related lymphedema (BCRL) is a common phenomenon. When lymphedema is diagnosed late, options for treatment are diminished. Therefore, early diagnosis and treatment are very important to alter the potential deleterious evolution. Lymphofluoroscopy visualizes the superficial lymphatic architecture in detail, giving the opportunity to detect a disturbance in the lymphatic transport (i.e. dermal backflow) before the lymphedema is clinically visible.

The main objective is to investigate if there is an additional effect of a compression garment on top of the usual care (i.e. information and exercises) in patients with early disturbance of the lymphatic transport after breast cancer treatment. Development of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy is investigated.

Methodology

All patients scheduled for breast cancer surgery with unilateral axillary lymph node dissection or sentinel node biopsy in the Multidisciplinary Breast Clinic of the University Hospitals Leuven are being considered. Patients are assessed before surgery and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively. At each visit a clinical assessment is performed determining the volume difference between both arms and hands (through circumference measurements and water displacement), the water content, the extracellular fluid, the pitting status and the skinfold thickness. Quality of life questionnaires are filled in. At each visit a lymphofluoroscopy is performed as well. When a disturbance of the lymphatic transport is seen on lymphofluoroscopy, without the presence of clinical lymphedema, the patient is randomized in either a control group receiving usual care or a preventive treatment group receiving usual care and a compression garment (whether or not combined with a glove).

Ethics and dissemination

The trial is conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol has been

approved by the Ethical Committee of the University Hospitals Leuven. Results will be disseminated by peer-reviewed scientific journals and presentation at international congresses.

Trial registration number NCT 03210311

Conclusion

The investigators hypothesize that development of clinical BCRL can be prevented and/or the dermal backflow can be stabilized or improved, if a preventive treatment with compression garment is started in the early phase of disturbance.

STRENGTHS AND LIMITATIONS

- This is the first study to investigate the additional effect of early treatment in breast cancer patients with a disturbance on lymphofluoroscopy.
- This is a prospective, randomized controlled trial.
- Lymphofluoroscopy and clinical measurements are performed preoperative and at regular times up to three years after surgery for breast cancer.
- This study is powered for the primary outcomes incidence of clinical lymphedema and deterioration of dermal backflow.

Key words: Lymphedema, ICG lymphofluoroscopy, near-infrared fluorescence, early detection

INTRODUCTION

Lymphedema is a chronic and debilitating disease caused by imbalance between lymph production and lymph transport. It reduces patient's quality of life by limb enlargement but also by other physical and psychosocial problems, e.g. decreased mobility, recurrent infections, stress and decreased ability to perform occupational activities.[1,2,3]

Breast cancer-related lymphedema (BCRL) is a secondary lymphedema of the upper limb that can occur after treatment for breast cancer. Incidence of BCRL vary in literature, especially since the introduction of less invasive techniques such as sentinel node procedures and radiotherapy. According to a review of DiSipio et al., the incidence of arm lymphedema was about four times higher in women who had an axillary lymph node dissection (19.9%) than after sentinel lymph node biopsy (5.6%).[4,5] A study by Rockson et al. suggested that in almost 75% of the cases, lymphedema is established within the first year after breast cancer treatment.[6] A volume difference between both limbs of 5 to 10% is normally used to define clinical lymphedema [4,7]

Lymphedema can progress from a soft pitting edema to a hard fibrotic or soft fatty and non-pitting edema because of lipogenesis, fibrosis, inflammation, lymphangiogenesis and immunosuppression. [8,9] There is no consensus concerning the best measuring tool to detect the development of BCRL.[10,11] Volume increase of the limb can be assessed with circumference measurements[12] or with the water displacement method.[13,14] A relative volume change between both arms is used, comparing preoperative measurements between the affected arm and the healthy arm, to the postoperative measurements.[7] In addition, the increase of water content in the edematous limb can be assessed by the pitting test,[15] by measuring the extracellular fluid (bioelectrical impedance spectroscopy)[16] or by measuring the water content of the skin (tissue dielectric constant).[17,18] Measurement of the skinfold thickness (Stemmer sign) can be performed, which is the typical sign for lymphedema.[19]

Historically lymphangiography has been the technique to image the lymphatic system. This technique is difficult to perform and has become obsolete.[20] Lymphoscintigraphy has replaced lymphangiography and became the new standard for imaging the lymphatic system. With lymphoscintigraphy a radionuclide (^{99m}Tc-labeled tracer) is injected and followed by sequential gamma imaging.[21,22] This technique not only provides dynamic imaging of the lymphatics and the lymph nodes, but also provides semi-quantitative data of radionuclide transport and lymph node absorption. Near-infrared fluorescence imaging or lymphofluoroscopy is another minimally invasive technique. The injection of indocyanine green (ICG) intradermally allows to visualize lymphatics in the upper 2 cm of the skin using an infrared camera system, capturing the fluorescence.[23,24] It provides real-time relatively high-resolution images and detailed information about the superficial lymphatic transport.[25] The images themselves are classified in different patterns: a normal linear lymph transport pattern and three

dysfunctional dermal backflow (DB) patterns. The first dysfunctional pattern is the splash pattern, representing a dispersed tracer in tortuous lymphatic channels. The second is the stardust pattern, which demonstrates spotted fluorescent signals, representing the effusion of lymph fluid into the interstitium. The last type is the diffuse pattern wherein the tracer is widely distributed without identifiable spots. In this pattern, besides accumulation in the lymphatic capillaries and lymph precollectors, lymph stagnates in the interstitium.[25,26] Different studies have demonstrated that lymphofluoroscopy is a valid imaging technique to evaluate superficial lymphatic transport in patients with BCRL[27,28] and can be used for early detection of BCRL.[29]

To prevent further evolution to fibrous and fatty tissue, early start of BCRL treatment is recommended.[30,31] Previous studies demonstrated that early detection of BCRL with clinical measurement tools such as bioelectrical impedance spectroscopy and volume measurements and subsequently early start of manual lymph drainage and exercise, reduces the rate of clinical lymphedema.[32,33] Encouraging participation in regular exercise and maintaining healthy body weight as well as giving information such as avoiding infection, heat and tight clothing are guidelines to prevent lymphedema.[34] The previous studies investigated the effect of early treatment by using clinical assessments. The optimal tool to use remains unclear, and furthermore patient subjective symptoms and extremity volume can vary depending on the timing of measurement (morning and evening), the temperature, the activities performed by the patient during the day,…[35,36] thus not reliable for lymphedema diagnosis. Subclinical lymphedema should be diagnosed with lymphatic imaging.

Therefore, the aim of this study is to investigate the additional effect of wearing a compression garment on top of the usual care (i.e. exercise and information), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy, in patients developing early disturbance after treatment for breast cancer.

METHODOLOGY

Trial design

This study is a prospective randomised controlled trial. Figure 1 gives an overview of the participant flow in the trial. All participants are assessed at the Department of Vascular Surgery of the University Hospitals Leuven. The trial started in November 2017 and will end in May 2023.

The trial has been approved by the Ethical Committee of the University Hospitals Leuven (CME reference S60382, EudraCT Number 2017-002306-12). The study has been registered in clinicaltrials.gov (NCT 03210311).

Patient and public involvement

The protocol was discussed extensively with the oncologists of the Multidisciplinary Breast Clinic. Patients with BCRL were involved in the trial design and the methods of assessing the lymphedema. They were informed through information sessions at the center for lymphedema. The results of the study will be communicated in a symposium organized for patients recruited in the study and the patients whom were involved in the trial design.

Participants

All patients scheduled for breast surgery combined with either unilateral axillary lymph node dissection (ALND) or sentinel node biopsy (SNB) in the Multidisciplinary Breast Clinic Center at the University Hospitals Leuven are screened for participation in the study.

Recruitment started in November 2017. Inclusion criteria were 1) Age ≥18y, 2) women/men with breast cancer and scheduled for unilateral ALND or SNB, 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) edema of the upper limb from other causes, 2) cannot participate during the entire study period, 3) mentally or physically unable to participate in the study, 4) contra-indication for the use of ICG: allergy to ICG, iodine, hyperthyroidism, 5) metastatic disease.

All patients receives written as well as oral information. All included patients sign an informed consent document prior to the start of the study.

Assessments

Figure 1 gives an overview of the different assessments and their timing in the trial. All assessments are performed at baseline and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively.

Near-infrared fluorescence imaging of the lymphatic system or lymphofluoroscopy

All lymphofluoroscopic assessments are performed by one person (ST) who is blinded to the participant's data as well as to the assigned group if relevant.

During lymphofluoroscopy, ICG is injected intradermally in the first and fourth webspace of the hand on the affected side. An infrared camera system (PDE, Hamamatsu®) captures the fluorescence. The procedure consists of three consecutive phases (table 1): an early phase, a break and a late phase. All information about the lymphatic transport is documented in a standard evaluation document and in case of disturbance, this information is drawn on a body diagram according to the legend (Figure 2).

Clinical assessments

The clinical assessments are performed by one assessor. In order to ensure blinding of the assessor, participants are asked not to share any information concerning their treatment (e.g. wearing compression garment or not) neither to wear their compression material during evaluations. In addition, the assessor is blinded to previous measurement data in order to avoid being influenced by previous results.

Table 2 and 3 provides a detailed overview of the clinical evaluation methods and procedures performed. Figure 3 shows the reference points used for the local clinical assessments.

Randomization and allocation sequence generation

After visualization of an early disturbance of the lymphatic transport, without the presence of clinical lymphedema, patients are randomized in either the control group or the preventive treatment group. Randomization is performed according to 'www.randomization.com'. This generator randomizes each subject to a single treatment by using the method of randomly permuted blocks. Assessments are performed by a person blinded to the treatment allocation groups.

Interventions

During hospitalization all participants receive information about the prevention of lymphedema. They are advised to avoid lifting heavy objects, but to use the affected arm as normally as possible. Limb constriction and extremes of temperatures should be avoided. In case of heaviness the arm should be elevated. Skin care is recommended, and gain in body weight should be avoided to prevent lymphedema. Patients receive a brochure which outlines these guidelines.

Participants are prescribed exercise therapy, which is started during hospitalization with low level mobilizing exercises for the hand, elbow and shoulder. After hospitalization, these exercises are continued. Patients who underwent ALND are going to a physical therapist nearby to continue physical therapy such as passive mobilization of the shoulder, stretching and transverse strain of the breast muscles, scar tissue massage and active mobilizing and stabilizing exercises. This starts twice a week and frequency is gradually diminished. Exercises are continued until a full range of motion is reached. When a seroma is present intensity of exercises is diminished. Patients who underwent SNB are not routinely seen by a physical therapist after discharge. If functional shoulder problems are seen at discharge or at follow-up consultation, physical therapy is prescribed. Patients are encouraged to do exercises at home twice a day until full range of motion is reached.

If early disturbance is seen on lymphofluoroscopy at a control visit, the patient is randomized in either the preventive treatment group or the control group. In the control group, the usual care is continued consisting of preventive measures and exercises as described above. The participants in the preventive treatment group receive the usual care and a compression garment whether or not combined with a glove on top. The compression garment is measured by an experienced compression specialist. The first choice is a round knitted custom-made compression garment, compression class 2 (23 -32 mmHg). If patients are not comfortable with this garment, a flat-knitted garment is ordered. If the hand shows swelling after wearing the garment, a glove is measured. Patients need to wear the garment/glove at daytime during the remaining follow-up time of the trial. Written instructions for washing and maintenance of the garment and glove are given. Patients receive a new garment/glove every 6 months. A compression questionnaire is filled in at every visit to assess adherence and adverse events of the compression material.

If clinical lymphedema is established the patient receives the normal standard of care treatment for lymphedema with decongestive lymphatic therapy. Patients are referred to a specialized physical therapist or to the UZ Leuven center for lymphedema.

Primary outcomes

The primary outcomes are the incidence of clinical lymphedema of the arm/hand measured by circumference measurements and volume displacement defined as 5% volume increase compared to the contralateral side (first primary outcome) and the proportion of subjects with deterioration of the dermal backflow measured by lymphofluoroscopy (second primary outcome) (see table 2).

Secondary outcomes

Secondary outcome measures are: the incidence of clinical lymphedema of the arm/hand based on the extracellular fluid content, based on the water content, based on thickening of the skinfold, the relative change of arm volume, the severity of disturbance of lymphatic transport, the change in functional problems related to the lymphedema and the change in health-related quality of life (see table 3).

Sample size calculation

For both hypotheses a sample size calculation is performed.

For the hypothesis that the incidence rate of clinical lymphedema will be lower in the preventive treatment group than in the control group, we estimate that 50% of the patients in the control group will develop clinical lymphedema in the first year after the randomization compared to 5% in the preventive treatment group (wearing a compression garment). The 5% is based on previous studies.[30-32] A study of Stout[30] treated patients, diagnosed with subclinical lymphedema, defined as a volume difference between both limbs of ≥ 3%, with a compression garment. The incidence of lymphedema (stage I/II) at 5 year was 5.6%. Another trial showed that the same type of treatment reduced the incidence of lymphedema to 4.4%.[31] The 50% incidence of clinical lymphedema in the control group is based on expert opinion.

The sample size calculation is based on the formula in Diggle for a longitudinal study for showing a time-averaged treatment effect for a binary outcome. Four time points per patient are foreseen (12m, 18m, 24m, 36m). Conservatively a high correlation of 0.90 between repeated measurements is assumed (higher correlation means larger sample size). Based on a power of 80% and 2.5% significance level (with a Bonferroni correction for multiple testing given that we test two outcomes, and keeping a family-wise alpha of 5%), we need a sample size of 14 patients per group. Taking into account a drop-out rate of 10%, 16 patient per group or a total of 32 randomized patients are needed.

For the hypothesis that patients in the preventive treatment group will have less deterioration of dermal backflow visualized by lymphofluoroscopy, we estimate that a deterioration of the dermal backflow can be expected in 40% of the cases in the preventive treatment group in contrast to 90% in the control group. There is one publication studying early detection with lymphofluoroscopy and the changes of the dermal backflow pattern in case of early treatment. Therapy consists of exercise, skin care, elevation and the use of a compression garment. This trial shows that only three out of 35 patients with dermal backflow deteriorate during the follow-up.[29] Deterioration was described as a change in severity of the dermal backflow pattern. In our study also the area of dermal backflow is taken into account, therefore we estimate a higher rate of deterioration. The 90% deterioration in the

control group is based on expert opinion. The analysis is performed on a binary response (worsening versus stable condition/ improvement). Sample size calculation is completely analogous to the first outcome, leading to a total sample size of 30 patients after taking into account 10% of drop-out.

To calculate the total amount of patients to be included in the present trial two prospective observational studies about the incidence of subclinical lymphedema where considered [30-32] and one study about lymphofluoroscopic observations.[29] In the study by Akita, 196 patients are included in a 1-year follow-up study with lymphofluoroscopy. Twenty-five percent of the patients developed a dermal backflow pattern on lymphofluoroscopy.[29] The largest of both sample sizes, i.e. 32 patients, is adopted. We estimate that in 25% of the patients an early disturbance will be seen, hence 128 patients are included in the trial.

Statistical methods

Logistic regression analysis will be used for both primary endpoints, studying the difference between the preventive treatment and control group over the follow-up period. Generalized estimating equations (GEE) are used to account for repeated measurement. Model covariates include time and treatment group. The main effect of the preventive treatment group is estimated and presented by odds ratios with 95% confidence intervals. Both analyses are tested at the 2.5% significance level.
All data is analyzed according the intention to treat principle.
A 5% level of significance is applied for all secondary analyses.

Monitoring

There are no indications for setting up a data monitoring committee.
No adverse events (AE) are expected. AE will be reported during the entire trial period, i.e. 36 months.
It will be specified that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case files).

DISCUSSION

This is the first randomized controlled clinical trial investigating the additional effect of wearing a compression garment, to the usual care (i.e. information and exercises), on the incidence of clinical

lymphedema and/or deterioration of the dermal backflow visualized by near infrared fluorescence imaging, in patients with early disturbance of the lymphatic transport (i.e. dermal backflow) after treatment for breast cancer. If treatment can start in this early phase of disturbance, further evolution to clinical lymphedema can perhaps be prevented.

ETHICS AND DISSEMINATION

The trial is conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents has been approved by the Ethical Committee of the University Hospitals Leuven (CME reference S60382, EudraCT Number 2017-002306-12). The study has been registered in clinicaltrials.gov (NCT 03210311).

The study can and will be conducted only on the basis of prior informed consent by the participants, or their legal representatives, to participate in the study. The investigator will obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the study in compliance with all applicable laws, regulations and the approval of the Ethics Committee. The investigator will retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.
The investigator will treat all information and data relating to the study disclosed as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).
Data are anonymous if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.
When data are coded, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers is stored separately (site file) from the research data and replaced with a unique code to create a new identity for the subject. The data are stored on a shared file. Only the principle investigator, sub-investigators and project co-workers (after permission from the principle investigator) have access to the patient file.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The results of the study will be send for publication to a peer-review journal. Participants and healthcare providers will be invited for a symposium to communicate the trial results.

ACKNOWLEDGMENTS

The authors are very grateful to the Multidisciplinary Breast Clinic for collaborating in this study. The authors also extend very grateful thanks to the study participants and the patients who were involved in the design of the study.

CONTRIBUTERSHIP STATEMENT

ST drafted the manuscript. ST is the principal investigator of the DEARLY trial. BBH, IF, ND, IN and PN contributed substantially to the establishment of the protocol, revised the manuscript for important intellectual content and provided input according to their area of expertise. All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Protocol near-infrared fluorescence imaging

Step		description	reporting
Preparation	0.1 Dilution of ICG	Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml	
	0.2 Camera	Camera is held perpendicular to the observed skin at distance of 15 cm (best focus)	
	0.3 Injection of ICG	Intradermal injection in 1st (ulnar injection point) and 4th web space (radial injection point) dorsally in the hand 0.2 ml of the diluted solution is injected in each injection point	Time of injection
Early phase	1.1 Rest: 1 min	Hand in resting position on table	Linear transport starting from ulnar injection point: Yes / No (if "yes", after …… sec) Linear transport starting from radial injection point: Yes / No (if "yes", after …… sec)
	1.2 Stimulation: 3 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors is stimulated by the assessor	
	1.3 Scan with camera and measuring	1) of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region, 2) of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the contralateral axilla, 3) of the scapular region: from the ipsilateral to the contralateral axilla, 4) of the pectoral region: from the ipsilateral to the contralateral axilla	After scan, reporting on an assessment form: - Number of lymph collectors - Of each lymph collector: length (measured with tapeline in cm), location and normal versus dilated situation - Presence of splash, stardust and diffuse pattern and location (fingers, hand, proximal/ distal and ventral/ dorsal lower or upper arm, breast and trunk) - Number of lymph nodes (cubital, humeral, axillary, retroclavicular)

Break	30 min		
Late phase	3.1 Scan with camera and measuring	See step 1.3	See step 1.3
	3.2 Drawing on skin and body diagram	If disturbance is seen lymph collectors and dermal backflow (splash, stardust and diffuse) are designed on a body diagram (see figure 2)	Design on body diagram if disturbance is seen

Table 2. Overview of measurement method and calculation of the primary outcomes

Outcome parameter	Measurement time, method, material	Calculation
Cumulative incidence of clinical lymphedema defined as: ≥5% increase of relative arm volume difference compared to pre-surgical value	Before surgery, at 12M, 18M, 24M and 36M. With perimeter Circumferences at olecranon and 4, 8, 12, 16 and 20cm above and under olecranon of arm at affected and healthy side[12] With volumeter, weighing balance and recipient Water displacement method hand[13,14]	0 = No clinical lymphedema 1 = Clinical lymphedema Relative arm volume difference compared to pre-surgical value = relative arm volume difference at assessment – relative arm volume difference at baseline Relative arm volume difference = (absolute arm volume difference/ arm volume healthy side) x 100 Absolute arm volume difference = arm volume affected side – arm volume healthy side Arm volume = sum of volume of different arm segments determined by circumference measurements + hand volume

		Arm segment = $4 \times (C_1^2+C_1C_2+C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment (formula of the truncated cone)[12] Hand volume = volume measured with volumeter
Proportion of subjects with deterioration of the dermal backflow	At 12M, 18M, 24M and 36M. With lymphofluoroscopy: injecting ICG in the hand of the affected arm[26], protocol see table 1	0 = Stabilization or improvement 1 = Deterioration Stabilization: stable area of dermal backflow OR stable dermal backflow pattern Improvement: diminished area of dermal backflow OR diminished severity of dermal backflow pattern Deterioration: increased area of dermal backflow OR increased severity of dermal backflow pattern

Table 3. Overview of measurement method and calculation of the secondary outcomes

Outcome parameter	Measurement time, method, material	Calculation
Incidence of lymphedema based on pitting status	At 12M, 18M, 24M and 36M. The therapist gives a vertical pressure with the thumb for 5 seconds at the 7 reference points (see figure 3)[15]	0 = The skin immediately returns to starting position 1 = Pitting is present
Incidence of lymphedema based on skinfold thickness	At 12M, 18M, 24M and 36M. The examiner picks up the skinfolds between thumb and index finger at the 7 reference points (see figure 3).[19] The skinfold thickness of the edematous side is compared to the non-edematous side (Stemmer sign).	0 = No increase in skinfold thickness 1 = An increase in skinfold thickness
Incidence of lymphedema based on the amount of extracellular fluid	Before surgery, at 12M, 18M, 24M and 36M. Impedimed L-dex U400[16] Reference points On each hand, one double electrode is placed on the dorsum of the hand On the right foot, one double	0= Patients with a score of <10 L-Dex units or with an increase of < 10 units from baseline 1 = Patients with a score of >10 L-Dex units or with an increase of ≥ 10 units from baseline[31]

	electrode is placed on the dorsum of the foot.	
Incidence of lymphedema based on the water content	At 12M, 18M, 24M and 36M. MoistureMeter D Compact (Delfin Technologies) measured at the 7 reference points (see figure 3)[18]	Ratio PWC = PWC healthy side / PWC affected side 0 = ratio PWC < 1.2 1 = ratio PWC ≥ 1.2
Relative change of arm volume difference (in %)	Before surgery, at 12M, 18M, 24M and 36M.	Relative arm volume difference = relative volume difference at assessment – relative volume difference at baseline See table 2 for further explanation.
Severity of disturbance of lymphatic transport	At 12M, 18M, 24M and 36M With lymphofluoroscopy, protocol see table 1.	For every region (fingers, ventral/dorsal hand, proximal/distal ventral/dorsal lower and upper arm, breast and dorsal region) the presence of linear, splash, stardust or diffuse pattern is scored. 0= linear pattern 1= splash pattern 2= stardust pattern 3= diffuse pattern Maximum score is 39 points.
Problems in functioning related to development	At 12M, 18M, 24M and 36M. Using Lymf-ICF questionnaire[37]	Total score and physical function score, mental function score, household activities score,

of lymphedema (score 0-100)	Filled out by patient	mobility activities score and life and social activities score A lower score indicates less problems in functioning
Health related quality of life	At 12M, 18M, 24M and 36M. Using Mc Gill questionnaire[38] (Dutch version) Filled out by patient	A lower score indicates a lower Quality of Life

Figure 1. Flow of participants

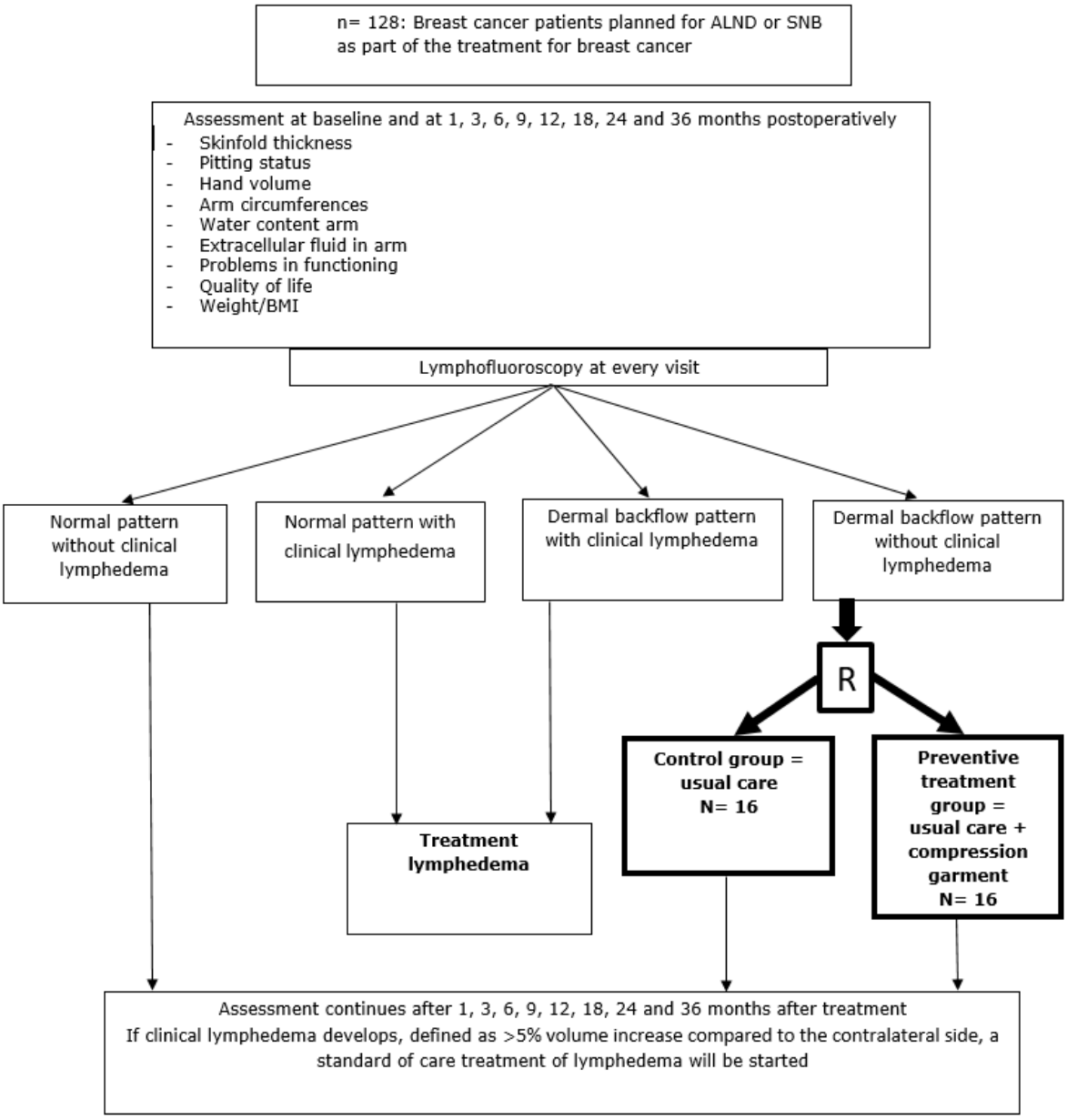


Figure 2. Example of body diagram

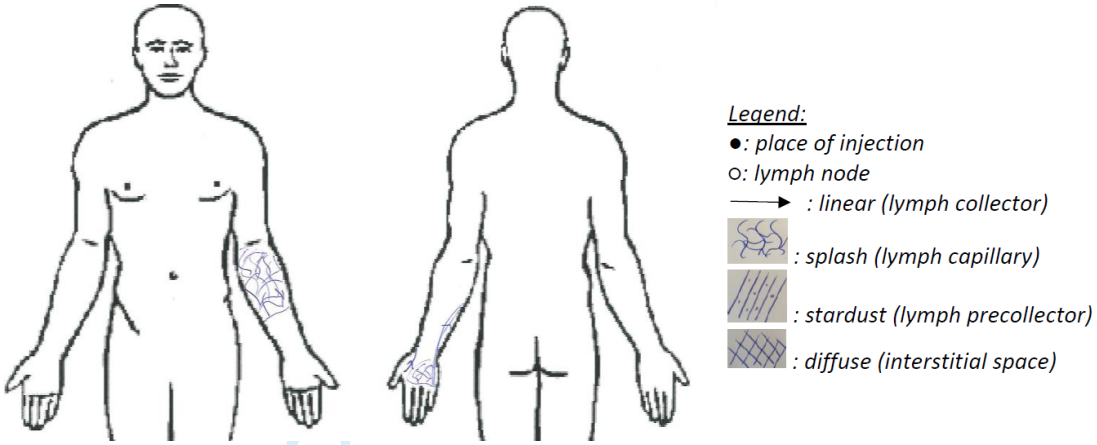
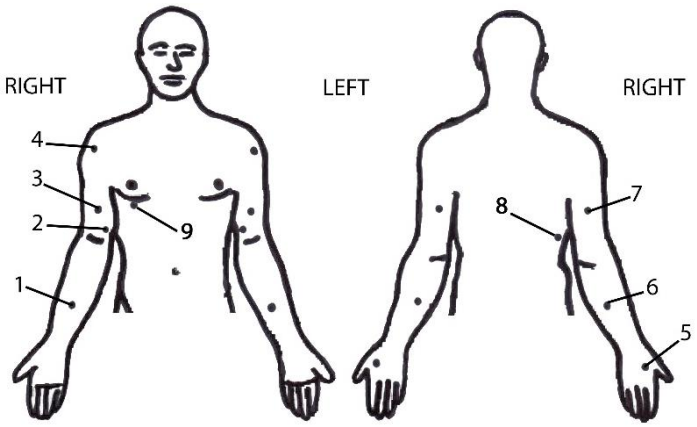


Figure 3: Description of the reference points needed for the local clinical assessments



1. **Ventral side forearm:**
   15cm distally of the elbow crease
2. **Medial side upper arm:**
   3cm proximally of the medial epicondyle of the humerus
3. **Ventral side upper arm:**
   7cm proximally of the elbow crease
4. **Shoulder:**
   5cm distally of the lateral border of the acromion
   in the direction of the lateral epicondyle of the humerus
5. **Hand:**
   Central point between dorsal side thumb and index finger
6. **Dorsal side forearm:**
   10cm distally of the proximal border of the olecranon
7. **Dorsal side upper arm:**
   7cm proximally of the proximal border of the olecranon
8. **Trunk:**
   5cm distally of the dorsal axillary fold
9. **Breast:**
   Lumpectomy: 3cm distally of the nipple (in case of mastectomy: 3cm distally from the middle of the scar)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

Methods: Participants, interventions, and outcomes

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

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

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

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

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

Appendices

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

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