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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035337
Article Type:	Protocol
Date Submitted by the Author:	28-Oct-2019
Complete List of Authors:	Wolfs, Joost; Maastricht University Medical Centre+, Beugels, Jop; Maastricht University Medical Centre+, Plastic & Reconstructive Surgery Kimman, Merel; Maastricht Universitair Medisch Centrum+, Piatkowski de Grzymala, Andrzej; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery Heuts, Esther; Maastricht University Medical Centre+, Surgery Keuter, Xavier; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery Tielemans, Hanneke; Radboudumc, Plastic, Reconstructive & Hand Surgery Ulrich, Dietmar; Radboudumc, Plastic, Reconstructive & Hand Surgery van der Hulst , R; Maastricht University Medical Center, Plastic surgery Qiu, Shan Shan; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery
Keywords:	PLASTIC & RECONSTRUCTIVE SURGERY, Breast surgery < SURGERY, Plastic & reconstructive surgery < SURGERY

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

J.A.G.N. **Wolfs** *MD*[1], J. **Beugels** *MD*[1], M. **Kimman** *PhD*[2], A. **Piatkowski** *MD PhD*[1], E.M. **Heuts** *MD PhD*[3], X.H.A. **Keuter** *MD PhD*[1], H.J.P. **Tielemans** *MD*[4], D.J.O. **Ulrich** *MD PhD*[4], R.R.W.J. **van der Hulst** *MD PhD*[1], S.S. **Qiu** *MD PhD*[1].

Author affiliations

1 Department of Plastic and Reconstructive Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

2 Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, Netherlands

3 Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

4 Department of Plastic and Reconstructive Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

Corresponding author

Shan Shan Qiu, *MD PhD*

Department of Plastic, Reconstructive and Hand surgery

Maastricht University Medical Center

P. Debyelaan 25, 6229 HX Maastricht, The Netherlands

Telephone: (+31) 043-3875474

Fax: (+31) 043-3875473

Email: shanshan.qiushao@mumc.nl

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

will be disseminated in presentations at academic conferences, publications in peer-reviewed journals, and other news media.

Registration details. The study is registered in the trial register www.clinicaltrials.gov with number NCT02790021.

Strengths and limitations of this study

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

Key words

Breast cancer lymphedema, lymphaticovenous anastomosis, conservative treatment, randomized controlled trial, quality of life

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,

infections of the skin are regularly seen in a severe stadium of lymphedema, such as erysipelas or cellulitis (4, 8).

Conservative therapy

Complex decongestive therapy (CDT), currently accepted as the standard treatment method 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 stockings, manual lymphatic drainage, and exercise therapy (14, 20, 21). A systematic review concluded that compression stockings in combination with manual lymph drainage induces a significant limb volume reduction of 17 to 60 % (22). Another RCT demonstrated a 29% reduction in excess limb volume with combined conservative therapy (23). However, after reaching maximum limb volume reduction, compression stockings 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) (24). Due to advancements, microvascular surgery is more developed and anastomoses in vessels as small as 0.3mm in diameter are made possible.

Several studies on lymphatic super microsurgery performing LVA are available (25-36). Most of the studies describe results on both upper and lower limb lymphedema and not only secondary lymphedema (25, 33). Nevertheless, studies mention a volume or circumference decrease between 30% and 61%, and positive results on subjective complaints

with low incidence or no complications (25-27, 29, 30, 35, 36). Furthermore, 56% of the patients eventually were able to discontinue compression stockings after an LVA procedure(25).

Many studies have been performed but most of them report on a small study population. Furthermore most of them were retrospective, few were prospective, yet none of them were randomized. Another disadvantage is the heterogeneity of the patient population, assessment modalities, and inconsistent reporting of outcomes and complications (25, 28, 33).

The aim of this multicenter RCT is to examine HRQoL and cost-effectiveness of LVA compared with CDT in patients with BCRL.

Methods and analysis

Study Design

The LYMPH trial is a multicenter, non-blinded, randomized controlled trial and will be conducted in the Maastricht University Medical Centre, Radboud University Medical Centre, Zuyderland Medical Centre, and Canisius-Wilhelmina Hospital in the Netherlands.

Enrolment will take place at the outpatient clinics of the participating hospitals. The inclusion and exclusion criteria are listed in Table 1. A total of 120 women must be recruited after a period of two years. After inclusion and informed consent, participants will be randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per a computer generated randomization schedule stratified by site using block randomization. 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)
- Viable lymphatic vessels as determined by ICG lymphography, stage ≤ 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 measured

Group 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

lymphatic drainage (MLD), exercises aimed at improvement of mobility/range of motion in the shoulder, elbow or wrist joints, and compression therapy through bandaging. CDT in the second treatment phase is aimed at maintenance of the achieved limb volume/ circumference reduction through compression therapy with therapeutic elastic stocking for the arm. Skincare, mobility exercises, and MLD is continued in this phase if needed (14, 22).

Complex decongestive therapy

Patients allocated to group A will be referred to one of the following dedicated lymphedema (physical-/skin-) therapy clinics 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 identified with lymphedema 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.

<u>Group B: Surgical treatment</u>

Lymphaticovenous anastomosis

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

Before making the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is injected at the site of incision to achieve local anesthesia and optimal hemostasis.
The following steps of the operation are performed using a surgical microscope. Based on the ICG lymphography mapping, incisions of 1 to 2 cm are made at the predetermined sites. Lymphatic vessels are identified and an anastomosis is performed with a similarly sized adjacent recipient vein in the subdermal plane. The anastomosis is usually performed in an end-to-end fashion in case both the lymphatic vessel and vein have approximately the same caliber (otherwise end-to-side). The end-to-end anastomose is created with an 11-0 suture. The patency of the LVA is confirmed by direct visual examination under the microscope. On average 1 to 4 anastomosis are performed in a lymphedematous arm. The superficial wound is closed using 4-0 Ethilon covered by adhesive plasters and a bandage. The operation length is approximately two to three hours (27).

Post-operative treatment

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

Sample size calculation

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

Comparing LVA to conservative treatment, the minimal difference in health-related quality of life (HRQoL) that is considered as clinically relevant is 15 points (15% decrease on the 0 to 100 scale) on the Lymph-ICF questionnaire at 12 months follow-up (38).

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

Using the numbers described above a sample size calculation results in a sample size of 60 patients in each group.

Outcomes

Primary outcome

The primary outcome is HRQoL at 12 months follow-up. To assess the effectiveness of the treatment we will use the Dutch version of the "Lymphedema Functioning, Disability and Health" (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in function, activity limitations, and participation restrictions of patients with arm lymphedema. It is a validated, disease-specific questionnaire, consisting of 29 items (questions) across 5 domains. Each item is scored on a VAS ranging from 0 to 100. The total score on the Lymph-ICF is equal to the sum of the item scores divided by the total number of answered items. A higher score on the Lymph-ICF indicates more impact in the functioning in the daily life related to arm lymphedema.

HRQoL will be measured at baseline and 3, 6, 12, 18 and 24 months after randomization.

Secondary outcomes

Secondary outcomes are the societal costs, QALYs, incremental cost-effectiveness, discontinuation of conservative treatment, and excess limb volume. Assessment will be done at baseline and 3, 6, 12, 18, and 24 months after randomization.

Costs include health care related costs, costs to patients and family, and costs due to lost productivity. Complete individual level hospital resource use data (e.g. surgical intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be measured using medical records and provider information systems. Resource use outside the hospital (e.g. lymphedema therapy, general practitioner visits, out-of-pocket expenses such as for therapeutic elastic stockings and over-the counter drugs, travel costs, and quantities of lost paid work) will be determined by means of prospective cost diaries as kept by participants. The cost dairy developed for this study is an adapted version of the MCQ and PCQ (39). The Dutch manual for costing research will be used to determine prices for each volume of resource use (40).

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

The EQ-5D-5L examines a patient's HRQoL on the day of the interview. It consist of the EQ-5D-5L descriptive system and a Visual Analog Scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Responses to the 5 items result in a patient's health state that can be transformed into an index score representing a HRQoL-weight, ranging between 0 (death) and 1 (perfect health) (43). These index scores are combined with length of life to calculate the QALYs. The EQ VAS records the patient's self-

rated health with endpoints labelled ‘the best health you can imagine’ at the top and ‘the worst health you can imagine’ at the bottom.

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 stockings, 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 limb and a so called ICG lymphography is performed in search for viable lymphatic vessels. This is a technique using near-infrared fluorescence imaging (NIRF). After 0.05 ml of ICG (5mg/ml) is injected, a near-infrared camera is used to visualize the lymphatic vessels. Proximal to the injection sites fluorescent stains are identified. When using the images as a guide, the lymphatic pathways and the sites for incisions for lymphaticovenous anastomoses are marked with a pen and a color picture is taken. These color pictures are used to identify

the location when LVA will be performed. NIRF will be done at introduction visit and patency testing after 12 and 24 months.

Data analysis

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

Economic evaluation

An economic evaluation will be performed alongside the clinical trial to determine the cost-effectiveness of LVA compared to CDT. The design of the economic evaluation follows the principles of a cost-utility analysis and adheres to the Dutch guideline for economic evaluations in health care and the Dutch manual for costing research (44, 45) Outcome 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).

In the case of missing values occur, this will be solved by imputation by means of mean substitution.

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 is stored immediately in the online database of CASTOR EDC ©. The investigator and project leader only have access to this database with an account with password. Identifying data will be stored in coded form; the key to the form is known only to the supervisor, the investigator, the Dutch Health Care Inspectorate (IGJ), the study monitors, and the members of the review committee.

Harms

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

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

Auditing

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

Protocol amendments

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

Patient and public involvement

Patients were not involved in the development of the research question, study design or recruitment into the study.

Ethical considerations

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

Dissemination

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

References

1. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol. 2008;26(35):5689-96.

2. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat. 2011;130(3):981-91.

3. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. Breast Cancer Res Treat. 2003;79(1):47-57.

4. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. World J Clin Oncol. 2014;5(3):241-7.

5. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. Acta Oncol. 2010;49(3):347-53.

6. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer. 1998;83(12 Suppl American):2776-81.

7. Chachaj A, Malyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudelko M, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. Psychooncology. 2010;19(3):299-305.

8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.

9. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study. Psychooncology. 2014;23(9):1049-56.

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 NvvDe. Richtlijn lymfoedeem. Multidisciplinaire evidence-based richtlijn. www.lymfoedeem.nl; 2014.

15. Richtlijn mammacarcinoom. 2012. Avaiable from: www.oncoline.nl

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.

20. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic drainage and intermittent pneumatic compression pump use in the treatment of lymphedema after mastectomy: a randomized controlled trial. Breast Cancer. 2015;22(3):300-7.

21. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-related lymphedema after intensive decongestive physiotherapy. Breast Cancer Res Treat. 2007;101(3):285-90.

22. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary interventions for cancer-related lymphedema: a systematic review and meta-analysis. Cancer. 2011;117(6):1136-48.

23. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. J Clin Oncol. 2013;31(30):3758-63.

24. O'Brien BM. Replantation and reconstructive microvascular surgery. Part II. Ann R Coll Surg Engl. 1976;58(3):171-82.

25. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. Plast Reconstr Surg. 2014;133(4):905-13.

26. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. Plast Reconstr Surg. 2010;126(3):752-8.

27. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. Plast Reconstr Surg. 2013;132(5):1305-14.

28. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. Breast Cancer Res Treat. 2009;113(2):199-206.

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

30. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg. 2000;16(6):437-42.

31. Mihara M, Hara H, Hayashi Y, Iida T, Araki J, Yamamoto T, et al. Upper-limb lymphedema treated aesthetically with lymphaticovenous anastomosis using indocyanine green lymphography and noncontact vein visualization. J Reconstr Microsurg. 2012;28(5):327-32.

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

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

34. Torrisi JS, Joseph WJ, Ghanta S, Cuzzone DA, Albano NJ, Savetsky IL, et al. Lymphaticovenous bypass decreases pathologic skin changes in upper extremity breast cancer-related lymphedema. Lymphat Res Biol. 2015;13(1):46-53.

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

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

37. Masia J, Pons G, Nardulli ML. Combined Surgical Treatment in Breast Cancer-Related Lymphedema. J Reconstr Microsurg. 2016;32(1):16-27.

38. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Phys Ther. 2011;91(6):944-57.

39. Bouwmans Cea. Handleiding *i*MTA Medical Cost Questionnaire (iMCQ). 2013.

40. Lopez Penha TR, van Roozendaal LM, Smidt ML, Boersma LJ, von Meyenfeldt MF, Voogd AC, et al. The changing role of axillary treatment in breast cancer: Who will remain at risk for developing arm morbidity in the future? Breast. 2015;24(5):543-7.

41. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

42. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment. Health Qual Life Outcomes. 2009;7:11.

43. Versteegh M VM, Evers MAAS, de Wit GA, Prenger R. Dutch Tariff for the Five-Level Version of EQ-5D. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2016.

44. Zorginstituut. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015.

45. Zorginstituut. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg; 2015.

Footnotes

Author Contributions

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

Funding

This work was supported by ZonMw, grant number 80-85200-98-91044 and Academic Hospital of Maastricht (azM).

ZonMw

Postbus 93 245

2509 AE Den Haag

Telefoon 070 349 51 11

Fax 070 349 51 00

E-mail info@zonmw.nl

azM

Postbus 5800

6202 AZ Maastricht

Tel: 043 387 6543

Competing interests

None declared.

Patient consent for publication

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

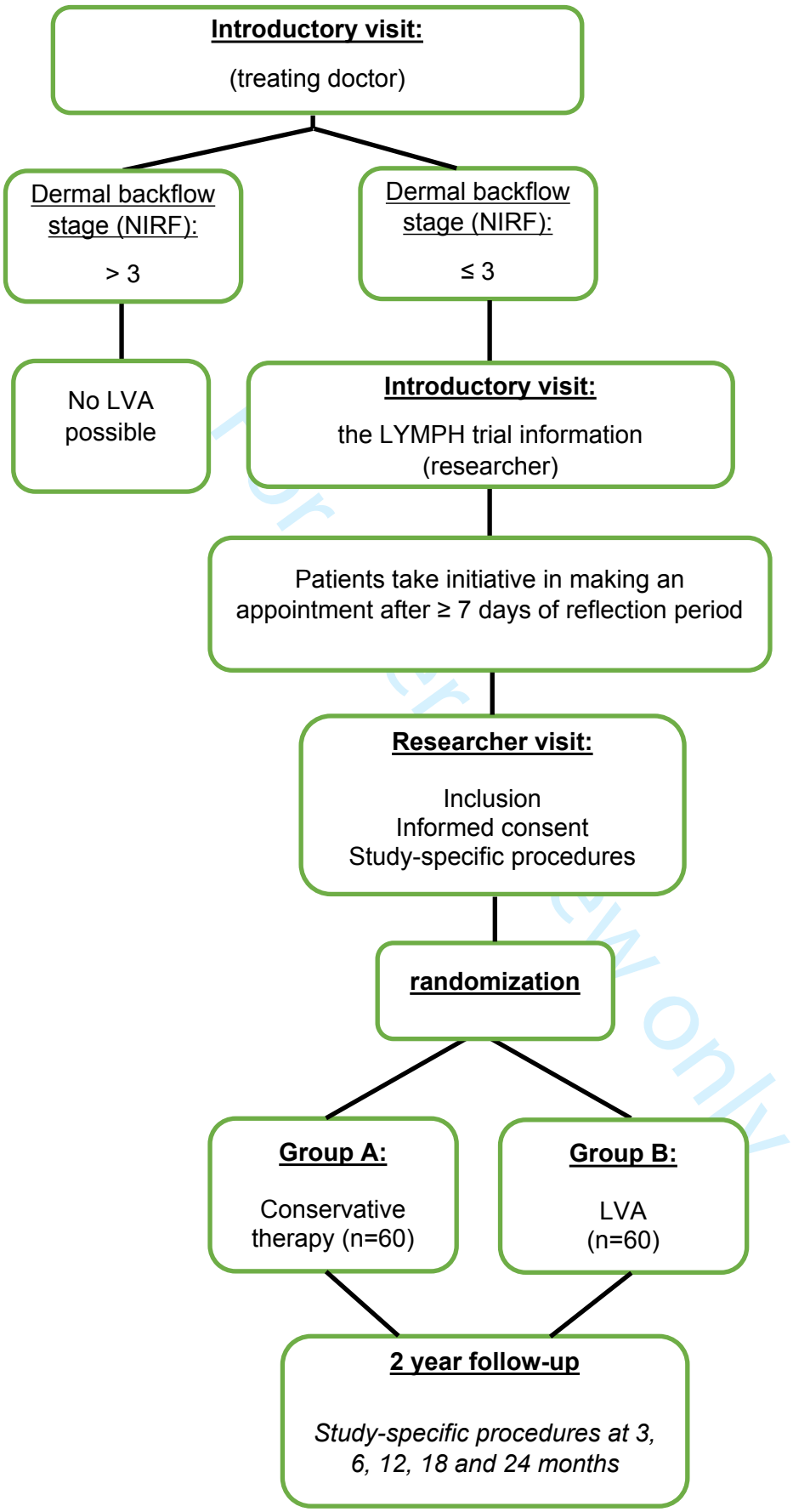

Fig 1 Flowchart: overview of the study design

SPIRIT

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

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, Fig 1
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-14
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
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

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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
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)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035337.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Dec-2019
Complete List of Authors:	Wolfs, Joost; Maastricht University Medical Centre+, Beugels, Jop; Maastricht University Medical Centre+, Plastic & Reconstructive Surgery Kimman, Merel; Maastricht Universitair Medisch Centrum+, Piatkowski de Grzymala, Andrzej; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery Heuts, Esther; Maastricht University Medical Centre+, Surgery Keuter, Xavier; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery Tielemans, Hanneke; Radboudumc, Plastic, Reconstructive & Hand Surgery Ulrich, Dietmar; Radboudumc, Plastic, Reconstructive & Hand Surgery van der Hulst , R; Maastricht University Medical Center, Plastic surgery Qiu, Shan Shan; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Dermatology, Surgery
Keywords:	PLASTIC & RECONSTRUCTIVE SURGERY, Breast surgery < SURGERY, Plastic & reconstructive surgery < SURGERY

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

J.A.G.N. **Wolfs** *MD*[1], J. **Beugels** *MD*[1], M. **Kimman** *PhD*[2], A. **Piatkowski** *MD PhD*[1], E.M. **Heuts** *MD PhD*[3], X.H.A. **Keuter** *MD PhD*[1], H.J.P. **Tielemans** *MD*[4], D.J.O. **Ulrich** *MD PhD*[4], R.R.W.J. **van der Hulst** *MD PhD*[1], S.S. **Qiu** *MD PhD*[1].

Author affiliations

1 Department of Plastic and Reconstructive Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

2 Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, Netherlands

3 Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

4 Department of Plastic and Reconstructive Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

Corresponding author

Shan Shan Qiu, *MD PhD*

Department of Plastic, Reconstructive and Hand surgery

Maastricht University Medical Center

P. Debyelaan 25, 6229 HX Maastricht, The Netherlands

Telephone: (+31) 043-3875474

Fax: (+31) 043-3875473

Email: shanshan.qiushao@mumc.nl

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 weather 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.

Registration details. The study is registered in the trial register www.clinicaltrials.gov with number NCT02790021.

Strengths and limitations of this study

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

Key words

Breast cancer lymphedema, lymphaticovenous anastomosis, conservative treatment, randomized controlled trial, quality of life

Study title

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

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, however, 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 (5, 16-20). Limb swelling may present with symptoms of heaviness, tightness, pain, and loss of normal arm 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) (1, 7, 11, 13, 21). Moreover, infections of the skin are regularly seen in a severe stadium of lymphedema, such as erysipelas or cellulitis (2, 8, 21).

Conservative therapy

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

randomized. Another disadvantage is the heterogeneity of the patient population, assessment modalities, and inconsistent reporting of outcomes and complications (27, 30, 34).

The aim of this multicenter RCT is to examine HRQoL and (cost-)effectiveness of LVA compared with CDT in a large homogenous group of patients with BCRL.

Methods and analysis

Study Design

The LYMPH trial is a multicenter, non-blinded, randomized controlled trial and will be conducted in the Maastricht University Medical Center, Radboud University Medical Center, Zuyderland Medical Center, and Canisius-Wilhelmina Hospital in the Netherlands.

Enrolment will take place at the outpatient clinics of the participating hospitals. The inclusion and exclusion criteria are listed in Table 1. A total of 120 women must be recruited after a period of two years. After inclusion and informed consent, participants will be randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per a computer generated randomization schedule stratified by site using block randomization. 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

used in this study. Ongoing conservative treatment and the frequency is controlled by the skin therapist. All information regarding conservative treatment is noted in the patient diary.

Group B: Surgical treatment

Lymphaticovenous anastomosis

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

Before making the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is injected at the site of incision to achieve local anesthesia and optimal hemostasis.

The following steps of the operation are performed using a surgical microscope. Based on the ICG lymphography mapping, incisions of 1 to 2 cm are made at the predetermined sites. Lymphatic vessels are identified and an anastomosis is performed with a similarly sized adjacent recipient vein in the subdermal plane. The anastomosis is usually performed in an end-to-end fashion in case both the lymphatic vessel and vein have approximately the same caliber (otherwise end-to-side). The end-to-end anastomosis is created with an 11-0 suture. The patency of the LVA is confirmed by direct visual examination under the microscope. On average 1 to 4 anastomosis are performed in a lymphedematous arm. The superficial wound is closed using 4-0 Ethilon covered by adhesive plasters and a bandage. The operation length is approximately two to three hours (29).

Post-operative treatment

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

After 3 months, the plastic surgeon will determine whether conservative therapy can be reduced or stopped, depending on the decrease of subjective complaints and swelling of the arm. The frequency of manual lymphatic drainage will be controlled by the skin therapist and noted in the patient diary.

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

Sample size calculation

We made the following assumptions for the calculation of the sample size to show a statistically significant and clinically relevant difference in quality of life between treatment groups at 12 months follow-up as measured with the Lymph-ICF questionnaire:
Comparing LVA to conservative treatment, the minimal difference in HRQoL that is considered as clinically relevant is 15 points (15% decrease on the 0 to 100 scale) on the Lymph-ICF questionnaire at 12 months follow-up (46).
To be able to achieve a power of 80%, a total of 45 patients are needed per treatment group, when the standard deviation is 25%, using an alpha of 0.05. If a drop-out rate (loss-to-follow-up and patients with missing data) of 25% is taken into account, a sample size of 60 patients per study group is required and a total of 120 patients will be randomized.

Outcomes

Primary outcome

The primary outcome is HRQoL at 12 months follow-up. To assess the effectiveness of the treatment we will use the Dutch version of the "Lymphedema Functioning, Disability and Health" (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in

function, activity limitations, and participation restrictions of patients with upper limb lymphedema. It is a validated, disease-specific questionnaire, consisting of 29 items (questions) across 5 domains. Each item is scored on a VAS ranging from 0 to 100. The total score on the Lymph-ICF is equal to the sum of the item scores divided by the total number of answered items. A higher score on the Lymph-ICF indicates more impact in the functioning in the daily life related to upper limb lymphedema (46).

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

Secondary outcomes

Secondary outcomes are the societal costs, QALYs, incremental cost-effectiveness, discontinuation of conservative treatment, and excess limb volume. Assessment will be done at baseline and 3, 6, 12, 18, and 24 months after informed consent (Group A), or after surgery (Group B).

Costs include health care related costs, costs to patients and family, and costs due to lost productivity. Complete individual level hospital resource use data (e.g. surgical intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be measured using medical records and provider information systems. Resource use outside the hospital (e.g. lymphedema therapy, general practitioner visits, out-of-pocket expenses such as for therapeutic elastic garment and over-the counter drugs, travel costs, and quantities of lost paid work) will be determined by means of prospective cost diaries as kept by participants. The cost dairy developed for this study is an adapted version of the MCQ and PCQ (47). The Dutch manual for costing research will be used to determine prices for each volume of resource use (48).

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

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

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

Data analysis

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

Economic evaluation

An economic evaluation will be performed alongside the clinical trial to determine the cost-effectiveness of LVA compared to CDT. The design of the economic evaluation follows the principles of a cost-utility analysis and adheres to the Dutch guideline for economic evaluations in health care and the Dutch manual for costing research (52, 53). Outcome 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 database with an account with password. Identifying data will be stored in coded form; the key to the form is known only to the supervisor, the investigator, the Dutch Health Care Inspectorate (IGJ), the study monitors, and the members of the review committee.

Harms

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

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

Auditing

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

Protocol amendments

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

Patient and public involvement

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

Ethical considerations

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

Dissemination

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

References

1. Vignes S, Fau-Prudhomot P, Simon L, Sanchez-Brechot ML, Arrault M, Locher F. Impact of breast cancer-related lymphedema on working women. Support Care Cancer. 2019.

2. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. World J Clin Oncol. 2014;5(3):241-7.

3. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat. 2011;130(3):981-91.

4. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. Acta Oncol. 2010;49(3):347-53.

5. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol. 2008;26(35):5689-96.

6. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. Breast Cancer Res Treat. 2003;79(1):47-57.

7. Chachaj A, Malyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudelko M, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. Psychooncology. 2010;19(3):299-305.

8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.

9. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study. Psychooncology. 2014;23(9):1049-56.

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 NvvDe. 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.

20. Johnson AR, Kimball S, Epstein S, Recht A, Lin SJ, Lee BT, et al. Lymphedema Incidence After Axillary Lymph Node Dissection: Quantifying the Impact of Radiation and the Lymphatic Microsurgical Preventive Healing Approach. Ann Plast Surg. 2019;82(4S Suppl 3):S234-S41.

21. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. J Am Acad Dermatol. 2017;77(6):1009-20.

22. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic drainage and intermittent pneumatic compression pump use in the treatment of lymphedema after mastectomy: a randomized controlled trial. Breast Cancer. 2015;22(3):300-7.

23. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-related lymphedema after intensive decongestive physiotherapy. Breast Cancer Res Treat. 2007;101(3):285-90.

24. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary interventions for cancer-related lymphedema: a systematic review and meta-analysis. Cancer. 2011;117(6):1136-48.

25. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. J Clin Oncol. 2013;31(30):3758-63.

26. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg. 2000;16(6):437-42.

27. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. Plast Reconstr Surg. 2014;133(4):905-13.

28. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. Plast Reconstr Surg. 2010;126(3):752-8.

29. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. Plast Reconstr Surg. 2013;132(5):1305-14.

30. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. Breast Cancer Res Treat. 2009;113(2):199-206.

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

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

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

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

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

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

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

38. Winters H, Tielemans HJP, Verhulst AC, Paulus VAA, Slater NJ, Ulrich DJO. The Long-term Patency of Lymphaticovenular Anastomosis in Breast Cancer-Related Lymphedema. Ann Plast Surg. 2019;82(2):196-200.

39. Salgarello M, Mangialardi ML, Pino V, Gentileschi S, Visconti G. A Prospective Evaluation of Health-Related Quality of Life following Lymphaticovenular Anastomosis for Upper and Lower Extremities Lymphedema. J Reconstr Microsurg. 2018;34(9):701-7.

40. Giacalone G, Yamamoto T. Supermicrosurgical lymphaticovenous anastomosis for a patient with breast lymphedema secondary to breast cancer treatment. Microsurgery. 2017;37(6):680-3.

41. Cornelissen AJM, Kool M, Lopez Penha TR, Keuter XHA, Piatkowski AA, Heuts E, et al. Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: a prospective study on quality of life. Breast Cancer Res Treat. 2017;163(2):281-6.

42. Winters H, Tielemans HJP, Hameeteman M, Paulus VAA, Beurskens CH, Slater NJ, et al. The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema. Breast Cancer Res Treat. 2017;165(2):321-7.

43. Executive C. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology. 2016;49(4):170-84.

44. Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I. Indocyanine Green Lymphography Findings in Limb Lymphedema. J Reconstr Microsurg. 2016;32(1):72-9.

45. Masia J, Pons G, Nardulli ML. Combined Surgical Treatment in Breast Cancer-Related Lymphedema. J Reconstr Microsurg. 2016;32(1):16-27.

46. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Phys Ther. 2011;91(6):944-57.

47. Bouwmans Cea. Handleiding *i*MTA Medical Cost Questionnaire (iMCQ). 2013.

48. Lopez Penha TR, van Roozendaal LM, Smidt ML, Boersma LJ, von Meyenfeldt MF, Voogd AC, et al. The changing role of axillary treatment in breast cancer: Who will remain at risk for developing arm morbidity in the future? Breast. 2015;24(5):543-7.

49. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

50. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment. Health Qual Life Outcomes. 2009;7:11.

51. Versteegh M VM, Evers MAAS, de Wit GA, Prenger R. Dutch Tariff for the Five-Level Version of EQ-5D. . Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2016.

52. Zorginstituut. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015.

53. Zorginstituut. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.; 2015.

Footnotes

Author Contributions

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

Funding

This work was supported by ZonMw, grant number 80-85200-98-91044 and Academic Hospital of Maastricht (azM).

ZonMw

Postbus 93 245

2509 AE Den Haag

Telefoon 070 349 51 11

Fax 070 349 51 00

E-mail info@zonmw.nl

azM

Postbus 5800

6202 AZ Maastricht

Tel: 043 387 6543

Competing interests

None declared.

Patient consent for publication

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

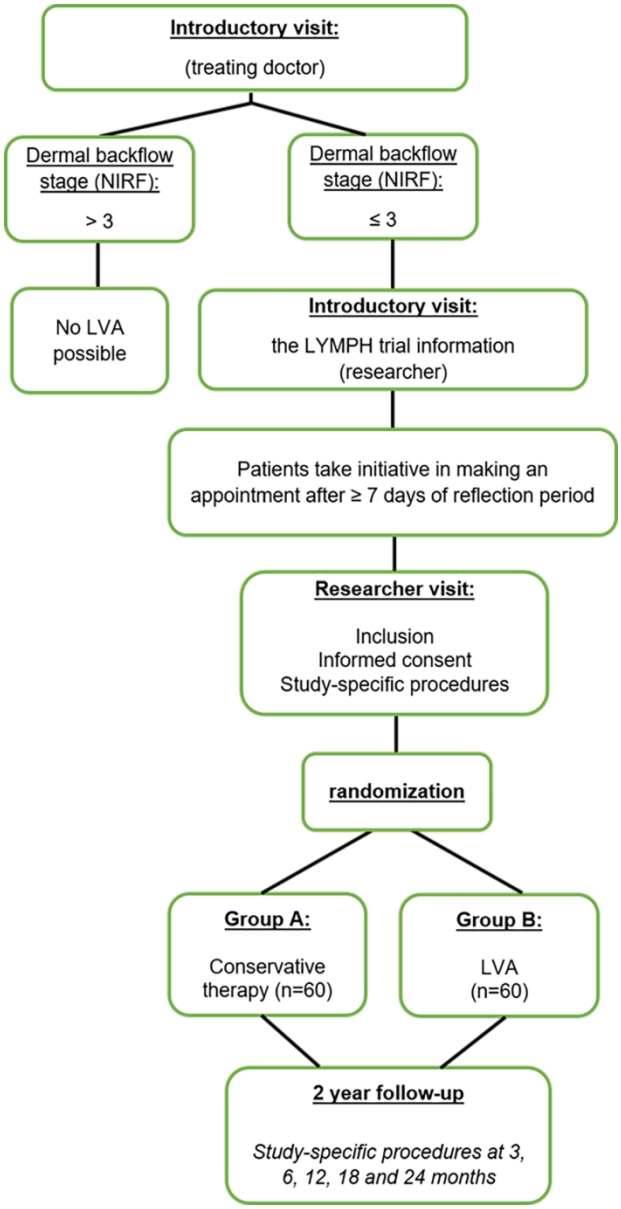

Figure 1 Flowchart: overview of the study design

97x190mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	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

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, Fig 1
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-14
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
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

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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
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)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035337.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Dec-2019
Complete List of Authors:	Wolfs, Joost; Maastricht University Medical Centre+, Beugels, Jop; Maastricht University Medical Centre+, Plastic & Reconstructive Surgery Kimman, Merel; Maastricht Universitair Medisch Centrum+, Piatkowski de Grzymala, Andrzej; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery Heuts, Esther; Maastricht University Medical Centre+, Surgery Keuter, Xavier; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery Tielemans, Hanneke; Radboudumc, Plastic, Reconstructive & Hand Surgery Ulrich, Dietmar; Radboudumc, Plastic, Reconstructive & Hand Surgery van der Hulst , R; Maastricht University Medical Center, Plastic surgery Qiu, Shan Shan; Maastricht University Medical Centre+, Plastic, Reconstructive, and Hand surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Dermatology, Surgery
Keywords:	PLASTIC & RECONSTRUCTIVE SURGERY, Breast surgery < SURGERY, Plastic & reconstructive surgery < SURGERY

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

J.A.G.N. **Wolfs** *MD*[1], J. **Beugels** *MD*[1], M. **Kimman** *PhD*[2], A. **Piatkowski** *MD PhD*[1], E.M. **Heuts** *MD PhD*[3], X.H.A. **Keuter** *MD PhD*[1], H.J.P. **Tielemans** *MD*[4], D.J.O. **Ulrich** *MD PhD*[4], R.R.W.J. **van der Hulst** *MD PhD*[1], S.S. **Qiu** *MD PhD*[1].

Author affiliations

1 Department of Plastic and Reconstructive Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

2 Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, Netherlands

3 Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

4 Department of Plastic and Reconstructive Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

Corresponding author

Shan Shan Qiu, *MD PhD*

Department of Plastic, Reconstructive and Hand surgery

Maastricht University Medical Center

P. Debyelaan 25, 6229 HX Maastricht, The Netherlands

Telephone: (+31) 043-3875474

Fax: (+31) 043-3875473

Email: shanshan.qiushao@mumc.nl

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 weather 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.

Registration details. The study is registered in the trial register www.clinicaltrials.gov with number NCT02790021.

Strengths and limitations of this study

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

Key words

Breast cancer lymphedema, lymphaticovenous anastomosis, conservative treatment, randomized controlled trial, quality of life

Study title

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

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, however, 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 (5, 16-20). Limb swelling may present with symptoms of heaviness, tightness, pain, and loss of normal arm 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) (1, 7, 11, 13, 21). Moreover, infections of the skin are regularly seen in a severe stadium of lymphedema, such as erysipelas or cellulitis (2, 8, 21).

Conservative therapy

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

randomized. Another disadvantage is the heterogeneity of the patient population, assessment modalities, and inconsistent reporting of outcomes and complications (27, 30, 34).

The aim of this multicenter RCT is to examine HRQoL and (cost-)effectiveness of LVA compared with CDT in a large homogenous group of patients with BCRL.

Methods and analysis

Study Design

The LYMPH trial is a multicenter, non-blinded, randomized controlled trial and will be conducted in the Maastricht University Medical Center, Radboud University Medical Center, Zuyderland Medical Center, and Canisius-Wilhelmina Hospital in the Netherlands.

Enrolment will take place at the outpatient clinics of the participating hospitals. The inclusion and exclusion criteria are listed in Table 1. A total of 120 women must be recruited after a period of two years. After inclusion and informed consent, participants will be randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per a computer generated randomization schedule stratified by site using block randomization. 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 used in this study. See the Supplementary Data for the CDT protocol. Ongoing conservative

treatment and the frequency is controlled by the skin therapist. All information regarding conservative treatment is noted in the patient diary.

Group B: Surgical treatment

Lymphaticovenous anastomosis

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

Before making the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is injected at the site of incision to achieve local anesthesia and optimal hemostasis.

The following steps of the operation are performed using a surgical microscope. Based on the ICG lymphography mapping, incisions of 1 to 2 cm are made at the predetermined sites. Lymphatic vessels are identified and an anastomosis is performed with a similarly sized adjacent recipient vein in the subdermal plane. The anastomosis is usually performed in an end-to-end fashion in case both the lymphatic vessel and vein have approximately the same caliber (otherwise end-to-side). The end-to-end anastomosis is created with an 11-0 suture. The patency of the LVA is confirmed by direct visual examination under the microscope. On average 1 to 4 anastomosis are performed in a lymphedematous arm. The superficial wound is closed using 4-0 Ethilon covered by adhesive plasters and a bandage. The operation length is approximately two to three hours (29).

Postoperative treatment

From 2 weeks after surgery, when the stitches are removed, patients will be treated with conservative therapy the same way and in the same frequency as preoperatively (45). The participants are treated by the same method as group A if needed, as described in phase 2 (maintenance phase) of the CDT protocol. After 3 months, the plastic surgeon will determine

whether conservative therapy can be reduced or stopped, depending on the decrease of subjective complaints and swelling of the arm. The frequency of manual lymphatic drainage will be controlled by the skin therapist and noted in the patient diary.

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

Sample size calculation

We made the following assumptions for the calculation of the sample size to show a statistically significant and clinically relevant difference in quality of life between treatment groups at 12 months follow-up as measured with the Lymph-ICF questionnaire:
Comparing LVA to conservative treatment, the minimal difference in HRQoL that is considered as clinically relevant is 15 points (15% decrease on the 0 to 100 scale) on the Lymph-ICF questionnaire at 12 months follow-up (46).
To be able to achieve a power of 80%, a total of 45 patients are needed per treatment group, when the standard deviation is 25%, using an alpha of 0.05. If a drop-out rate (loss-to-follow-up and patients with missing data) of 25% is taken into account, a sample size of 60 patients per study group is required and a total of 120 patients will be randomized.

Outcomes

Primary outcome

The primary outcome is HRQoL at 12 months follow-up. To assess the effectiveness of the treatment we will use the Dutch version of the "Lymphedema Functioning, Disability and Health" (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in function, activity limitations, and participation restrictions of patients with upper limb

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

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

Secondary outcomes

Secondary outcomes are the societal costs, QALYs, incremental cost-effectiveness, discontinuation of conservative treatment, and excess limb volume. Assessment will be done at baseline and 3, 6, 12, 18, and 24 months after informed consent (Group A), or after surgery (Group B).

Costs include health care related costs, costs to patients and family, and costs due to lost productivity. Complete individual level hospital resource use data (e.g. surgical intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be measured using medical records and provider information systems. Resource use outside the hospital (e.g. lymphedema therapy, general practitioner visits, out-of-pocket expenses such as for therapeutic elastic garment and over-the counter drugs, travel costs, and quantities of lost paid work) will be determined by means of prospective cost diaries as kept by participants. The cost dairy developed for this study is an adapted version of the MCQ and PCQ (47). The Dutch manual for costing research will be used to determine prices for each volume of resource use (48).

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

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

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

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

Data analysis

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

Economic evaluation

An economic evaluation will be performed alongside the clinical trial to determine the cost-effectiveness of LVA compared to CDT. The design of the economic evaluation follows the principles of a cost-utility analysis and adheres to the Dutch guideline for economic evaluations in health care and the Dutch manual for costing research (52, 53). Outcome

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

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

Harms

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

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

Auditing

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

Protocol amendments

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

Patient and public involvement

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

Ethical considerations

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

Dissemination

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

References

1. Vignes S, Fau-Prudhomot P, Simon L, Sanchez-Brechot ML, Arrault M, Locher F. Impact of breast cancer-related lymphedema on working women. Support Care Cancer. 2019.

2. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. World J Clin Oncol. 2014;5(3):241-7.

3. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat. 2011;130(3):981-91.

4. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. Acta Oncol. 2010;49(3):347-53.

5. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol. 2008;26(35):5689-96.

6. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. Breast Cancer Res Treat. 2003;79(1):47-57.

7. Chachaj A, Malyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudelko M, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. Psychooncology. 2010;19(3):299-305.

8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.

9. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study. Psychooncology. 2014;23(9):1049-56.

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 NvvDe. 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.

20. Johnson AR, Kimball S, Epstein S, Recht A, Lin SJ, Lee BT, et al. Lymphedema Incidence After Axillary Lymph Node Dissection: Quantifying the Impact of Radiation and the Lymphatic Microsurgical Preventive Healing Approach. Ann Plast Surg. 2019;82(4S Suppl 3):S234-S41.

21. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. J Am Acad Dermatol. 2017;77(6):1009-20.

22. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic drainage and intermittent pneumatic compression pump use in the treatment of lymphedema after mastectomy: a randomized controlled trial. Breast Cancer. 2015;22(3):300-7.

23. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-related lymphedema after intensive decongestive physiotherapy. Breast Cancer Res Treat. 2007;101(3):285-90.

24. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary interventions for cancer-related lymphedema: a systematic review and meta-analysis. Cancer. 2011;117(6):1136-48.

25. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. J Clin Oncol. 2013;31(30):3758-63.

26. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg. 2000;16(6):437-42.

27. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. Plast Reconstr Surg. 2014;133(4):905-13.

28. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. Plast Reconstr Surg. 2010;126(3):752-8.

29. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. Plast Reconstr Surg. 2013;132(5):1305-14.

30. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11

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

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

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

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

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

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

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

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

38. Winters H, Tielemans HJP, Verhulst AC, Paulus VAA, Slater NJ, Ulrich DJO. The Long-term Patency of Lymphaticovenular Anastomosis in Breast Cancer-Related Lymphedema. Ann Plast Surg. 2019;82(2):196-200.

39. Salgarello M, Mangialardi ML, Pino V, Gentileschi S, Visconti G. A Prospective Evaluation of Health-Related Quality of Life following Lymphaticovenular Anastomosis for Upper and Lower Extremities Lymphedema. J Reconstr Microsurg. 2018;34(9):701-7.

40. Giacalone G, Yamamoto T. Supermicrosurgical lymphaticovenous anastomosis for a patient with breast lymphedema secondary to breast cancer treatment. Microsurgery. 2017;37(6):680-3.

41. Cornelissen AJM, Kool M, Lopez Penha TR, Keuter XHA, Piatkowski AA, Heuts E, et al. Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: a prospective study on quality of life. Breast Cancer Res Treat. 2017;163(2):281-6.

42. Winters H, Tielemans HJP, Hameeteman M, Paulus VAA, Beurskens CH, Slater NJ, et al. The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema. Breast Cancer Res Treat. 2017;165(2):321-7.

43. Executive C. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology. 2016;49(4):170-84.

44. Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I. Indocyanine Green Lymphography Findings in Limb Lymphedema. J Reconstr Microsurg. 2016;32(1):72-9.

45. Masia J, Pons G, Nardulli ML. Combined Surgical Treatment in Breast Cancer-Related Lymphedema. J Reconstr Microsurg. 2016;32(1):16-27.

46. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Phys Ther. 2011;91(6):944-57.

47. Bouwmans Cea. Handleiding *i*MTA Medical Cost Questionnaire (iMCQ). 2013.

48. Lopez Penha TR, van Roozendaal LM, Smidt ML, Boersma LJ, von Meyenfeldt MF, Voogd AC, et al. The changing role of axillary treatment in breast cancer: Who will remain at risk for developing arm morbidity in the future? Breast. 2015;24(5):543-7.

49. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

50. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment. Health Qual Life Outcomes. 2009;7:11.

51. Versteegh M VM, Evers MAAS, de Wit GA, Prenger R. Dutch Tariff for the Five-Level Version of EQ-5D. . Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2016.

52. Zorginstituut. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015.

53. Zorginstituut. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.; 2015.

Footnotes

Author Contributions

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

Funding

This work was supported by ZonMw, grant number 80-85200-98-91044 and Academic Hospital of Maastricht (azM).

ZonMw

Postbus 93 245

2509 AE Den Haag

Telefoon 070 349 51 11

Fax 070 349 51 00

E-mail info@zonmw.nl

azM

Postbus 5800

6202 AZ Maastricht

Tel: 043 387 6543

Competing interests

None declared.

Patient consent for publication

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

Figure Legends

Figure 1 Flowchart: overview of the study design

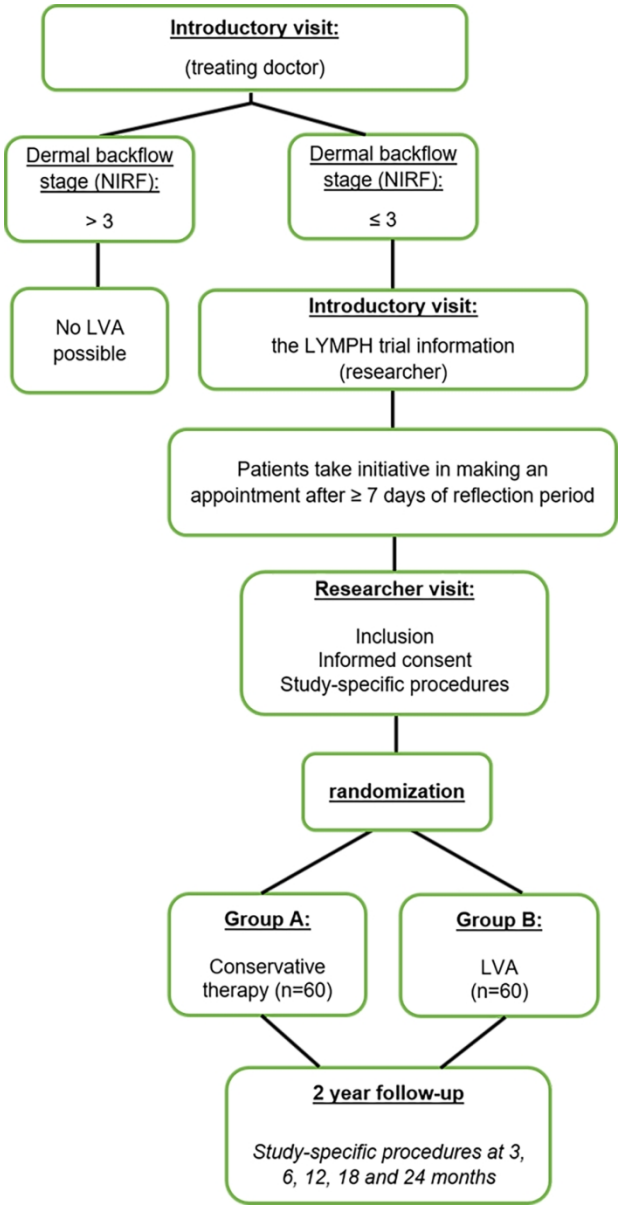

Figure 1 Flowchart: overview of the study design

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

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

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, Fig 1
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-14
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 14
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
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

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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
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)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.