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Improving the quality of life of patients with breast cancer-related lymphedema by lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized controlled trial.

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Manuscripts

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3 **Improving the quality of life of patients with breast cancer-related lymphedema by**
4 **lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized**
5 **controlled trial.**
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Abstract

Introduction. Early breast cancer detection and advancements in treatment options have resulted in an increase of breast cancer survivors. An increasing number of women are living with the long-term effects of breast cancer treatment, making the quality of survivorship an increasingly important goal. Breast cancer-related lymphedema (BCRL) is one of the most underestimated complications of breast cancer treatment with a reported incidence of 20%. A microsurgical technique called lymphaticovenous anastomosis (LVA) might be a promising treatment modality for patients with BCRL.

The main objective is to assess whether LVA is more effective than the current standard therapy (conservative treatment) in terms of improvement in quality of life and cost-effectiveness.

Methods and analysis. A multicenter, randomized controlled trial, carried out in two academic and two community hospitals in the Netherlands. The study population includes 120 women over the age of 18 who underwent treatment for breast cancer including axillary treatment (SLNB or ALNT) and/or axillary radiotherapy, presenting with an early stage lymphedema of the arm, viable lymphatic vessels, and received at least three months conservative treatment. Sixty participants will undergo the LVA operation and the other sixty will continue conservative treatment, both with a follow-up of 24 months.

The primary outcome is the health-related quality of life. The secondary outcomes are (in)direct costs, QALYs, cost-effectiveness ratio, discontinuation rate of conservative treatment, and excess limb volume.

Ethics and dissemination. The study was approved by the Ethics Committee of Maastricht University Medical Centre on 19 December 2018 (NL67059.068.18). The results of this study

1
2
3 will be disseminated in presentations at academic conferences, publications in peer-reviewed
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5 journals, and other news media.
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9 **Registration details.** The study is registered in the trial register www.clinicaltrials.gov with
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11 number NCT02790021.
12
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14 15 16 17 18 **Strengths and limitations of this study** 19

- 20 - This is the first multicenter RCT that compares lymphaticovenous anastomosis
21 operation with conservative therapy (the standard care) in patients with breast cancer-
22 related lymphedema.
23
24
- 25 - Effectiveness of lymphaticovenous anastomosis is examined in terms of patient-
26 relevant, clinical and economic outcomes; health-related quality of life, excess limb
27 volume, discontinuation rate of conservative treatment, societal costs, and cost-
28 effectiveness.
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- 31 - This study contains digital questionnaires with automatic warnings in case of blank
32 answers to minimize missing data.
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- 35 - Cost-effectiveness analysis may not be generalizable to other countries.
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47 **Key words** 48

49 Breast cancer lymphedema, lymphaticovenous anastomosis, conservative treatment,
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51 randomized controlled trial, quality of life
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Study title

Long study title: *Improving the quality of life of patients with breast cancer-related lymphedema by lymphaticovenous anastomosis (LVA): A multicenter randomized controlled trial protocol.*

Study Acronym: *LYMPH trial*

Introduction

An increasing number of women survive breast cancer due to advancements in treatment options. As a result, the number of women living with the long-term effects of breast cancer treatment grows, making the quality of survivorship more relevant. Between 8-56% of breast cancer survivors develop arm or shoulder problems such as restricted shoulder mobility, shoulder pain, and lymphedema (1-6), with one of the most underestimated and debilitating morbidities of them all being upper-limb lymphedema.

Up to 70% of the patients who develop breast cancer-related lymphedema (BCRL) do so within the first two years post-treatment, cases have been described of women developing upper limb lymphedema 20 years or later after initial treatment (7-13). In the Netherlands, between 7% and 30% of the 14,000 annual patients with invasive breast cancer will develop lymphedema depending on certain treatment and patient related risk factors (14, 15).

The following risk factors are associated with the development (and severity) of BCRL: the extent of breast/axillary surgery, adjuvant radiation, (neo-)adjuvant chemotherapy, the number of positive nodes, treatment in dominant limb, and obesity (1, 16-19). Limb swelling may present with symptoms of heaviness, tightness, pain, and loss of normal upper-limb function and range of motion. The negative psychological effects brought on by the impairments of activities in daily life and reduced limb aesthetics constitute an additional burden and decrease in health-related quality of life (HRQoL) (7, 11, 13). Moreover,

1
2
3 infections of the skin are regularly seen in a severe stadium of lymphedema, such as
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5 erysipelas or cellulitis (4, 8).
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10 *Conservative therapy*

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12 Complex decongestive therapy (CDT), currently accepted as the standard treatment
13
14 method for lymphedema, is initially aimed at alleviating symptoms without curative intent,
15
16 which for most patients means lifelong treatment and a constant reminder of the breast cancer
17
18 period. CDT includes general skin care, patient education, compression therapy with
19
20 compression bandages and stockings, manual lymphatic drainage, and exercise therapy (14,
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22 20, 21). A systematic review concluded that compression stockings in combination with
23
24 manual lymph drainage induces a significant limb volume reduction of 17 to 60 % (22).
25
26 Another RCT demonstrated a 29% reduction in excess limb volume with combined
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28 conservative therapy (23). However, after reaching maximum limb volume reduction,
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30 compression stockings are lifelong necessary for the patients to maintain the volume
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32 reduction obtained.
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40 *Lymphaticovenous anastomosis*

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42 Connections can be made between the lymphatic and venous systems to divert static
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44 lymph fluid away from the obstruction site in a technique called lymphaticovenous
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46 anastomosis (LVA) (24). Due to advancements, microvascular surgery is more developed and
47
48 anastomoses in vessels as small as 0.3mm in diameter are made possible.
49
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51
52 Several studies on lymphatic super microsurgery performing LVA are available (25-
53
54 36). Most of the studies describe results on both upper and lower limb lymphedema and not
55
56 only secondary lymphedema (25, 33). Nevertheless, studies mention a volume or
57
58 circumference decrease between 30% and 61%, and positive results on subjective complaints
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3 with low incidence or no complications (25-27, 29, 30, 35, 36). Furthermore, 56% of the
4
5 patients eventually were able to discontinue compression stockings after an LVA
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7 procedure(25).
8
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10 Many studies have been performed but most of them report on a small study
11
12 population. Furthermore most of them were retrospective, few were prospective, yet none of
13
14 them were randomized. Another disadvantage is the heterogeneity of the patient population,
15
16 assessment modalities, and inconsistent reporting of outcomes and complications (25, 28, 33).
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19 The aim of this multicenter RCT is to examine HRQoL and cost-effectiveness of LVA
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21 compared with CDT in patients with BCRL.
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27 **Methods and analysis**

28 **Study Design**

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34 The LYMPH trial is a multicenter, non-blinded, randomized controlled trial and will
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36 be conducted in the Maastricht University Medical Centre, Radboud University Medical
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38 Centre, Zuyderland Medical Centre, and Canisius-Wilhelmina Hospital in the Netherlands.
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43 Enrolment will take place at the outpatient clinics of the participating hospitals. The
44
45 inclusion and exclusion criteria are listed in Table 1. A total of 120 women must be recruited
46
47 after a period of two years. After inclusion and informed consent, participants will be
48
49 randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per
50
51 a computer generated randomization schedule stratified by site using block randomization.
52
53 The start date of the study is November 2018 and the estimated completion date of the study
54
55 is November 2022. An overview of the study design is shown in Figure 1.
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Table 1 Inclusion and exclusion criteria

Inclusion criteria

- Woman over 18 years old
- Breast cancer treatment with SLNB, ALND, or axillary Rt
- Early stage lymphedema of the arm (stage 1 – 2a on ISL classification)
- Viable lymphatic vessels as determined by ICG lymphography, stage \leq 3.
- At least three months conservative therapy (standard of care)
- Primary breast cancer
- Unilateral disease and treatment
- Informed consent

Exclusion criteria

- History of earlier lymph reconstruction efforts
- Recurrent breast cancer
- Distant breast cancer metastases
- Bilateral lymphedema
- Primary congenital lymphedema

SLNB; Sentinel Lymph Node Biopsy, ALND; Axillary Lymph Node Dissection, Rt; radiotherapy, ISL; International Society of Lymphology

Interventions to be measuredGroup A: Conservative Therapy

The current standard of treatment for BCRL is a combination of different methods of conservative therapy, also known as complex decongestive therapy (CDT) (14). CDT incorporates two stages of treatment. The first treatment phase entails skincare, manual

1
2
3 lymphatic drainage (MLD), exercises aimed at improvement of mobility/range of motion in
4
5 the shoulder, elbow or wrist joints, and compression therapy through bandaging. CDT in the
6
7 second treatment phase is aimed at maintenance of the achieved limb volume/ circumference
8
9 reduction through compression therapy with therapeutic elastic stocking for the arm. Skincare,
10
11 mobility exercises, and MLD is continued in this phase if needed (14, 22).
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17 *Complex decongestive therapy*

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19 Patients allocated to group A will be referred to one of the following dedicated
20
21 lymphedema (physical-/skin-) therapy clinics according to their place of residence for
22
23 continuation of standard conservative therapy. Only standard conservative therapy, as they
24
25 would have gotten if not participating in this study, will take place in these clinics, no study
26
27 measurements.
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31 All women identified with lymphedema will be treated according to a protocol which
32
33 is already in use for patients not participating in this study, since it is considered as the best
34
35 available standard care. To be able to compare the outcomes for the conservative therapy
36
37 group, a standardized treatment protocol using the standard lymphatic drainage methods
38
39 applied in the Netherlands and Germany ('Verdonkmethod' and 'Asdonkmethod',
40
41 respectively), will be used in this study.
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49 Group B: Surgical treatment

50 51 *Lymphaticovenous anastomosis*

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53 LVA is a relative minimally invasive registered procedure which can be performed
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55 under local anesthesia. The patient lies comfortable on the operation table and a limb table is
56
57 used. The limb is then prepared for surgery.
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2
3 Before making the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is
4
5 injected at the site of incision to achieve local anesthesia and optimal hemostasis.
6

7
8 The following steps of the operation are performed using a surgical microscope. Based on the
9
10 ICG lymphography mapping, incisions of 1 to 2 cm are made at the predetermined sites.
11

12 Lymphatic vessels are identified and an anastomosis is performed with a similarly sized
13
14 adjacent recipient vein in the subdermal plane. The anastomosis is usually performed in an
15
16 end-to-end fashion in case both the lymphatic vessel and vein have approximately the same
17
18 caliber (otherwise end-to-side). The end-to-end anastomose is created with an 11-0 suture.
19

20
21 The patency of the LVA is confirmed by direct visual examination under the microscope. On
22
23 average 1 to 4 anastomosis are performed in a lymphedematous arm. The superficial wound is
24
25 closed using 4-0 Ethilon covered by adhesive plasters and a bandage. The operation length is
26
27 approximately two to three hours (27).
28
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32 33 *Post-operative treatment*

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35 After surgery, patients will be treated with conservative therapy for 3 months (37).
36
37 After this period, it will be determined whether conservative therapy can be reduced or
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39 stopped. Follow-up moments will be at 3, 6, 12, 18 and 24 months post-operatively. The same
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41 follow-up moments apply for the CDT group.
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48 **Sample size calculation**

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50 We made the following assumptions for the calculation of the sample size to show a
51
52 statistically significant and clinically relevant difference in quality of life between treatment
53
54 groups at 12 months follow-up as measured with the Lymph-ICF:
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3 Comparing LVA to conservative treatment, the minimal difference in health-related quality of
4 life (HRQoL) that is considered as clinically relevant is 15 points (15% decrease on the 0 to
5 100 scale) on the Lymph-ICF questionnaire at 12 months follow-up (38).
6
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8
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10 To be able to achieve a power of 80%, a total of 45 patients are needed per treatment group,
11 when the standard deviation is 25%, using an alpha of 0.05. If a drop-out rate (loss-to-follow-
12 up and patients with missing data) of 25% is taken into account, a sample size of 60 patients
13 per treatment group is required and a total of 120 patients will be randomized.
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19 Using the numbers described above a sample size calculation results in a sample size of 60
20 patients in each group.
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23 24 25 **Outcomes**

26 27 28 *Primary outcome*

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30
31 The primary outcome is HRQoL at 12 months follow-up. To assess the effectiveness
32 of the treatment we will use the Dutch version of the “Lymphedema Functioning, Disability
33 and Health” (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in
34 function, activity limitations, and participation restrictions of patients with arm lymphedema.
35
36
37 It is a validated, disease-specific questionnaire, consisting of 29 items (questions) across 5
38 domains. Each item is scored on a VAS ranging from 0 to 100. The total score on the Lymph-
39 ICF is equal to the sum of the item scores divided by the total number of answered items. A
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51
52 HRQoL will be measured at baseline and 3, 6, 12, 18 and 24 months after
53 randomization.
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58 59 60 *Secondary outcomes*

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3 Secondary outcomes are the societal costs, QALYs, incremental cost-effectiveness,
4
5 discontinuation of conservative treatment, and excess limb volume. Assessment will be done
6
7 at baseline and 3, 6, 12, 18, and 24 months after randomization.
8
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10 Costs include health care related costs, costs to patients and family, and costs due to
11
12 lost productivity. Complete individual level hospital resource use data (e.g. surgical
13
14 intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be
15
16 measured using medical records and provider information systems. Resource use outside the
17
18 hospital (e.g. lymphedema therapy, general practitioner visits, out-of-pocket expenses such as
19
20 for therapeutic elastic stockings and over-the counter drugs, travel costs, and quantities of lost
21
22 paid work) will be determined by means of prospective cost diaries as kept by participants.
23
24 The cost diary developed for this study is an adapted version of the MCQ and PCQ (39). The
25
26 Dutch manual for costing research will be used to determine prices for each volume of
27
28 resource use (40).
29
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31

32
33 The EQ-5D-5L is a generic HRQoL measure that can be used to calculate QALYs to
34
35 be used in the economic evaluation (41). The EQ-5D is a questionnaire responsive to changes
36
37 in health in breast cancer patients after conclusion of treatment (42).
38
39

40 The EQ-5D-5L examines a patient's HRQoL on the day of the interview. It consist of
41
42 the EQ-5D-5L descriptive system and a Visual Analog Scale (EQ VAS). The descriptive
43
44 system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and
45
46 anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate
47
48 problems, severe problems and extreme problems. Responses to the 5 items result in a
49
50 patient's health state that can be transformed into an index score representing a HRQoL-
51
52 weight, ranging between 0 (death) and 1 (perfect health) (43). These index scores are
53
54 combined with length of life to calculate the QALYs. The EQ VAS records the patient's self-
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1
2
3 rated health with endpoints labelled ‘the best health you can imagine’ at the top and ‘the worst
4 health you can imagine’ at the bottom.
5
6

7 Discontinuation of conservative treatment will be assessed with a patient diary to
8 record the frequency of treatments received (i.e. skin therapy visits, number of stockings,
9 etc.).
10
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12

13
14 Lastly, bilateral limb volume measurements will be done using VECTRA 3D imaging
15 and the water displacement method. The excess limb volume is measured as the difference in
16 volume between the affected and unaffected limb, which is reported as a percentage of the
17 volume of the unaffected limb. A relative volume reduction (relative to the unaffected arm) as
18 well as an absolute volume reduction (volume reduction of the affected arm at next
19 measurement) will be calculated. The calculated volume will be corrected for the body mass
20 index and for volume differences between the dominant and non-dominant arm.
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30 Besides using the water displacement method, volume measurement will also be done
31 by arm circumference measurement using tape. Both arms will be measured during every visit
32 at the level of the olecranon, 5 and 10 centimeters proximally, 5 and 10 centimeters distally, at
33 the level of the wrist and the dorsum of the hand.
34
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40 In the out-patient clinic, a fluorescent marker, called indocyanine green (ICG) is
41 injected intracutaneously into the second and fourth finger webspace of the lymphedematous
42 limb and a so called ICG lymphography is performed in search for viable lymphatic vessels.
43 This is a technique using near-infrared fluorescence imaging (NIRF). After 0.05 ml of ICG
44 (5mg/ml) is injected, a near-infrared camera is used to visualize the lymphatic vessels.
45 Proximal to the injection sites fluorescent stains are identified. When using the images as a
46 guide, the lymphatic pathways and the sites for incisions for lymphaticovenous anastomoses
47 are marked with a pen and a color picture is taken. These color pictures are used to identify
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2
3 the location when LVA will be performed. NIRF will be done at introduction visit and
4
5 patency testing after 12 and 24 months.
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10 **Data analysis**

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12
13 For the HRQoL a paired Student's t-test will be used to evaluate the changes in quality
14
15 of life scores and in limb volume measurements between pre-inclusion and the different post-
16
17 inclusion periods of time within individuals from the same study group. For each of the
18
19 follow-up moments (3, 6, 12, 18 and 24 months) the change in quality of life from baseline
20
21 will be compared between groups using the two sample unpaired t-test, to evaluate short- and
22
23 long-term treatment effects. If baseline imbalance is present, assessed qualitatively, adjusted
24
25 differences per follow-up moment will be computed using linear regression. In addition to
26
27 statistical testing per follow-up measurement, a linear mixed-effects model will be used to test
28
29 for an overall difference between the two groups. To account for clustering of measurements
30
31 at the patient-level, a model with a random intercept and random slope will be used.
32
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38 *Economic evaluation*

39
40 An economic evaluation will be performed alongside the clinical trial to determine the cost-
41
42 effectiveness of LVA compared to CDT. The design of the economic evaluation follows the
43
44 principles of a cost-utility analysis and adheres to the Dutch guideline for economic
45
46 evaluations in health care and the Dutch manual for costing research (44, 45) Outcome
47
48 measures for the economic evaluation will be costs, health-related quality of life, and quality
49
50 adjusted life years (QALYs). The trial-based evaluation adopts a societal perspective and has
51
52 a time horizon of two years.
53
54
55

56 An incremental cost-effectiveness ratio (ICER), i.e. cost per QALY gained, will be
57
58 calculated by dividing the difference in costs between the two treatments with the difference
59
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1
2
3 in QALYs. Bootstrapping techniques will be used to summarize the uncertainty in estimates
4
5 of incremental costs, effects, and the ICER. In addition, cost-effectiveness acceptability
6
7 curves (CEACs) will show the probability that LVA is cost-effective compared to
8
9 conservative treatment, given the observed data, for a range of maximum monetary values
10
11 that a decision-maker might be willing to pay for a QALY gained.
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16 The impact of uncertainty surrounding deterministic parameters (for example prices) on the
17
18 ICER will be explored using one-way sensitivity analyses. Results, presented in a tornado
19
20 diagram, can help determine which parameters are key drivers of the cost-effectiveness
21
22 results. Pre-determined subgroup analyses will address possible variation between patients
23
24 (heterogeneity).
25
26

27
28 In the case of missing values occur, this will be solved by imputation by means of mean
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30 substitution.
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33 34 **Ethics and Dissemination**

35 36 37 **Data monitoring**

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41 Data will be handled confidentially. Source data will be stored by the investigator in a
42
43 locked place. Data of all measurements during follow-up moments, (Serious) Adverse Events
44
45 and digital questionnaires including patient cost diary is stored immediately in the online
46
47 database of CASTOR EDC ©. The investigator and project leader only have access to this
48
49 database with an account with password. Identifying data will be stored in coded form; the
50
51 key to the form is known only to the supervisor, the investigator, the Dutch Health Care
52
53 Inspectorate (IGJ), the study monitors, and the members of the review committee.
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58 59 **Harms**

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2
3 Adverse events (AEs) are defined as any undesirable experience occurring to a subject
4 during the study, whether or not considered related to the trial procedure. Adverse events
5 related to the LVA operation or conservative therapy that have a possible impact on the
6 lymphedema and reported spontaneously by the subject or observed by the investigator or his
7 staff will be recorded directly in CASTOR EDC.
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14 The research team will report the serious adverse event (SAEs) through the web portal
15 *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first
16 knowledge for SAEs that result in death or are life threatening followed by a period of
17 maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported
18 within a period of maximum 15 days after the research team has first knowledge of the
19 serious adverse events.
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29 **Auditing**

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33 Monitoring of the conduct of the study will be done by the Clinical Trial Center
34 Maastricht on a frequent basis following their protocol as is requested by the Board.
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40 **Protocol amendments**

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42
43 Any modifications to the protocol which may impact the study will be notified to the
44 METC that gave a favourable opinion prior to implementation.
45
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49 **Patient and public involvement**

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52 Patients were not involved in the development of the research question, study design
53 or recruitment into the study.
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58 **Ethical considerations**

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2
3 This study will be conducted according to the principles of the Declaration of
4 Helsinki, recently changed in Fortaleza (2013) and in accordance with the Medical Research
5 Involving Human Subjects Act (WMO). The study was approved by the Ethics Committee of
6 Maastricht University Medical Centre on 19 December 2018 (NL67059.068.18). The study is
7 registered in the trial register www.clinicaltrials.gov with number NCT02790021.
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15 16 **Dissemination**

17 The results of this study will be disseminated in presentations at academic
18 conferences, publications in peer-reviewed journals and other news media. Data will be kept
19 confidential and will not be shared with the public. Requests for data sharing for appropriate
20 research purposes will be considered on an individual basis after trial completion and after
21 publication of primary manuscripts.
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34 35 **References**

- 36
37 1. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and
38 quality of life in breast cancer survivors: the Iowa Women's Health Study. *J Clin Oncol.*
39 2008;26(35):5689-96.
40
41
- 42
43 2. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in
44 breast cancer survivors, the Iowa Women's Health Study. *Breast Cancer Res Treat.*
45 2011;130(3):981-91.
46
47
48
- 49
50 3. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely
51 affects quality of life: results of a 5-year prospective study in breast cancer patients. *Breast*
52 *Cancer Res Treat.* 2003;79(1):47-57.
53
54
55
- 56
57 4. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and
58 management. *World J Clin Oncol.* 2014;5(3):241-7.
59
60

- 1
2
3 5. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast
4
5 cancer survivors are associated with reduced health and poorer physical quality of life. *Acta*
6
7 *Oncol.* 2010;49(3):347-53.
8
- 9
10 6. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. *Cancer.*
11
12 1998;83(12 Suppl American):2776-81.
13
- 14
15 7. Chachaj A, Malyszczak K, Pyszczel K, Lukas J, Tarkowski R, Pudelko M, et al.
16
17 Physical and psychological impairments of women with upper limb lymphedema following
18
19 breast cancer treatment. *Psychooncology.* 2010;19(3):299-305.
20
- 21
22 8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema
23
24 after breast cancer: a systematic review and meta-analysis. *Lancet Oncol.* 2013;14(6):500-15.
25
- 26
27 9. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial
28
29 impact of lymphedema-related distress among breast cancer survivors in the WHEL Study.
30
31 *Psychooncology.* 2014;23(9):1049-56.
32
- 33
34 10. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact
35
36 of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology.*
37
38 2013;22(7):1466-84.
39
- 40
41 11. Oliveri JM, Day JM, Alfano CM, Herndon JE, 2nd, Katz ML, Bittoni MA, et al.
42
43 Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-
44
45 diagnosis: CALGB 79804. *J Cancer Surviv.* 2008;2(4):233-42.
46
- 47
48 12. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast
49
50 carcinoma survivors 20 years after diagnosis. *Cancer.* 2001;92(6):1368-77.
51
- 52
53 13. Voogd AC, Ververs JM, Vingerhoets AJ, Roumen RM, Coebergh JW, Crommelin
54
55 MA. Lymphoedema and reduced shoulder function as indicators of quality of life after
56
57 axillary lymph node dissection for invasive breast cancer. *Br J Surg.* 2003;90(1):76-81.
58
59
60

- 1
2
3 14. Venereologie NvvDe. Richtlijn lymfoedeem. Multidisciplinaire evidence-based
4
5 richtlijn. www.lymfoedeem.nl; 2014.
6
7
- 8 15. Richtlijn mammacarcinoom. 2012. Available from: www.oncoline.nl
9
- 10 16. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity
11
12 results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary
13
14 dissection. *J Surg Oncol*. 2010;102(2):111-8.
15
16
- 17 17. Coriddi M, Khansa I, Stephens J, Miller M, Boehmler J, Tiwari P. Analysis of factors
18
19 contributing to severity of breast cancer-related lymphedema. *Ann Plast Surg*. 2015;74(1):22-
20
21 5.
22
- 23 18. Monleon S, Murta-Nascimento C, Bascuas I, Macia F, Duarte E, Belmonte R.
24
25 Lymphedema Predictor Factors after Breast Cancer Surgery: A Survival Analysis. *Lymphat*
26
27 *Res Biol*. 2015;13(4):268-74.
28
29
- 30 19. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk
31
32 of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment
33
34 factors. *Ann Surg Oncol*. 2009;16(7):1959-72.
35
36
- 37 20. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic
38
39 drainage and intermittent pneumatic compression pump use in the treatment of lymphedema
40
41 after mastectomy: a randomized controlled trial. *Breast Cancer*. 2015;22(3):300-7.
42
43
- 44 21. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-
45
46 related lymphedema after intensive decongestive physiotherapy. *Breast Cancer Res Treat*.
47
48 2007;101(3):285-90.
49
50
- 51 22. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary
52
53 interventions for cancer-related lymphedema: a systematic review and meta-analysis. *Cancer*.
54
55 2011;117(6):1136-48.
56
57
58
59
60

- 1
2
3 23. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al.
4
5 Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in
6
7 women with breast cancer. *J Clin Oncol*. 2013;31(30):3758-63.
8
9
10 24. O'Brien BM. Replantation and reconstructive microvascular surgery. Part II. *Ann R*
11
12 *Coll Surg Engl*. 1976;58(3):171-82.
13
14 25. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a
15
16 systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue
17
18 transplantation. *Plast Reconstr Surg*. 2014;133(4):905-13.
19
20
21 26. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer
22
23 patients: a prospective study. *Plast Reconstr Surg*. 2010;126(3):752-8.
24
25
26 27. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive
27
28 lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg*.
29
30 2013;132(5):1305-14.
31
32
33 28. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous
34
35 anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11
36
37 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of
38
39 the literature. *Breast Cancer Res Treat*. 2009;113(2):199-206.
40
41
42 29. Furukawa H, Osawa M, Saito A, Hayashi T, Funayama E, Oyama A, et al.
43
44 Microsurgical lymphaticovenous implantation targeting dermal lymphatic backflow using
45
46 indocyanine green fluorescence lymphography in the treatment of postmastectomy
47
48 lymphedema. *Plast Reconstr Surg*. 2011;127(5):1804-11.
49
50
51 30. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical
52
53 lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J*
54
55 *Reconstr Microsurg*. 2000;16(6):437-42.
56
57
58
59
60

- 1
2
3 31. Mihara M, Hara H, Hayashi Y, Iida T, Araki J, Yamamoto T, et al. Upper-limb
4 lymphedema treated aesthetically with lymphaticovenous anastomosis using indocyanine
5 green lymphography and noncontact vein visualization. *J Reconstr Microsurg.*
6
7
8
9
10 2012;28(5):327-32.
11
12 32. Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, Gorai K, et al. Treatment of
13 lymphedema with lymphaticovenular anastomoses. *Int J Clin Oncol.* 2005;10(5):304-10.
14
15 33. Penha TR, Ijsbrandy C, Hendrix NA, Heuts EM, Voogd AC, von Meyenfeldt MF, et
16 al. Microsurgical techniques for the treatment of breast cancer-related lymphedema: a
17 systematic review. *J Reconstr Microsurg.* 2013;29(2):99-106.
18
19 34. Torrisi JS, Joseph WJ, Ghanta S, Cuzzzone DA, Albano NJ, Savetsky IL, et al.
20 Lymphaticovenous bypass decreases pathologic skin changes in upper extremity breast
21 cancer-related lymphedema. *Lymphat Res Biol.* 2015;13(1):46-53.
22
23 35. Yamamoto Y, Horiuchi K, Sasaki S, Sekido M, Furukawa H, Oyama A, et al. Follow-
24 up study of upper limb lymphedema patients treated by microsurgical lymphaticovenous
25 implantation (MLVI) combined with compression therapy. *Microsurgery.* 2003;23(1):21-6.
26
27 36. Cornelissen AJM, Beugels J, Ewalds L, Heuts EM, Keuter XHA, Piatkowski A, et al.
28 Effect of Lymphaticovenous Anastomosis in Breast Cancer-Related Lymphedema: A Review
29 of the Literature. *Lymphat Res Biol.* 2018;16(5):426-34.
30
31 37. Masia J, Pons G, Nardulli ML. Combined Surgical Treatment in Breast Cancer-
32 Related Lymphedema. *J Reconstr Microsurg.* 2016;32(1):16-27.
33
34 38. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR.
35 Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and
36 validity. *Phys Ther.* 2011;91(6):944-57.
37
38 39. Bouwmans Cea. Handleiding iMTA Medical Cost Questionnaire (iMCQ). 2013.
39
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42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
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2
3 40. Lopez Penha TR, van Roozendaal LM, Smidt ML, Boersma LJ, von Meyenfeldt MF,
4
5 Voogd AC, et al. The changing role of axillary treatment in breast cancer: Who will remain at
6
7 risk for developing arm morbidity in the future? *Breast*. 2015;24(5):543-7.
8
9
10 41. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and
11
12 preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*.
13
14 2011;20(10):1727-36.
15
16 42. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in
17
18 breast cancer patients in their first year after treatment. *Health Qual Life Outcomes*.
19
20 2009;7:11.
21
22 43. Versteegh M VM, Evers MAAS, de Wit GA, Prenger R. Dutch Tariff for the Five-
23
24 Level Version of EQ-5D. *Value in health: the journal of the International Society for*
25
26 *Pharmacoeconomics and Outcomes Research*. 2016.
27
28 44. Zorginstituut. *Kostenhandleiding: Methodologie van kostenonderzoek en*
29
30 *referentieprijzen voor economische evaluaties in de gezondheidszorg*. 2015.
31
32 45. Zorginstituut. *Richtlijn voor het uitvoeren van economische evaluaties in de*
33
34 *gezondheidszorg*; 2015.
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Footnotes

Author Contributions

44
45
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47
48 *JB, AP, EH, DU, RH, and SQ* conceived the study and initiated the study design. *MK* provided
49
50 statistical and cost-effectiveness expertise. *JW, XK, HT, DU, and SQ* completed the study
51
52 design and protocol. All authors contributed to refinement of the study protocol and approved
53
54 the final version.
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Competing interests

None declared.

Patient consent for publication

Informed consent will be signed by every participant and obtained by the researcher after inclusion.

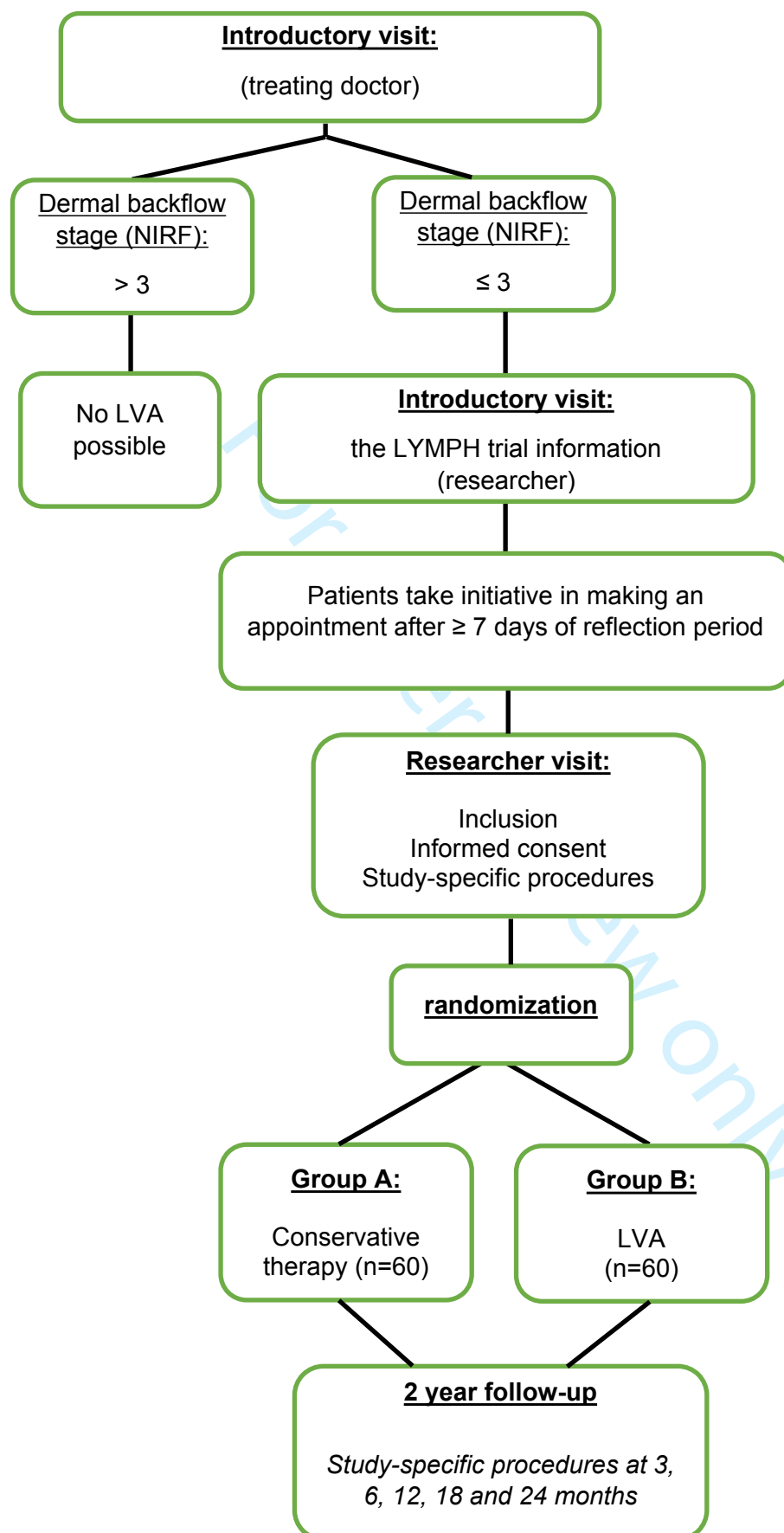


Fig 1 Flowchart: overview of the study design



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 16
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	V4, 15-04-2019
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	22
	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	NA
	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)	NA

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 4-6
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention

5

6 6b Explanation for choice of comparators 4-6

7

8 Objectives 7 Specific objectives or hypotheses 6

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
 11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 6

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 6
 17 be collected. Reference to where list of study sites can be obtained

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 7
 20 individuals who will perform the interventions (eg, surgeons, psychotherapists)

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 7-9
 23 administered

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose NA
 26 change in response to harms, participant request, or improving/worsening disease)

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence NA
 29 (eg, drug tablet return, laboratory tests)

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial NA

32

33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
 35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, 10-13
 36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
 37 efficacy and harm outcomes is strongly recommended

38

39

40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 6, Fig 1
 41 participants. A schematic diagram is highly recommended (see Figure)

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1	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	9, 10
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

10	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	6
11				
12				
13				
14				
15				
16	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	NA
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, Fig 1
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

33	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	10-14
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39		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	3
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1	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	14, 15
2				
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4				
5	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	13, 14
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
9				
10		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)	14
11				
12				
13				

14 **Methods: Monitoring**

15				
16	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	15
17				
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22		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	NA
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24				
25	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	15
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
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32 **Ethics and dissemination**

33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
35				
36				
37	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)	15
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22, Fig 1
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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	14
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
11				
12				
13	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	Contractual agreement is present
14				
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18	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	Insurance is included in case of harm
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20				
21				
22	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	16
23				
24				
25				
26				
27		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
28				
29		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
30				
31	Appendices			
32				
33	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Model provided by Central Committee on Research Involving Human Subjects (CCMO)
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1	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA
2	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	

4 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
5 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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For peer review only

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BMJ Open

Improving the quality of life of patients with breast cancer-related lymphedema by lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized controlled trial.

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Secondary Subject Heading:	Dermatology, Surgery
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Manuscripts

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3 **Improving the quality of life of patients with breast cancer-related lymphedema by**
4 **lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized**
5 **controlled trial.**
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Abstract

Introduction. Early breast cancer detection and advancements in treatment options have resulted in an increase of breast cancer survivors. An increasing number of women are living with the long-term effects of breast cancer treatment, making the quality of survivorship an increasingly important goal. Breast cancer-related lymphedema (BCRL) is one of the most underestimated complications of breast cancer treatment with a reported incidence of 20%. A microsurgical technique called lymphaticovenous anastomosis (LVA) might be a promising treatment modality for patients with BCRL.

The main objective is to assess whether LVA is more effective than the current standard therapy (conservative treatment) in terms of improvement in quality of life and whether it is cost-effective.

Methods and analysis. A multicenter, randomized controlled trial, carried out in two academic and two community hospitals in the Netherlands. The study population includes 120 women over the age of 18 who underwent treatment for breast cancer including axillary treatment (sentinel lymph node biopsy or axillary lymph node dissection) and/or axillary radiotherapy, presenting with an early stage lymphedema of the arm, viable lymphatic vessels, and received at least three months conservative treatment. Sixty participants will undergo the LVA operation and the other sixty will continue their regular conservative treatment, both with a follow-up of 24 months.

The primary outcome is the health-related quality of life. Secondary outcomes are societal costs, QALYs, cost-effectiveness ratio, discontinuation rate of conservative treatment, and excess limb volume.

Ethics and dissemination. The study was approved by the Ethics Committee of Maastricht University Medical Center on 19 December 2018 (NL67059.068.18). The results of this study will be disseminated in presentations at academic conferences, publications in peer-reviewed journals, and other news media.

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2
3 **Registration details.** The study is registered in the trial register www.clinicaltrials.gov with
4
5 number NCT02790021.
6
7

8 **Strengths and limitations of this study**

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- 10
11 - This multicenter RCT compares the lymphaticovenous anastomosis operation with
12
13 conservative therapy (the standard care) in patients with breast cancer-related
14
15 lymphedema.
16
17 - Effectiveness of lymphaticovenous anastomosis is examined in terms of patient-
18
19 relevant, clinical, and economic outcomes; health-related quality of life, excess limb
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21 volume, discontinuation rate of conservative treatment, societal costs, and cost-
22
23 effectiveness.
24
25 - This study contains digital questionnaires and a patient diary with automatic warnings
26
27 in case of blank answers to minimize missing data.
28
29 - Blinding of patients or researcher is not possible in this study due to visible scars
30
31 postoperatively.
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33 - Cost-effectiveness analysis may not be generalizable to other countries.
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42 **Key words**

43
44 Breast cancer lymphedema, lymphaticovenous anastomosis, conservative treatment,
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46 randomized controlled trial, quality of life
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52 **Study title**

53
54 Long study title: *Improving the quality of life of patients with breast cancer-related*
55
56 *lymphedema by lymphaticovenous anastomosis (LVA): Study protocol of a multicenter*
57
58 *randomized controlled trial.*
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3 Study Acronym: *LYMPH trial*
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7 **Introduction**

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10 An increasing number of women survive breast cancer due to advancements in
11 treatment options. As a result, the number of women living with the long-term effects of
12 breast cancer treatment grows, making the quality of survivorship more relevant. Between 8-
13 56% of breast cancer survivors develop arm or shoulder problems such as restricted shoulder
14 mobility, shoulder pain, and lymphedema (1-6), with one of the most underestimated and
15 debilitating morbidities of them all being upper limb lymphedema.
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23 Up to 70% of the patients who develop breast cancer-related lymphedema (BCRL) do
24 so within the first two years post-treatment, however, cases have been described of women
25 developing upper limb lymphedema 20 years or later after initial treatment (7-13). In the
26 Netherlands, between 7% and 30% of the 14,000 annual patients with invasive breast cancer
27 will develop lymphedema depending on certain treatment and patient related risk factors (14,
28 15).
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37 The following risk factors are associated with the development (and severity) of
38 BCRL: the extent of breast/axillary surgery, adjuvant radiation, (neo-)adjuvant chemotherapy,
39 the number of positive nodes, treatment in dominant limb, and obesity (5, 16-20). Limb
40 swelling may present with symptoms of heaviness, tightness, pain, and loss of normal arm
41 function and range of motion. The negative psychological effects brought on by the
42 impairments of activities in daily life and reduced limb aesthetics constitute an additional
43 burden and decrease in health-related quality of life (HRQoL) (1, 7, 11, 13, 21). Moreover,
44 infections of the skin are regularly seen in a severe stadium of lymphedema, such as
45 erysipelas or cellulitis (2, 8, 21).
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Conservative therapy

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Complex decongestive therapy (CDT), currently accepted as the standard treatment for lymphedema, is initially aimed at alleviating symptoms without curative intent, which for most patients means lifelong treatment and a constant reminder of the breast cancer period. CDT includes general skin care, patient education, compression therapy with compression bandages and garment, manual lymphatic drainage, and exercise therapy (14, 22, 23). A systematic review concluded that compression garment in combination with manual lymph drainage induces a significant limb volume reduction of 17 to 60 % (24). Another RCT demonstrated a 29% reduction in excess limb volume with combined conservative therapy (25). However, after reaching maximum limb volume reduction, compression garment are lifelong necessary for the patients to maintain the volume reduction obtained.

Lymphaticovenous anastomosis

Connections can be made between the lymphatic and venous systems to divert static lymph fluid away from the obstruction site in a technique called lymphaticovenous anastomosis (LVA) (26). Due to advancements, microvascular surgery is more developed and anastomoses in vessels as small as 0.3 mm in diameter are made possible.

Several studies on lymphatic super microsurgery performing LVA are available (26-41). Most of the studies describe results on both upper and lower limb lymphedema and not only secondary lymphedema (27, 34). Nevertheless, studies mention a volume or circumference decrease between 30% and 61%, and positive results on subjective complaints with low incidence or no complications (26-29, 31, 36-39, 41). Furthermore, more than half of the patients eventually were able to discontinue compression garment after an LVA procedure (27, 42).

Many studies have been performed, mostly reporting on a small study population. Furthermore, the majority were retrospective, few were prospective, yet none of them were

1
2 randomized. Another disadvantage is the heterogeneity of the patient population, assessment
3 modalities, and inconsistent reporting of outcomes and complications (27, 30, 34).
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7 The aim of this multicenter RCT is to examine HRQoL and (cost-)effectiveness of
8 LVA compared with CDT in a large homogenous group of patients with BCRL.
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12 13 14 15 **Methods and analysis**

16 17 18 19 **Study Design**

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22 The LYMPH trial is a multicenter, non-blinded, randomized controlled trial and will
23 be conducted in the Maastricht University Medical Center, Radboud University Medical
24 Center, Zuyderland Medical Center, and Canisius-Wilhelmina Hospital in the Netherlands.
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29
30 Enrolment will take place at the outpatient clinics of the participating hospitals. The
31 inclusion and exclusion criteria are listed in Table 1. A total of 120 women must be recruited
32 after a period of two years. After inclusion and informed consent, participants will be
33 randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per
34 a computer generated randomization schedule stratified by site using block randomization.
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This computer generated randomization is done within the electronic Case Report Form
(eCRF) in CASTOR EDC ©. Since only early stage lymphedema patients are included and no
large imbalances are expected, no stratification for other demographic data are applied.

Blinding is not possible in this study, since the operation scars on the arm are easily
detectable during the study measurements. However, HRQoL is the primary outcome which is
examined by a digital standardized questionnaire. The patients only have access to the
questionnaires and the researcher has no influence on this data. The start date of the study is

November 2018 and the estimated completion date of the study is November 2022. An overview of the study design is shown in Figure 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria

- Woman over 18 years old
- Breast cancer treatment with SLNB, ALND, or axillary Rt
- Early stage lymphedema of the arm (stage 1 – 2a on ISL classification) (43)
- Viable lymphatic vessels as determined by ICG lymphography, stage ≤ 3 (44)
- At least three months conservative therapy (standard of care)
- Primary breast cancer
- Unilateral disease and treatment
- Informed consent

Exclusion criteria

- History of earlier lymph reconstruction efforts
- Recurrent breast cancer
- Distant breast cancer metastases
- Bilateral lymphedema
- Primary congenital lymphedema

SLNB; Sentinel Lymph Node Biopsy, ALND; Axillary Lymph Node Dissection, Rt; radiotherapy, ISL; International Society of Lymphology, ICG; Indocyanine Green

Interventions to be measured

Group A: Conservative Therapy

The current standard treatment for BCRL is a combination of different methods of conservative therapy, also known as complex decongestive therapy (CDT) (14). CDT incorporates two stages of treatment. The first treatment phase entails skincare, manual lymphatic drainage (MLD), exercises aimed at improvement of mobility/range of motion in the shoulder, elbow or wrist joints, and compression therapy through bandaging. Most patients already underwent this phase short after the diagnosis of lymphedema. CDT in the second treatment phase is aimed at maintenance of the achieved limb volume/ circumference reduction through compression therapy with therapeutic elastic compression garment for the arm. Skincare, mobility exercises, and MLD is continued in this phase if needed (14, 24). Since CDT aim to alleviate symptoms without curative intent, this treatment is mostly lifelong needed. In this study, the patients are followed for 2 years during their regular conservative treatment.

Complex decongestive therapy

Patients allocated to group A will be referred to one of the following dedicated lymphedema (physical-/skin-) therapy clinics, if not already treated by one, according to their place of residence for continuation of standard conservative therapy. Only standard conservative therapy, as they would have gotten if not participating in this study, will take place in these clinics, no study measurements.

All women in this study group will be treated according to a protocol which is already in use for patients not participating in this study, since it is considered as the best available standard care. To be able to compare the outcomes for the conservative therapy group, a standardized treatment protocol using the standard lymphatic drainage methods applied in the Netherlands and Germany ('Verdonkmethod' and 'Asdonkmethod', respectively), will be

1
2 used in this study. Ongoing conservative treatment and the frequency is controlled by the skin
3
4 therapist. All information regarding conservative treatment is noted in the patient diary.
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10 11 12 13 14 Group B: Surgical treatment

15 16 *Lymphaticovenous anastomosis*

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18 LVA is a relative minimally invasive registered procedure which can be performed
19 under local anesthesia. The patient lies comfortable on the operation table and a limb table is
20 used. The limb is then prepared for surgery.
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24 Before making the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is
25 injected at the site of incision to achieve local anesthesia and optimal hemostasis.
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29 The following steps of the operation are performed using a surgical microscope. Based on the
30 ICG lymphography mapping, incisions of 1 to 2 cm are made at the predetermined sites.
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33
34 Lymphatic vessels are identified and an anastomosis is performed with a similarly sized
35 adjacent recipient vein in the subdermal plane. The anastomosis is usually performed in an
36 end-to-end fashion in case both the lymphatic vessel and vein have approximately the same
37 caliber (otherwise end-to-side). The end-to-end anastomosis is created with an 11-0 suture.
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40
41 The patency of the LVA is confirmed by direct visual examination under the microscope. On
42 average 1 to 4 anastomosis are performed in a lymphedematous arm. The superficial wound is
43 closed using 4-0 Ethilon covered by adhesive plasters and a bandage. The operation length is
44 approximately two to three hours (29).
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52 53 54 55 *Post-operative treatment*

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57 From 2 weeks after surgery, when the stitches are removed, patients will be treated
58 with conservative therapy the same way and in the same frequency as preoperatively (45).
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3 After 3 months, the plastic surgeon will determine whether conservative therapy can be
4 reduced or stopped, depending on the decrease of subjective complaints and swelling of the
5 arm. The frequency of manual lymphatic drainage will be controlled by the skin therapist and
6 noted in the patient diary.
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14 Follow-up moments for both groups will be at 3, 6, 12, 18, and 24 months. For group
15 A the follow-up starts from the day of the informed consent signing and for group B from the
16 day of the surgery.
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21 22 23 24 **Sample size calculation**

25
26 We made the following assumptions for the calculation of the sample size to show a
27 statistically significant and clinically relevant difference in quality of life between treatment
28 groups at 12 months follow-up as measured with the Lymph-ICF questionnaire:
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30

31
32 Comparing LVA to conservative treatment, the minimal difference in HRQoL that is
33 considered as clinically relevant is 15 points (15% decrease on the 0 to 100 scale) on the
34 Lymph-ICF questionnaire at 12 months follow-up (46).
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39
40 To be able to achieve a power of 80%, a total of 45 patients are needed per treatment group,
41 when the standard deviation is 25%, using an alpha of 0.05. If a drop-out rate (loss-to-follow-
42 up and patients with missing data) of 25% is taken into account, a sample size of 60 patients
43 per study group is required and a total of 120 patients will be randomized.
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50 51 **Outcomes**

52 53 *Primary outcome*

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55 The primary outcome is HRQoL at 12 months follow-up. To assess the effectiveness
56 of the treatment we will use the Dutch version of the “Lymphedema Functioning, Disability
57 and Health” (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in
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1
2 function, activity limitations, and participation restrictions of patients with upper limb
3 lymphedema. It is a validated, disease-specific questionnaire, consisting of 29 items
4
5 (questions) across 5 domains. Each item is scored on a VAS ranging from 0 to 100. The total
6
7 score on the Lymph-ICF is equal to the sum of the item scores divided by the total number of
8
9 answered items. A higher score on the Lymph-ICF indicates more impact in the functioning in
10
11 the daily life related to upper limb lymphedema (46).
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15
16 HRQoL will be measured at baseline and 3, 6, 12, 18 and 24 months after informed
17
18 consent (Group A), or after surgery (Group B).
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22 23 *Secondary outcomes*

24
25 Secondary outcomes are the societal costs, QALYs, incremental cost-effectiveness,
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27 discontinuation of conservative treatment, and excess limb volume. Assessment will be done
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29 at baseline and 3, 6, 12, 18, and 24 months after informed consent (Group A), or after surgery
30
31 (Group B).
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35 Costs include health care related costs, costs to patients and family, and costs due to
36
37 lost productivity. Complete individual level hospital resource use data (e.g. surgical
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39 intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be
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41 measured using medical records and provider information systems. Resource use outside the
42
43 hospital (e.g. lymphedema therapy, general practitioner visits, out-of-pocket expenses such as
44
45 for therapeutic elastic garment and over-the counter drugs, travel costs, and quantities of lost
46
47 paid work) will be determined by means of prospective cost diaries as kept by participants.
48
49 The cost dairy developed for this study is an adapted version of the MCQ and PCQ (47). The
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51 Dutch manual for costing research will be used to determine prices for each volume of
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53 resource use (48).
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3 The EQ-5D-5L is a generic HRQoL measure that can be used to calculate QALYs to
4 be used in the economic evaluation (49). The EQ-5D is a questionnaire responsive to changes
5 in health in breast cancer patients after conclusion of treatment (50).
6
7

8
9 The EQ-5D-5L examines a patient's HRQoL on the day of the interview. It consist of
10 the EQ-5D-5L descriptive system and a Visual Analog Scale (EQ VAS). The descriptive
11 system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and
12 anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate
13 problems, severe problems and extreme problems. Responses to the 5 items result in a
14 patient's health state that can be transformed into an index score representing a HRQoL-
15 weight, ranging between 0 (death) and 1 (perfect health) (51). These index scores are
16 combined with length of life to calculate the QALYs. The EQ VAS records the patient's self-
17 rated health with endpoints labelled 'the best health you can imagine' at the top and 'the worst
18 health you can imagine' at the bottom.
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32 Discontinuation of conservative treatment will be assessed with a patient diary to
33 record the frequency of treatments received (i.e. skin therapy visits, number of compression
34 garment, etc.).
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39 Lastly, bilateral limb volume measurements will be done using VECTRA 3D imaging
40 and the water displacement method. The excess limb volume is measured as the difference in
41 volume between the affected and unaffected limb, which is reported as a percentage of the
42 volume of the unaffected limb. A relative volume reduction (relative to the unaffected arm) as
43 well as an absolute volume reduction (volume reduction of the affected arm at next
44 measurement) will be calculated. The calculated volume will be corrected for the body mass
45 index and for volume differences between the dominant and non-dominant arm.
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54 Besides using the water displacement method, volume measurement will also be done
55 by arm circumference measurement using tape. Both arms will be measured during every visit
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1
2 at the level of the olecranon, 5 and 10 centimeters proximally, 5 and 10 centimeters distally, at
3
4 the level of the wrist, and the dorsum of the hand.
5
6

7 In the out-patient clinic, a fluorescent marker, called indocyanine green (ICG) is
8
9 injected intracutaneously into the second and fourth finger webspace of the lymphedematous
10
11 limb and a so called ICG lymphography is performed in search for viable lymphatic vessels.
12
13 This is a technique using near-infrared fluorescence imaging (NIRF). After 0.05 ml of ICG
14
15 (5mg/ml) is injected per webspace, a near-infrared camera is used to visualize the lymphatic
16
17 vessels. Proximal to the injection sites fluorescent stains are identified. When using the
18
19 images as a guide, the lymphatic pathways and the sites for incisions for lymphaticovenous
20
21 anastomoses are marked with a pen and a color picture is taken. These color pictures are used
22
23 to identify the location when LVA will be performed. NIRF will be done at introduction visit
24
25 and after 12 and 24 months.
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33 **Data analysis**

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35 For the HRQoL a paired Student's t-test will be used to evaluate the changes in quality
36
37 of life scores and in limb volume measurements between pre-inclusion and the different post-
38
39 inclusion periods of time within individuals from the same study group. For each of the
40
41 follow-up moments (3, 6, 12, 18 and 24 months) the change in quality of life from baseline
42
43 will be compared between groups using the two sample unpaired t-test, to evaluate short- and
44
45 long-term treatment effects. If baseline imbalance is present, assessed qualitatively, adjusted
46
47 differences per follow-up moment will be computed using linear regression. In addition to
48
49 statistical testing per follow-up measurement, a linear mixed-effects model will be used to test
50
51 for an overall difference between the two groups. To account for clustering of measurements
52
53 at the patient-level, a model with a random intercept and random slope will be used.
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Economic evaluation

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2
3 An economic evaluation will be performed alongside the clinical trial to determine the cost-
4 effectiveness of LVA compared to CDT. The design of the economic evaluation follows the
5 principles of a cost-utility analysis and adheres to the Dutch guideline for economic
6 evaluations in health care and the Dutch manual for costing research (52, 53). Outcome
7 measures for the economic evaluation will be costs, health-related quality of life, and quality
8 adjusted life years (QALYs). The trial-based evaluation adopts a societal perspective and has
9 a time horizon of two years.

10
11
12 An incremental cost-effectiveness ratio (ICER), i.e. cost per QALY gained, will be
13 calculated by dividing the difference in costs between the two treatments with the difference
14 in QALYs. Bootstrapping techniques will be used to summarize the uncertainty in estimates
15 of incremental costs, effects, and the ICER. In addition, cost-effectiveness acceptability
16 curves (CEACs) will show the probability that LVA is cost-effective compared to
17 conservative treatment, given the observed data, for a range of maximum monetary values
18 that a decision-maker might be willing to pay for a QALY gained.

19
20
21 The impact of uncertainty surrounding deterministic parameters (for example prices) on the
22 ICER will be explored using one-way sensitivity analyses. Results, presented in a tornado
23 diagram, can help determine which parameters are key drivers of the cost-effectiveness
24 results. Pre-determined subgroup analyses will address possible variation between patients
25 (heterogeneity).

26
27
28 Missing values will be imputed using mean substitution or multiple imputation, as
29 appropriate.

30 31 32 **Ethics and Dissemination**

33 34 35 **Data monitoring**

1
2
3 Data will be handled confidentially. Source data will be stored by the investigator in a
4 locked place. Data of all measurements during follow-up moments, (Serious) Adverse Events
5 and digital questionnaires including patient cost diary are stored immediately in the online
6 database of CASTOR EDC ©. The investigator and project leader only have access to this
7 database with an account with password. Identifying data will be stored in coded form; the
8 key to the form is known only to the supervisor, the investigator, the Dutch Health Care
9 Inspectorate (IGJ), the study monitors, and the members of the review committee.
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20 **Harms**

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22
23 Adverse events (AEs) are defined as any undesirable experience occurring to a subject
24 during the study, whether or not considered related to the trial procedure. Adverse events
25 related to the LVA operation or conservative therapy that have a possible impact on the
26 lymphedema and reported spontaneously by the subject or observed by the investigator or his
27 staff will be recorded directly in CASTOR EDC ©.
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35 The research team will report the serious adverse event (SAEs) through the web portal
36 *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first
37 knowledge for SAEs that result in death or are life threatening followed by a period of
38 maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported
39 within a period of maximum 15 days after the research team has first knowledge of the
40 serious adverse events.
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50 **Auditing**

51
52
53 Monitoring of the conduct of the study will be done by the Clinical Trial Center
54 Maastricht on a frequent basis following their protocol as is requested by the Board.
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60 **Protocol amendments**

1
2
3 Any modifications to the protocol which may impact the study will be notified to the
4 METC that gave a favourable opinion prior to implementation.
5
6
7

8 **Patient and public involvement**

9

10
11 The Dutch Network for Lymphedema and Lipedema (NLNet), and the Patient
12 Advocacy Group (PAG), a joint initiative from the Breast Cancer Research Group (BOOG) of
13 the Dutch breast cancer association (BVN), were consulted. They provided feedback from the
14 patients' perspective on our research protocol, patient participation and implementation plan,
15 feasibility, patient information sheet, outcome parameters, and the burden for the patients.
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24 **Ethical considerations**

25

26
27 This study will be conducted according to the principles of the Declaration of
28 Helsinki, recently changed in Fortaleza (2013) and in accordance with the Medical Research
29 Involving Human Subjects Act (WMO). The study was approved by the Ethics Committee of
30 Maastricht University Medical Center on 19 December 2018 (NL67059.068.18). The study is
31 registered in the trial register www.clinicaltrials.gov with number NCT02790021.
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40 **Dissemination**

41

42 The results of this study will be disseminated in presentations at academic
43 conferences, publications in peer-reviewed journals and other news media. Data will be kept
44 confidential and will not be shared with the public. Requests for data sharing for appropriate
45 research purposes will be considered on an individual basis after trial completion and after
46 publication of primary manuscripts.
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58 **References**

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60

- 1
2
3 1. Vignes S, Fau-Prudhomot P, Simon L, Sanchez-Brechot ML, Arrault M, Locher F.
4
5 Impact of breast cancer-related lymphedema on working women. *Support Care Cancer*. 2019.
6
- 7 2. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and
8
9 management. *World J Clin Oncol*. 2014;5(3):241-7.
10
- 11 3. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in
12
13 breast cancer survivors, the Iowa Women's Health Study. *Breast Cancer Res Treat*.
14
15 2011;130(3):981-91.
16
- 17 4. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast
18
19 cancer survivors are associated with reduced health and poorer physical quality of life. *Acta*
20
21 *Oncol*. 2010;49(3):347-53.
22
- 23 5. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and
24
25 quality of life in breast cancer survivors: the Iowa Women's Health Study. *J Clin Oncol*.
26
27 2008;26(35):5689-96.
28
- 29 6. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely
30
31 affects quality of life: results of a 5-year prospective study in breast cancer patients. *Breast*
32
33 *Cancer Res Treat*. 2003;79(1):47-57.
34
- 35 7. Chachaj A, Malyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudelko M, et al.
36
37 Physical and psychological impairments of women with upper limb lymphedema following
38
39 breast cancer treatment. *Psychooncology*. 2010;19(3):299-305.
40
41
- 42 8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema
43
44 after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14(6):500-15.
45
- 46 9. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial
47
48 impact of lymphedema-related distress among breast cancer survivors in the WHEL Study.
49
50 *Psychooncology*. 2014;23(9):1049-56.
51
52
53
54
55
56
57
58
59
60

10. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology*. 2013;22(7):1466-84.
11. Oliveri JM, Day JM, Alfano CM, Herndon JE, 2nd, Katz ML, Bittoni MA, et al. Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-diagnosis: CALGB 79804. *J Cancer Surviv*. 2008;2(4):233-42.
12. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer*. 2001;92(6):1368-77.
13. Voogd AC, Ververs JM, Vingerhoets AJ, Roumen RM, Coebergh JW, Crommelin MA. Lymphoedema and reduced shoulder function as indicators of quality of life after axillary lymph node dissection for invasive breast cancer. *Br J Surg*. 2003;90(1):76-81.
14. Venereologie NvvdDe. Richtlijn lymfoedeem. Multidisciplinaire evidence-based richtlijn. www.lymfoedeem.nl; 2014.
15. Richtlijn mammacarcinoom. 2012.
16. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. *J Surg Oncol*. 2010;102(2):111-8.
17. Coriddi M, Khansa I, Stephens J, Miller M, Boehmler J, Tiwari P. Analysis of factors contributing to severity of breast cancer-related lymphedema. *Ann Plast Surg*. 2015;74(1):22-5.
18. Monleon S, Murta-Nascimento C, Bascuas I, Macia F, Duarte E, Belmonte R. Lymphedema Predictor Factors after Breast Cancer Surgery: A Survival Analysis. *Lymphat Res Biol*. 2015;13(4):268-74.
19. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. *Ann Surg Oncol*. 2009;16(7):1959-72.

- 1
2
3 20. Johnson AR, Kimball S, Epstein S, Recht A, Lin SJ, Lee BT, et al. Lymphedema
4
5 Incidence After Axillary Lymph Node Dissection: Quantifying the Impact of Radiation and
6
7 the Lymphatic Microsurgical Preventive Healing Approach. *Ann Plast Surg.* 2019;82(4S
8
9 Suppl 3):S234-S41.
10
- 11 21. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. *J*
12
13 *Am Acad Dermatol.* 2017;77(6):1009-20.
14
- 15 22. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic
16
17 drainage and intermittent pneumatic compression pump use in the treatment of lymphedema
18
19 after mastectomy: a randomized controlled trial. *Breast Cancer.* 2015;22(3):300-7.
20
21
- 22 23. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-
23
24 related lymphedema after intensive decongestive physiotherapy. *Breast Cancer Res Treat.*
25
26 2007;101(3):285-90.
27
- 28 24. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary
29
30 interventions for cancer-related lymphedema: a systematic review and meta-analysis. *Cancer.*
31
32 2011;117(6):1136-48.
33
34
- 35 25. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al.
36
37 Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in
38
39 women with breast cancer. *J Clin Oncol.* 2013;31(30):3758-63.
40
41
- 42 26. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical
43
44 lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J*
45
46 *Reconstr Microsurg.* 2000;16(6):437-42.
47
48
- 49 27. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a
50
51 systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue
52
53 transplantation. *Plast Reconstr Surg.* 2014;133(4):905-13.
54
55
- 56 28. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer
57
58 patients: a prospective study. *Plast Reconstr Surg.* 2010;126(3):752-8.
59
60

- 1
2
3 29. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive
4 lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg.*
5 2013;132(5):1305-14.
6
7
8
9 30. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous
10 anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11
11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of
12 the literature. *Breast Cancer Res Treat.* 2009;113(2):199-206.
13
14
15
16
17 31. Furukawa H, Osawa M, Saito A, Hayashi T, Funayama E, Oyama A, et al.
18 Microsurgical lymphaticovenous implantation targeting dermal lymphatic backflow using
19 indocyanine green fluorescence lymphography in the treatment of postmastectomy
20 lymphedema. *Plast Reconstr Surg.* 2011;127(5):1804-11.
21
22
23
24
25
26
27 32. Mihara M, Hara H, Hayashi Y, Iida T, Araki J, Yamamoto T, et al. Upper-limb
28 lymphedema treated aesthetically with lymphaticovenous anastomosis using indocyanine
29 green lymphography and noncontact vein visualization. *J Reconstr Microsurg.*
30 2012;28(5):327-32.
31
32
33
34
35
36 33. Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, Gorai K, et al. Treatment of
37 lymphedema with lymphaticovenular anastomoses. *Int J Clin Oncol.* 2005;10(5):304-10.
38
39
40
41 34. Penha TR, Ijsbrandy C, Hendrix NA, Heuts EM, Voogd AC, von Meyenfeldt MF, et
42 al. Microsurgical techniques for the treatment of breast cancer-related lymphedema: a
43 systematic review. *J Reconstr Microsurg.* 2013;29(2):99-106.
44
45
46
47 35. Torrisi JS, Joseph WJ, Ghanta S, Cuzzone DA, Albano NJ, Savetsky IL, et al.
48 Lymphaticovenous bypass decreases pathologic skin changes in upper extremity breast
49 cancer-related lymphedema. *Lymphat Res Biol.* 2015;13(1):46-53.
50
51
52
53 36. Yamamoto Y, Horiuchi K, Sasaki S, Sekido M, Furukawa H, Oyama A, et al. Follow-
54 up study of upper limb lymphedema patients treated by microsurgical lymphaticovenous
55 implantation (MLVI) combined with compression therapy. *Microsurgery.* 2003;23(1):21-6.
56
57
58
59
60

- 1
2
3 37. Cornelissen AJM, Beugels J, Ewalds L, Heuts EM, Keuter XHA, Piatkowski A, et al.
4
5 Effect of Lymphaticovenous Anastomosis in Breast Cancer-Related Lymphedema: A Review
6
7 of the Literature. *Lymphat Res Biol*. 2018;16(5):426-34.
8
- 9
10 38. Winters H, Tielemans HJP, Verhulst AC, Paulus VAA, Slater NJ, Ulrich DJO. The
11
12 Long-term Patency of Lymphaticovenular Anastomosis in Breast Cancer-Related
13
14 Lymphedema. *Ann Plast Surg*. 2019;82(2):196-200.
15
- 16
17 39. Salgarello M, Mangialardi ML, Pino V, Gentileschi S, Visconti G. A Prospective
18
19 Evaluation of Health-Related Quality of Life following Lymphaticovenular Anastomosis for
20
21 Upper and Lower Extremities Lymphedema. *J Reconstr Microsurg*. 2018;34(9):701-7.
22
- 23
24 40. Giacalone G, Yamamoto T. Supermicrosurgical lymphaticovenous anastomosis for a
25
26 patient with breast lymphedema secondary to breast cancer treatment. *Microsurgery*.
27
28 2017;37(6):680-3.
29
- 30
31 41. Cornelissen AJM, Kool M, Lopez Penha TR, Keuter XHA, Piatkowski AA, Heuts E,
32
33 et al. Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: a
34
35 prospective study on quality of life. *Breast Cancer Res Treat*. 2017;163(2):281-6.
36
- 37
38 42. Winters H, Tielemans HJP, Hameeteman M, Paulus VAA, Beurskens CH, Slater NJ,
39
40 et al. The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema.
41
42 *Breast Cancer Res Treat*. 2017;165(2):321-7.
43
- 44
45 43. Executive C. The Diagnosis and Treatment of Peripheral Lymphedema: 2016
46
47 Consensus Document of the International Society of Lymphology. *Lymphology*.
48
49 2016;49(4):170-84.
50
- 51
52 44. Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I.
53
54 Indocyanine Green Lymphography Findings in Limb Lymphedema. *J Reconstr Microsurg*.
55
56 2016;32(1):72-9.
57
- 58
59 45. Masia J, Pons G, Nardulli ML. Combined Surgical Treatment in Breast Cancer-
60
61 Related Lymphedema. *J Reconstr Microsurg*. 2016;32(1):16-27.

- 1
2
3 46. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR.
4
5 Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and
6
7 validity. *Phys Ther.* 2011;91(6):944-57.
8
9
10 47. Bouwmans Cea. Handleiding iMTA Medical Cost Questionnaire (iMCQ). 2013.
11
12 48. Lopez Penha TR, van Roozendaal LM, Smidt ML, Boersma LJ, von Meyenfeldt MF,
13
14 Voogd AC, et al. The changing role of axillary treatment in breast cancer: Who will remain at
15
16 risk for developing arm morbidity in the future? *Breast.* 2015;24(5):543-7.
17
18 49. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and
19
20 preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.*
21
22 2011;20(10):1727-36.
23
24
25 50. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in
26
27 breast cancer patients in their first year after treatment. *Health Qual Life Outcomes.*
28
29 2009;7:11.
30
31
32 51. Versteegh M VM, Evers MAAS, de Wit GA, Prenger R. Dutch Tariff for the Five-
33
34 Level Version of EQ-5D. . *Value in health: the journal of the International Society for*
35
36 *Pharmacoeconomics and Outcomes Research.* 2016.
37
38
39 52. Zorginstituut. Kostenhandleiding: Methodologie van kostenonderzoek en
40
41 referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015.
42
43
44 53. Zorginstituut. Richtlijn voor het uitvoeren van economische evaluaties in de
45
46 gezondheidszorg.; 2015.
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Footnotes

Author Contributions

1
2 *JB, AP, EH, DU, RH, and SQ* conceived the study and initiated the study design. *MK* provided
3
4 statistical and cost-effectiveness expertise. *JW, XK, HT, DU, RH, and SQ* completed the study
5
6 design and protocol. All authors contributed to refinement of the study protocol and approved
7
8 the final version.
9
10

11 12 **Funding**

13
14
15
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17
18 Hospital of Maastricht (azM).
19
20

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48 49 **Competing interests**

50
51
52 None declared.
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55 56 **Patient consent for publication**

57
58
59 Informed consent will be signed by every participant and obtained by the researcher after
60
inclusion.

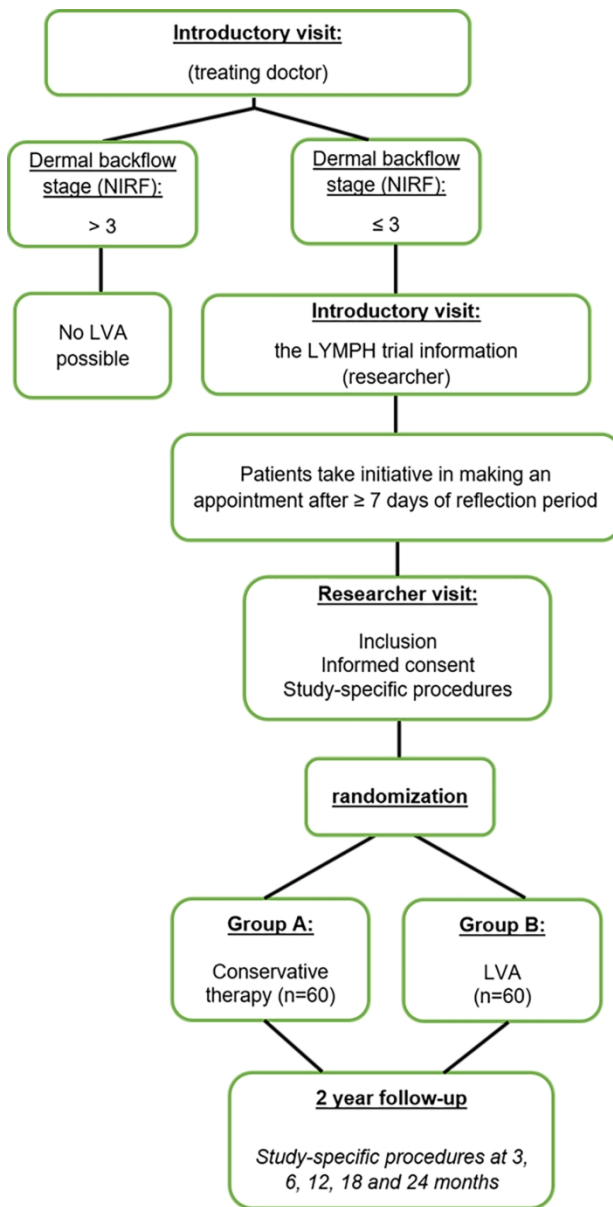


Figure 1 Flowchart: overview of the study design

97x190mm (300 x 300 DPI)



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	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 16
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	V4, 15-04-2019
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	22
	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	NA
	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)	NA

1 **Introduction**

2

3 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 4-6

4

5

6 6b Explanation for choice of comparators 4-6

7

8 Objectives 7 Specific objectives or hypotheses 6

9

10 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) 6

11

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 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 6

17

18

19 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) 7

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 7-9

23

24

25 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) NA

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial NA

32

33

34 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 10-13

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40 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) 6, Fig 1

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1	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	9, 10
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

10	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	6
11				
12				
13				
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15				
16	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	6
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, Fig 1
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

33	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	10-14
34				
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39		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	3
40				
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42				

1	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	14, 15
2				
3				
4				
5	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	13, 14
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
9				
10		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)	14
11				
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13				
14	Methods: Monitoring			
15				
16	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	15
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21				
22		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	NA
23				
24				
25	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	15
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
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37	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)	15
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22, Fig 1
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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6				
7	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	14
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
11				
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13	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	Contractual agreement is present
14				
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18	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	Insurance is included in case of harm
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21				
22	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	16
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27		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
28				
29		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
30				
31	Appendices			
32				
33	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Model provided by Central Committee on Research Involving Human Subjects (CCMO)
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1 Biological 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular NA
2 specimens analysis in the current trial and for future use in ancillary studies, if applicable
3

4 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
5 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
6 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.
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For peer review only

BMJ Open

Improving the quality of life of patients with breast cancer-related lymphedema by lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized controlled trial.

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Manuscripts

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3 **Improving the quality of life of patients with breast cancer-related lymphedema by**
4 **lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized**
5 **controlled trial.**
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Abstract

Introduction. Early breast cancer detection and advancements in treatment options have resulted in an increase of breast cancer survivors. An increasing number of women are living with the long-term effects of breast cancer treatment, making the quality of survivorship an increasingly important goal. Breast cancer-related lymphedema (BCRL) is one of the most underestimated complications of breast cancer treatment with a reported incidence of 20%. A microsurgical technique called lymphaticovenous anastomosis (LVA) might be a promising treatment modality for patients with BCRL.

The main objective is to assess whether LVA is more effective than the current standard therapy (conservative treatment) in terms of improvement in quality of life and whether it is cost-effective.

Methods and analysis. A multicenter, randomized controlled trial, carried out in two academic and two community hospitals in the Netherlands. The study population includes 120 women over the age of 18 who underwent treatment for breast cancer including axillary treatment (sentinel lymph node biopsy or axillary lymph node dissection) and/or axillary radiotherapy, presenting with an early stage lymphedema of the arm, viable lymphatic vessels, and received at least three months conservative treatment. Sixty participants will undergo the LVA operation and the other sixty will continue their regular conservative treatment, both with a follow-up of 24 months.

The primary outcome is the health-related quality of life. Secondary outcomes are societal costs, QALYs, cost-effectiveness ratio, discontinuation rate of conservative treatment, and excess limb volume.

Ethics and dissemination. The study was approved by the Ethics Committee of Maastricht University Medical Center on 19 December 2018 (NL67059.068.18). The results of this study will be disseminated in presentations at academic conferences, publications in peer-reviewed journals, and other news media.

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3 **Registration details.** The study is registered in the trial register www.clinicaltrials.gov with
4
5 number NCT02790021.
6
7

8 **Strengths and limitations of this study**

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- 10
11 - This multicenter RCT compares the lymphaticovenous anastomosis operation with
12
13 conservative therapy (the standard care) in patients with breast cancer-related
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15 lymphedema.
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17 - Effectiveness of lymphaticovenous anastomosis is examined in terms of patient-
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19 relevant, clinical, and economic outcomes; health-related quality of life, excess limb
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21 volume, discontinuation rate of conservative treatment, societal costs, and cost-
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23 effectiveness.
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25 - This study contains digital questionnaires and a patient diary with automatic warnings
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27 in case of blank answers to minimize missing data.
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29 - Blinding of patients or researcher is not possible in this study due to visible scars
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31 postoperatively.
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33 - Cost-effectiveness analysis may not be generalizable to other countries.
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42 **Key words**

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44 Breast cancer lymphedema, lymphaticovenous anastomosis, conservative treatment,
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46 randomized controlled trial, quality of life
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52 **Study title**

53
54 Long study title: *Improving the quality of life of patients with breast cancer-related*
55
56 *lymphedema by lymphaticovenous anastomosis (LVA): Study protocol of a multicenter*
57
58 *randomized controlled trial.*
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3 Study Acronym: *LYMPH trial*
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7 **Introduction**

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10 An increasing number of women survive breast cancer due to advancements in
11 treatment options. As a result, the number of women living with the long-term effects of
12 breast cancer treatment grows, making the quality of survivorship more relevant. Between 8-
13 56% of breast cancer survivors develop arm or shoulder problems such as restricted shoulder
14 mobility, shoulder pain, and lymphedema (1-6), with one of the most underestimated and
15 debilitating morbidities of them all being upper limb lymphedema.
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23 Up to 70% of the patients who develop breast cancer-related lymphedema (BCRL) do
24 so within the first two years post-treatment, however, cases have been described of women
25 developing upper limb lymphedema 20 years or later after initial treatment (7-13). In the
26 Netherlands, between 7% and 30% of the 14,000 annual patients with invasive breast cancer
27 will develop lymphedema depending on certain treatment and patient related risk factors (14,
28 15).
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37 The following risk factors are associated with the development (and severity) of
38 BCRL: the extent of breast/axillary surgery, adjuvant radiation, (neo-)adjuvant chemotherapy,
39 the number of positive nodes, treatment in dominant limb, and obesity (5, 16-20). Limb
40 swelling may present with symptoms of heaviness, tightness, pain, and loss of normal arm
41 function and range of motion. The negative psychological effects brought on by the
42 impairments of activities in daily life and reduced limb aesthetics constitute an additional
43 burden and decrease in health-related quality of life (HRQoL) (1, 7, 11, 13, 21). Moreover,
44 infections of the skin are regularly seen in a severe stadium of lymphedema, such as
45 erysipelas or cellulitis (2, 8, 21).
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Conservative therapy

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Complex decongestive therapy (CDT), currently accepted as the standard treatment for lymphedema, is initially aimed at alleviating symptoms without curative intent, which for most patients means lifelong treatment and a constant reminder of the breast cancer period. CDT includes general skin care, patient education, compression therapy with compression bandages and garment, manual lymphatic drainage, and exercise therapy (14, 22, 23). A systematic review concluded that compression garment in combination with manual lymph drainage induces a significant limb volume reduction of 17 to 60 % (24). Another RCT demonstrated a 29% reduction in excess limb volume with combined conservative therapy (25). However, after reaching maximum limb volume reduction, compression garment are lifelong necessary for the patients to maintain the volume reduction obtained.

Lymphaticovenous anastomosis

Connections can be made between the lymphatic and venous systems to divert static lymph fluid away from the obstruction site in a technique called lymphaticovenous anastomosis (LVA) (26). Due to advancements, microvascular surgery is more developed and anastomoses in vessels as small as 0.3 mm in diameter are made possible.

Several studies on lymphatic super microsurgery performing LVA are available (26-41). Most of the studies describe results on both upper and lower limb lymphedema and not only secondary lymphedema (27, 34). Nevertheless, studies mention a volume or circumference decrease between 30% and 61%, and positive results on subjective complaints with low incidence or no complications (26-29, 31, 36-39, 41). Furthermore, more than half of the patients eventually were able to discontinue compression garment after an LVA procedure (27, 42).

Many studies have been performed, mostly reporting on a small study population. Furthermore, the majority were retrospective, few were prospective, yet none of them were

1
2 randomized. Another disadvantage is the heterogeneity of the patient population, assessment
3 modalities, and inconsistent reporting of outcomes and complications (27, 30, 34).
4
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7 The aim of this multicenter RCT is to examine HRQoL and (cost-)effectiveness of
8 LVA compared with CDT in a large homogenous group of patients with BCRL.
9
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12 13 14 15 **Methods and analysis**

16 17 18 19 **Study Design**

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22 The LYMPH trial is a multicenter, non-blinded, randomized controlled trial and will
23 be conducted in the Maastricht University Medical Center, Radboud University Medical
24 Center, Zuyderland Medical Center, and Canisius-Wilhelmina Hospital in the Netherlands.
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30 Enrolment will take place at the outpatient clinics of the participating hospitals. The
31 inclusion and exclusion criteria are listed in Table 1. A total of 120 women must be recruited
32 after a period of two years. After inclusion and informed consent, participants will be
33 randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per
34 a computer generated randomization schedule stratified by site using block randomization.
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3 November 2018 and the estimated completion date of the study is November 2022. An
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5 overview of the study design is shown in Figure 1.
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11 **Table 1** Inclusion and exclusion criteria
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13
14 *Inclusion criteria*
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- 16
17 - Woman over 18 years old
18
19 - Breast cancer treatment with SLNB, ALND, or axillary Rt
20
21 - Early stage lymphedema of the arm (stage 1 – 2a on ISL classification) (43)
22
23 - Viable lymphatic vessels as determined by ICG lymphography, stage ≤ 3 (44)
24
25 - At least three months conservative therapy (standard of care)
26
27 - Primary breast cancer
28
29 - Unilateral disease and treatment
30
31 - Informed consent
32
33

34
35 *Exclusion criteria*
36

- 37
38 - History of earlier lymph reconstruction efforts
39
40 - Recurrent breast cancer
41
42 - Distant breast cancer metastases
43
44 - Bilateral lymphedema
45
46 - Primary congenital lymphedema
47
48

49 *SLNB; Sentinel Lymph Node Biopsy, ALND; Axillary Lymph Node Dissection, Rt;*
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51 *radiotherapy, ISL; International Society of Lymphology, ICG; Indocyanine Green*
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58 **Interventions to be measured**
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Group A: Conservative Therapy

The current standard treatment for BCRL is a combination of different methods of conservative therapy, also known as complex decongestive therapy (CDT) (14). CDT incorporates two stages of treatment. The first treatment phase entails skincare, manual lymphatic drainage (MLD), exercises aimed at improvement of mobility/range of motion in the shoulder, elbow or wrist joints, and compression therapy through bandaging. Most patients already underwent this phase short after the diagnosis of lymphedema. CDT in the second treatment phase is aimed at maintenance of the achieved limb volume/ circumference reduction through compression therapy with therapeutic elastic compression garment for the arm. Skincare, mobility exercises, and MLD is continued in this phase if needed (14, 24). Since CDT aim to alleviate symptoms without curative intent, this treatment is mostly lifelong needed. In this study, the patients are followed for 2 years during their regular conservative treatment.

Complex decongestive therapy

Patients allocated to group A will be referred to one of the following dedicated lymphedema (physical-/skin-) therapy clinics, if not already treated by one, according to their place of residence for continuation of standard conservative therapy. Only standard conservative therapy, as they would have gotten if not participating in this study, will take place in these clinics, no study measurements.

All women in this study group will be treated according to a protocol which is already in use for patients not participating in this study, since it is considered as the best available standard care. To be able to compare the outcomes for the conservative therapy group, a standardized treatment protocol using the standard lymphatic drainage methods applied in the Netherlands and Germany ('Verdonkmethod' and 'Asdonkmethod', respectively), will be used in this study. See the Supplementary Data for the CDT protocol. Ongoing conservative

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2 treatment and the frequency is controlled by the skin therapist. All information regarding
3 conservative treatment is noted in the patient diary.
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9 Group B: Surgical treatment

10 *Lymphaticovenous anastomosis*

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12 LVA is a relative minimally invasive registered procedure which can be performed
13 under local anesthesia. The patient lies comfortable on the operation table and a limb table is
14 used. The limb is then prepared for surgery.
15
16

17 Before making the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is
18 injected at the site of incision to achieve local anesthesia and optimal hemostasis.
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21 The following steps of the operation are performed using a surgical microscope. Based on the
22 ICG lymphography mapping, incisions of 1 to 2 cm are made at the predetermined sites.
23
24

25 Lymphatic vessels are identified and an anastomosis is performed with a similarly sized
26 adjacent recipient vein in the subdermal plane. The anastomosis is usually performed in an
27 end-to-end fashion in case both the lymphatic vessel and vein have approximately the same
28 caliber (otherwise end-to-side). The end-to-end anastomosis is created with an 11-0 suture.
29
30

31 The patency of the LVA is confirmed by direct visual examination under the microscope. On
32 average 1 to 4 anastomosis are performed in a lymphedematous arm. The superficial wound is
33 closed using 4-0 Ethilon covered by adhesive plasters and a bandage. The operation length is
34 approximately two to three hours (29).
35
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39

40 *Postoperative treatment*

41 From 2 weeks after surgery, when the stitches are removed, patients will be treated
42 with conservative therapy the same way and in the same frequency as preoperatively (45).
43
44

45 The participants are treated by the same method as group A if needed, as described in phase 2
46 (maintenance phase) of the CDT protocol. After 3 months, the plastic surgeon will determine
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3 whether conservative therapy can be reduced or stopped, depending on the decrease of
4
5 subjective complaints and swelling of the arm. The frequency of manual lymphatic drainage
6
7 will be controlled by the skin therapist and noted in the patient diary.
8
9

10
11 Follow-up moments for both groups will be at 3, 6, 12, 18, and 24 months. For group
12
13 A the follow-up starts from the day of the informed consent signing and for group B from the
14
15 day of the surgery.
16
17

21 22 **Sample size calculation**

23
24 We made the following assumptions for the calculation of the sample size to show a
25
26 statistically significant and clinically relevant difference in quality of life between treatment
27
28 groups at 12 months follow-up as measured with the Lymph-ICF questionnaire:
29

30
31 Comparing LVA to conservative treatment, the minimal difference in HRQoL that is
32
33 considered as clinically relevant is 15 points (15% decrease on the 0 to 100 scale) on the
34
35 Lymph-ICF questionnaire at 12 months follow-up (46).
36

37
38 To be able to achieve a power of 80%, a total of 45 patients are needed per treatment group,
39
40 when the standard deviation is 25%, using an alpha of 0.05. If a drop-out rate (loss-to-follow-
41
42 up and patients with missing data) of 25% is taken into account, a sample size of 60 patients
43
44 per study group is required and a total of 120 patients will be randomized.
45
46

47 48 **Outcomes**

49 50 51 *Primary outcome*

52
53 The primary outcome is HRQoL at 12 months follow-up. To assess the effectiveness
54
55 of the treatment we will use the Dutch version of the “Lymphedema Functioning, Disability
56
57 and Health” (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in
58
59 function, activity limitations, and participation restrictions of patients with upper limb
60

1
2 lymphedema. It is a validated, disease-specific questionnaire, consisting of 29 items
3
4 (questions) across 5 domains. Each item is scored on a VAS ranging from 0 to 100. The total
5
6 score on the Lymph-ICF is equal to the sum of the item scores divided by the total number of
7
8 answered items. A higher score on the Lymph-ICF indicates more impact in the functioning in
9
10 the daily life related to upper limb lymphedema (46).
11
12

13
14 HRQoL will be measured at baseline and 3, 6, 12, 18 and 24 months after informed
15
16 consent (Group A), or after surgery (Group B).
17
18

19 20 21 *Secondary outcomes*

22
23 Secondary outcomes are the societal costs, QALYs, incremental cost-effectiveness,
24
25 discontinuation of conservative treatment, and excess limb volume. Assessment will be done
26
27 at baseline and 3, 6, 12, 18, and 24 months after informed consent (Group A), or after surgery
28
29 (Group B).
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32
33 Costs include health care related costs, costs to patients and family, and costs due to
34
35 lost productivity. Complete individual level hospital resource use data (e.g. surgical
36
37 intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be
38
39 measured using medical records and provider information systems. Resource use outside the
40
41 hospital (e.g. lymphedema therapy, general practitioner visits, out-of-pocket expenses such as
42
43 for therapeutic elastic garment and over-the counter drugs, travel costs, and quantities of lost
44
45 paid work) will be determined by means of prospective cost diaries as kept by participants.
46
47 The cost diary developed for this study is an adapted version of the MCQ and PCQ (47). The
48
49 Dutch manual for costing research will be used to determine prices for each volume of
50
51 resource use (48).
52
53

54
55 The EQ-5D-5L is a generic HRQoL measure that can be used to calculate QALYs to
56
57 be used in the economic evaluation (49). The EQ-5D is a questionnaire responsive to changes
58
59 in health in breast cancer patients after conclusion of treatment (50).
60

1
2
3 The EQ-5D-5L examines a patient's HRQoL on the day of the interview. It consist of
4 the EQ-5D-5L descriptive system and a Visual Analog Scale (EQ VAS). The descriptive
5 system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and
6 anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate
7 problems, severe problems and extreme problems. Responses to the 5 items result in a
8 patient's health state that can be transformed into an index score representing a HRQoL-
9 weight, ranging between 0 (death) and 1 (perfect health) (51). These index scores are
10 combined with length of life to calculate the QALYs. The EQ VAS records the patient's self-
11 rated health with endpoints labelled 'the best health you can imagine' at the top and 'the worst
12 health you can imagine' at the bottom.

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Discontinuation of conservative treatment will be assessed with a patient diary to
record the frequency of treatments received (i.e. skin therapy visits, number of compression
garment, etc.).

Lastly, bilateral limb volume measurements will be done using VECTRA 3D imaging
and the water displacement method. The excess limb volume is measured as the difference in
volume between the affected and unaffected limb, which is reported as a percentage of the
volume of the unaffected limb. A relative volume reduction (relative to the unaffected arm) as
well as an absolute volume reduction (volume reduction of the affected arm at next
measurement) will be calculated. The calculated volume will be corrected for the body mass
index and for volume differences between the dominant and non-dominant arm.

Besides using the water displacement method, volume measurement will also be done
by arm circumference measurement using tape. Both arms will be measured during every visit
at the level of the olecranon, 5 and 10 centimeters proximally, 5 and 10 centimeters distally, at
the level of the wrist, and the dorsum of the hand.

In the out-patient clinic, a fluorescent marker, called indocyanine green (ICG) is
injected intracutaneously into the second and fourth finger webspace of the lymphedematous

1
2 limb and a so called ICG lymphography is performed in search for viable lymphatic vessels.
3
4 This is a technique using near-infrared fluorescence imaging (NIRF). After 0.05 ml of ICG
5
6 (5mg/ml) is injected per webspace, a near-infrared camera is used to visualize the lymphatic
7
8 vessels. Proximal to the injection sites fluorescent stains are identified. When using the
9
10 images as a guide, the lymphatic pathways and the sites for incisions for lymphaticovenous
11
12 anastomoses are marked with a pen and a color picture is taken. These color pictures are used
13
14 to identify the location when LVA will be performed. NIRF will be done at introduction visit
15
16 and after 12 and 24 months.
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24 **Data analysis**

25
26 For the HRQoL a paired Student's t-test will be used to evaluate the changes in quality
27
28 of life scores and in limb volume measurements between pre-inclusion and the different post-
29
30 inclusion periods of time within individuals from the same study group. For each of the
31
32 follow-up moments (3, 6, 12, 18 and 24 months) the change in quality of life from baseline
33
34 will be compared between groups using the two sample unpaired t-test, to evaluate short- and
35
36 long-term treatment effects. If baseline imbalance is present, assessed qualitatively, adjusted
37
38 differences per follow-up moment will be computed using linear regression. In addition to
39
40 statistical testing per follow-up measurement, a linear mixed-effects model will be used to test
41
42 for an overall difference between the two groups. To account for clustering of measurements
43
44 at the patient-level, a model with a random intercept and random slope will be used.
45
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51 *Economic evaluation*

52
53 An economic evaluation will be performed alongside the clinical trial to determine the cost-
54
55 effectiveness of LVA compared to CDT. The design of the economic evaluation follows the
56
57 principles of a cost-utility analysis and adheres to the Dutch guideline for economic
58
59 evaluations in health care and the Dutch manual for costing research (52, 53). Outcome
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measures for the economic evaluation will be costs, health-related quality of life, and quality adjusted life years (QALYs). The trial-based evaluation adopts a societal perspective and has a time horizon of two years.

An incremental cost-effectiveness ratio (ICER), i.e. cost per QALY gained, will be calculated by dividing the difference in costs between the two treatments with the difference in QALYs. Bootstrapping techniques will be used to summarize the uncertainty in estimates of incremental costs, effects, and the ICER. In addition, cost-effectiveness acceptability curves (CEACs) will show the probability that LVA is cost-effective compared to conservative treatment, given the observed data, for a range of maximum monetary values that a decision-maker might be willing to pay for a QALY gained.

The impact of uncertainty surrounding deterministic parameters (for example prices) on the ICER will be explored using one-way sensitivity analyses. Results, presented in a tornado diagram, can help determine which parameters are key drivers of the cost-effectiveness results. Pre-determined subgroup analyses will address possible variation between patients (heterogeneity).

Missing values will be imputed using mean substitution or multiple imputation, as appropriate.

Ethics and Dissemination

Data monitoring

Data will be handled confidentially. Source data will be stored by the investigator in a locked place. Data of all measurements during follow-up moments, (Serious) Adverse Events and digital questionnaires including patient cost diary are stored immediately in the online database of CASTOR EDC ©. The investigator and project leader only have access to this

1
2 database with an account with password. Identifying data will be stored in coded form; the
3
4 key to the form is known only to the supervisor, the investigator, the Dutch Health Care
5
6 Inspectorate (IGJ), the study monitors, and the members of the review committee.
7
8
9

10 **Harms**

11
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14 Adverse events (AEs) are defined as any undesirable experience occurring to a subject
15
16 during the study, whether or not considered related to the trial procedure. Adverse events
17
18 related to the LVA operation or conservative therapy that have a possible impact on the
19
20 lymphedema and reported spontaneously by the subject or observed by the investigator or his
21
22 staff will be recorded directly in CASTOR EDC ©.
23
24

25
26 The research team will report the serious adverse event (SAEs) through the web portal
27
28 *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first
29
30 knowledge for SAEs that result in death or are life threatening followed by a period of
31
32 maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported
33
34 within a period of maximum 15 days after the research team has first knowledge of the
35
36 serious adverse events.
37
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39

40 **Auditing**

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44 Monitoring of the conduct of the study will be done by the Clinical Trial Center
45
46 Maastricht on a frequent basis following their protocol as is requested by the Board.
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49

50 **Protocol amendments**

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54 Any modifications to the protocol which may impact the study will be notified to the
55
56 METC that gave a favourable opinion prior to implementation.
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58
59

60 **Patient and public involvement**

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3 The Dutch Network for Lymphedema and Lipedema (NLNet), and the Patient
4
5 Advocacy Group (PAG), a joint initiative from the Breast Cancer Research Group (BOOG) of
6
7 the Dutch breast cancer association (BVN), were consulted. They provided feedback from the
8
9 patients' perspective on our research protocol, patient participation and implementation plan,
10
11 feasibility, patient information sheet, outcome parameters, and the burden for the patients.
12
13

14 15 **Ethical considerations**

16
17
18 This study will be conducted according to the principles of the Declaration of
19
20 Helsinki, recently changed in Fortaleza (2013) and in accordance with the Medical Research
21
22 Involving Human Subjects Act (WMO). The study was approved by the Ethics Committee of
23
24 Maastricht University Medical Center on 19 December 2018 (NL67059.068.18). The study is
25
26 registered in the trial register www.clinicaltrials.gov with number NCT02790021.
27
28
29

30 31 **Dissemination**

32
33 The results of this study will be disseminated in presentations at academic
34
35 conferences, publications in peer-reviewed journals and other news media. Data will be kept
36
37 confidential and will not be shared with the public. Requests for data sharing for appropriate
38
39 research purposes will be considered on an individual basis after trial completion and after
40
41 publication of primary manuscripts.
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50 51 **References**

- 52
53 1. Vignes S, Fau-Prudhomot P, Simon L, Sanchez-Brechot ML, Arrault M, Locher F.
54
55 Impact of breast cancer-related lymphedema on working women. *Support Care Cancer*. 2019.
56
57 2. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and
58
59 management. *World J Clin Oncol*. 2014;5(3):241-7.
60

- 1
2
3 3. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in
4 breast cancer survivors, the Iowa Women's Health Study. *Breast Cancer Res Treat*.
5 2011;130(3):981-91.
6
- 7
8
9 4. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast
10 cancer survivors are associated with reduced health and poorer physical quality of life. *Acta*
11 *Oncol*. 2010;49(3):347-53.
12
- 13
14
15 5. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and
16 quality of life in breast cancer survivors: the Iowa Women's Health Study. *J Clin Oncol*.
17 2008;26(35):5689-96.
18
- 19
20
21 6. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely
22 affects quality of life: results of a 5-year prospective study in breast cancer patients. *Breast*
23 *Cancer Res Treat*. 2003;79(1):47-57.
24
- 25
26
27 7. Chachaj A, Malyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudelko M, et al.
28 Physical and psychological impairments of women with upper limb lymphedema following
29 breast cancer treatment. *Psychooncology*. 2010;19(3):299-305.
30
- 31
32
33 8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema
34 after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14(6):500-15.
35
- 36
37
38 9. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial
39 impact of lymphedema-related distress among breast cancer survivors in the WHEL Study.
40 *Psychooncology*. 2014;23(9):1049-56.
41
- 42
43
44 10. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact
45 of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology*.
46 2013;22(7):1466-84.
47
- 48
49
50 11. Oliveri JM, Day JM, Alfano CM, Herndon JE, 2nd, Katz ML, Bittoni MA, et al.
51 Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-
52 diagnosis: CALGB 79804. *J Cancer Surviv*. 2008;2(4):233-42.
53
54
55
56
57
58
59
60

- 1
2
3 12. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast
4 carcinoma survivors 20 years after diagnosis. *Cancer*. 2001;92(6):1368-77.
- 5
6
7 13. Voogd AC, Ververs JM, Vingerhoets AJ, Roumen RM, Coebergh JW, Crommelin
8 MA. Lymphoedema and reduced shoulder function as indicators of quality of life after
9 axillary lymph node dissection for invasive breast cancer. *Br J Surg*. 2003;90(1):76-81.
- 10
11
12 14. Venereologie NvvDe. Richtlijn lymfoedeem. Multidisciplinaire evidence-based
13 richtlijn. www.lymfoedeem.nl; 2014.
- 14
15
16 15. Richtlijn mammacarcinoom. 2012.
- 17
18
19 16. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity
20 results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary
21 dissection. *J Surg Oncol*. 2010;102(2):111-8.
- 22
23
24 17. Coriddi M, Khansa I, Stephens J, Miller M, Boehmler J, Tiwari P. Analysis of factors
25 contributing to severity of breast cancer-related lymphedema. *Ann Plast Surg*. 2015;74(1):22-
26 5.
- 27
28
29 18. Monleon S, Murta-Nascimento C, Bascuas I, Macia F, Duarte E, Belmonte R.
30 Lymphedema Predictor Factors after Breast Cancer Surgery: A Survival Analysis. *Lymphat*
31 *Res Biol*. 2015;13(4):268-74.
- 32
33
34 19. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk
35 of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment
36 factors. *Ann Surg Oncol*. 2009;16(7):1959-72.
- 37
38
39 20. Johnson AR, Kimball S, Epstein S, Recht A, Lin SJ, Lee BT, et al. Lymphedema
40 Incidence After Axillary Lymph Node Dissection: Quantifying the Impact of Radiation and
41 the Lymphatic Microsurgical Preventive Healing Approach. *Ann Plast Surg*. 2019;82(4S
42 Suppl 3):S234-S41.
- 43
44
45 21. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. *J*
46 *Am Acad Dermatol*. 2017;77(6):1009-20.

- 1
2
3 22. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic
4 drainage and intermittent pneumatic compression pump use in the treatment of lymphedema
5 after mastectomy: a randomized controlled trial. *Breast Cancer*. 2015;22(3):300-7.
6
7
8
- 9 23. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-
10 related lymphedema after intensive decongestive physiotherapy. *Breast Cancer Res Treat*.
11 2007;101(3):285-90.
12
13
14
- 15 24. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary
16 interventions for cancer-related lymphedema: a systematic review and meta-analysis. *Cancer*.
17 2011;117(6):1136-48.
18
19
20
21
22
- 23 25. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al.
24 Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in
25 women with breast cancer. *J Clin Oncol*. 2013;31(30):3758-63.
26
27
28
29
- 30 26. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical
31 lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J*
32 *Reconstr Microsurg*. 2000;16(6):437-42.
33
34
35
36
- 37 27. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a
38 systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue
39 transplantation. *Plast Reconstr Surg*. 2014;133(4):905-13.
40
41
42
43
- 44 28. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer
45 patients: a prospective study. *Plast Reconstr Surg*. 2010;126(3):752-8.
46
47
48
- 49 29. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive
50 lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg*.
51 2013;132(5):1305-14.
52
53
54
- 55 30. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous
56 anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11
57
58
59
60

1
2
3 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of
4
5 the literature. *Breast Cancer Res Treat.* 2009;113(2):199-206.

6
7 31. Furukawa H, Osawa M, Saito A, Hayashi T, Funayama E, Oyama A, et al.
8
9 Microsurgical lymphaticovenous implantation targeting dermal lymphatic backflow using
10
11 indocyanine green fluorescence lymphography in the treatment of postmastectomy
12
13 lymphedema. *Plast Reconstr Surg.* 2011;127(5):1804-11.

14
15
16 32. Mihara M, Hara H, Hayashi Y, Iida T, Araki J, Yamamoto T, et al. Upper-limb
17
18 lymphedema treated aesthetically with lymphaticovenous anastomosis using indocyanine
19
20 green lymphography and noncontact vein visualization. *J Reconstr Microsurg.*
21
22 2012;28(5):327-32.

23
24
25 33. Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, Gorai K, et al. Treatment of
26
27 lymphedema with lymphaticovenular anastomoses. *Int J Clin Oncol.* 2005;10(5):304-10.

28
29
30 34. Penha TR, Ijsbrandy C, Hendrix NA, Heuts EM, Voogd AC, von Meyenfeldt MF, et
31
32 al. Microsurgical techniques for the treatment of breast cancer-related lymphedema: a
33
34 systematic review. *J Reconstr Microsurg.* 2013;29(2):99-106.

35
36
37 35. Torrisi JS, Joseph WJ, Ghanta S, Cuzzzone DA, Albano NJ, Savetsky IL, et al.
38
39 Lymphaticovenous bypass decreases pathologic skin changes in upper extremity breast
40
41 cancer-related lymphedema. *Lymphat Res Biol.* 2015;13(1):46-53.

42
43
44 36. Yamamoto Y, Horiuchi K, Sasaki S, Sekido M, Furukawa H, Oyama A, et al. Follow-
45
46 up study of upper limb lymphedema patients treated by microsurgical lymphaticovenous
47
48 implantation (MLVI) combined with compression therapy. *Microsurgery.* 2003;23(1):21-6.

49
50
51 37. Cornelissen AJM, Beugels J, Ewalds L, Heuts EM, Keuter XHA, Piatkowski A, et al.
52
53 Effect of Lymphaticovenous Anastomosis in Breast Cancer-Related Lymphedema: A Review
54
55 of the Literature. *Lymphat Res Biol.* 2018;16(5):426-34.

- 1
2
3 38. Winters H, Tielemans HJP, Verhulst AC, Paulus VAA, Slater NJ, Ulrich DJO. The
4 Long-term Patency of Lymphaticovenular Anastomosis in Breast Cancer-Related
5 Lymphedema. *Ann Plast Surg.* 2019;82(2):196-200.
6
7
8
9 39. Salgarello M, Mangialardi ML, Pino V, Gentileschi S, Visconti G. A Prospective
10 Evaluation of Health-Related Quality of Life following Lymphaticovenular Anastomosis for
11 Upper and Lower Extremities Lymphedema. *J Reconstr Microsurg.* 2018;34(9):701-7.
12
13
14
15
16 40. Giacalone G, Yamamoto T. Supermicrosurgical lymphaticovenous anastomosis for a
17 patient with breast lymphedema secondary to breast cancer treatment. *Microsurgery.*
18
19 2017;37(6):680-3.
20
21
22
23 41. Cornelissen AJM, Kool M, Lopez Penha TR, Keuter XHA, Piatkowski AA, Heuts E,
24 et al. Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: a
25 prospective study on quality of life. *Breast Cancer Res Treat.* 2017;163(2):281-6.
26
27
28
29 42. Winters H, Tielemans HJP, Hameeteman M, Paulus VAA, Beurskens CH, Slater NJ,
30 et al. The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema.
31
32 *Breast Cancer Res Treat.* 2017;165(2):321-7.
33
34
35
36 43. Executive C. The Diagnosis and Treatment of Peripheral Lymphedema: 2016
37 Consensus Document of the International Society of Lymphology. *Lymphology.*
38
39 2016;49(4):170-84.
40
41
42
43 44. Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I.
44 Indocyanine Green Lymphography Findings in Limb Lymphedema. *J Reconstr Microsurg.*
45
46 2016;32(1):72-9.
47
48
49
50 45. Masia J, Pons G, Nardulli ML. Combined Surgical Treatment in Breast Cancer-
51 Related Lymphedema. *J Reconstr Microsurg.* 2016;32(1):16-27.
52
53
54
55 46. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR.
56 Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and
57 validity. *Phys Ther.* 2011;91(6):944-57.
58
59
60

- 1
2
3 47. Bouwmans Cea. Handleiding *i*MTA Medical Cost Questionnaire (iMCQ). 2013.
- 4
5 48. Lopez Penha TR, van Roozendaal LM, Smidt ML, Boersma LJ, von Meyenfeldt MF,
6
7 Voogd AC, et al. The changing role of axillary treatment in breast cancer: Who will remain at
8
9 risk for developing arm morbidity in the future? *Breast*. 2015;24(5):543-7.
- 10
11 49. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and
12
13 preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*.
14
15 2011;20(10):1727-36.
- 16
17 50. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in
18
19 breast cancer patients in their first year after treatment. *Health Qual Life Outcomes*.
20
21 2009;7:11.
- 22
23 51. Versteegh M VM, Evers MAAS, de Wit GA, Prenger R. Dutch Tariff for the Five-
24
25 Level Version of EQ-5D. . *Value in health: the journal of the International Society for*
26
27 *Pharmacoeconomics and Outcomes Research*. 2016.
- 28
29 52. Zorginstituut. Kostenhandleiding: Methodologie van kostenonderzoek en
30
31 referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015.
- 32
33 53. Zorginstituut. Richtlijn voor het uitvoeren van economische evaluaties in de
34
35 gezondheidszorg.; 2015.
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Footnotes

Author Contributions

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53 *JB, AP, EH, DU, RH, and SQ* conceived the study and initiated the study design. *MK* provided
54
55 statistical and cost-effectiveness expertise. *JW, XK, HT, DU, RH, and SQ* completed the study
56
57 design and protocol. All authors contributed to refinement of the study protocol and approved
58
59 the final version.
60

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Competing interests

None declared.

Patient consent for publication

Informed consent will be signed by every participant and obtained by the researcher after inclusion.

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3 **Figure Legends**
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6 **Figure 1** Flowchart: overview of the study design
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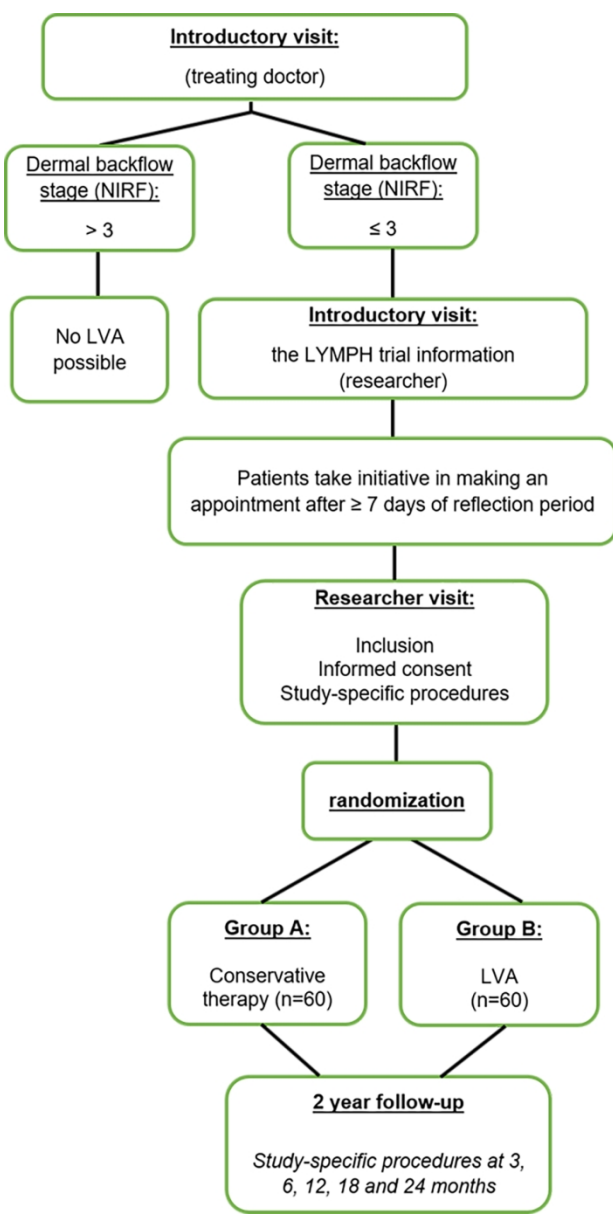


Figure 1 Flowchart: overview of the study design
97x190mm (300 x 300 DPI)

Complex Decongestive Therapy (CDT) protocol

The first phase, or initial treatment phase, of CDT entails general skin care, manual lymphatic drainage, exercises aimed at improvement of mobility/range of motion and compression therapy using bandages.

The second phase, or maintenance phase, of CDT is aimed at maintenance of the achieved limb volume reduction through compression therapy with use of therapeutic elastic compression garment for the arm. Skincare, mobility exercises and MLD is continued in this phase if needed.

First phase

Three months CDT before randomization (if not yet treated conservatively for ≥ 3 months)

Manual lymphatic drainage (MLD)

This is the manual stretching and pressure application to the skin in slow, rhythmic and circular motions to stimulate the activity in the lymphatic vessels to increase lymphatic fluid drainage. The pressure applied is adjusted to the type of edema. The MLD techniques are designed to stimulate lymph flow from distal to proximal lymphatics. The goal of MLD is to re-route the flow of stagnated lymphatic fluid around obstructed or blocked areas into the more centrally located healthy lymphatic vessels. The lymphatic fluid eventually drains into the venous system.

Skin care

Cleansing of the skin with a pH-neutral product and application of a perfume-free, pH-neutral cream to the skin of the patient.

Pre-treatment of the neck-shoulder region:

Patient is in supine position: start at supraclavicular lymph nodes in direction of the terminus

- Continue towards the 'm. sternocleidomastoideus', bilaterally;
- Proceed towards axillary lymph nodes (in direction of 'lymfatici centralis, lateralis & subscapularis').

Treatment of the flank:

- Start at infra-clavicular from sternum distally towards axilla ("anastomosis hold");
- Proceed towards pectoralis muscle to sternum, medial and distally towards axilla;
- Move from breast distally towards flank;
- Followed by the intercostal space, proceed to parasternal space
- Contra-lateral side; start parasternal then intercostal;
- Apply "anastomosis grip" across sternum towards contralateral axilla.

Patient moves from supine position towards flank position with skin therapist seated behind her; position scapula in protraction

- Continue with drainage towards contralateral side;
- Continue from the trans-dorsal anastomosis towards the axilla of the contralateral side.

Treatment of the arm:

Patient moves back to supine position:



- Drainage of the upper-arm ventrally and dorsally towards supra- and sub-clavicular lymph nodes respectively;
- Continue at 'cubitales profundi' and 'cubitales superficialis';
- Drainage of the underarm, ventral side towards 'cubitales profundi' and dorsally towards 'cubitale superficialis';

Treatment of the hand:

- Apply "carpal tunnel hold" for hand drainage;
- Dorsal side hand drain towards dorsal side underarm;
- Palmar side hand towards ventral side underarm;
- Fingers and thumb towards dorsal side underarm;

Finish treatment at the neck.

NB. In case of fibrosis; apply "fibrosis hold"

Compression therapy; multi-layered bandaging

- Apply padding on hand, fingers and arm with cotton tricot, synthetic wool (10 cm width) and gauze bandaging (4 cm width). Use a pressure pad in case of edema. Apply tape to fixate padding.
- Apply 6 cm short stretch bandage. Start at wrist, hand, underarm.
- Apply 10 cm short stretch bandage. Start at wrist towards proximal, bandage clockwise.
- Apply 10 cm short stretch bandage. Start at wrist towards proximal, bandage anti-clockwise.
- Bandage is only removed during the next treatment session by skin therapist.

Frequency and duration of conservative treatment during the first 3 months:

- CDT phase 1.1: will continue for 6 weeks, 3 times a week, during 45 minutes (30 minutes MLD and 15 minutes of skincare, compression therapy and exercises).
- CDT phase 1.2: measure arms for therapeutic elastic compression garment (pressure class 2). In addition continue complex decongestive therapy as in phase 1: two times a week in week 7 and 8, once a week from week 9 till 12.

Second phase

After randomization

After randomization, or if participants already had CDT as described in phase 1, phase 2 applies. CDT will be continued at least once a month during the rest of the study period. CDT is chronic care for this chronic disease which most of the time is necessary an entire lifetime, therefore the start of follow-up and ending of the treatment is unclear.

Manual lymphatic drainage (MLD)

MLD continues or starts as described in phase 1.

Compression therapy:

At least pressure class 2 elastic compression garment for the arm. A separate glove may be used as complement. Two garment are recommended for hygienic reasons and preserve elasticity of the garment.



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 16
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	V4, 15-04-2019
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	22
	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	NA
	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)	NA

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	4-6
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	4-6
7				
8	Objectives	7	Specific objectives or hypotheses	6
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	6
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	7-9
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	NA
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	NA
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
32				
33				
34	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	
35			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	10-13
36			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
37			efficacy and harm outcomes is strongly recommended	
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40	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	6, Fig 1
41			participants. A schematic diagram is highly recommended (see Figure)	
42				
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1	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	9, 10
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

10	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	6
11				
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16	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	6
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, Fig 1
22				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
28				
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31 **Methods: Data collection, management, and analysis**

33	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	10-14
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39		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	3
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1	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	14, 15
2				
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5	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	13, 14
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
9				
10		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)	14
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14	Methods: Monitoring			
15				
16	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	15
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22		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	NA
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25	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	15
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
35				
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37	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)	15
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22, Fig 1
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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7	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	14
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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13	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	Contractual agreement is present
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18	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	Insurance is included in case of harm
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22	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	16
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27		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
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29		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
30				
31	Appendices			
32				
33	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Model provided by Central Committee on Research Involving Human Subjects (CCMO)
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1	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA
2	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	

4 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
5 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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