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SurLym trial: Study protocol for a multicentre pragmatic randomised controlled trial on the added value of reconstructive lymphatic surgery to decongestive lymphatic therapy for the treatment of lymphoedema

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3 SurLym trial: Study protocol for a multicentre pragmatic randomised controlled trial on the added
4 value of reconstructive lymphatic surgery to decongestive lymphatic therapy for the treatment of
5 lymphoedema
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39
40 (FWO).

Trial registration data set

Primary registry and trial identifying number	ClinicalTrials.gov Identifier: NCT05064176
Date of registration in primary registry	24-8-2021
Secondary identifying numbers	Ethical Committee UZ Leuven: S63212; EudraCT: 2021-000397-29
Source of monetary and material support	Belgian Health Care Knowledge Centre
Sponsor	University Hospitals Leuven, Clinical Trial center, Herestraat 49, 3000 Leuven, Belgium
Contact for public and scientific queries	Nele.devoogdt@uzleuven.be
Public title	Added value of reconstructive lymphatic surgery to usual care in lymphoedema
Scientific title	Comparison of reconstructive lymphatic surgery versus no surgery, additional to decongestive lymphatic therapy (usual care), for the treatment of lymphoedema , through a multicenter, pragmatic 3andomized controlled trial
Acronym	SurLym-trial
Protocol version	V3.0 19-4-2022
Country of recruitment	Belgium
Health condition studied	Primary or secondary upper or lower limb lymphoedema stage 1 to 2b
Intervention	Intervention group: Reconstructive lymphatic surgery (i.e. LVA or LNT or combination), added to usual care Control group: Only usual care (no surgery)
Key inclusion and exclusion criteria	-Lymphoedema: upper/ lower limb; uni-/ bilateral; primary or secondary; stage 1 to 2b; $\geq 5\%$ volume difference or ≥ 2 minor/ 1 major lymphoscintigraphy criterion; total score or one domain score of Lymph-ICF questionnaire $\geq 25/100$ -History of DLT ($\geq 6M$) until minimal pitting, no liposuction/ reconstructive surgery in past

	-In case of lower limb lymphoedema: no CVI C4-C6, no DVT/ PTS -Age \geq 18 years, not pregnant, BMI \leq 35 -No allergy for ICG/ iodine; no increased activity/ benign tumor thyroid gland; no heparin use and severe renal insufficiency
Study type	Multicentre, pragmatic randomised controlled trial
Date of first enrolment	March 2022
Target sample size	180
Recruitment status	Recruiting
Primary endpoint	Lymphoedema-specific QOL, at 18 months post-baseline
Key secondary endpoints	Limb volume, at 18 months post-baseline Duration of wearing the compression garment, at 18 months post-baseline
Treatment duration	18 months (usual care)
Follow up duration	36 months

Abstract

Introduction

Lymphoedema is a chronic condition caused by lymphatic insufficiency. It leads to swelling of the limb/ midline region and an increased risk of infection. Lymphoedema is often associated with mental and physical problems limiting quality of life. The first choice of treatment is a conservative treatment, consisting of exercises, skin care, lymph drainage and compression. Reconstructive lymphatic surgery is also often performed, i.e. lymphovenous anastomoses (LVA), lymph node transfer (LNT), or a combination. Currently, scientific evidence for reconstructive lymphatic surgery is not of high quality. Therefore, the objective of this trial is to investigate the added value of reconstructive lymphatic surgery to the conservative treatment in patients with lymphoedema.

Methods and analysis

A multicentre randomised controlled and pragmatic trial was started since March 2022 in 3 Belgian university hospitals. Ninety patients with arm lymphoedema and 90 patients with leg lymphoedema will be included. All patients are randomised between conservative treatment alone (control group) or conservative treatment with reconstructive lymphatic surgery (intervention group). Assessments are performed at baseline and at 1, 3, 6, 12, 18, 24 and 36 months. The primary outcome is lymphoedema-specific quality of life at 18 months. Key secondary outcomes are limb volume and duration of wearing the compression garment at 18 months. The approach of reconstructive lymphatic surgery is based on pre-surgical investigations including clinical examination, lymphofluoroscopy, lymphoscintigraphy, lymph MRI or CT angiography (if needed). All patients receive conservative treatment during 36 months, which is applied by the patient's own physical therapist and by the patient self. From month 7-12, the hours a day of wearing the compression garment are gradually decreased.

Ethics and dissemination

The study has been approved by the ethical committees of University Hospitals Leuven, Ghent University Hospital and CHU UCL Namur. Results will be disseminated via peer-reviewed journals and presentations.

ClinicalTrials.gov Identifier: NCT05064176

Keywords: lymphedema, reconstructive surgery, surgical anastomosis, surgical flap

Word count: 4421 (up to data security and management), 5185 for all parts

Strengths and limitations of this study

- 1) This trial is stratified and powered for the effect of reconstructive surgery in both arm and leg lymphoedema and will permit a conclusion regarding the effect of reconstructive lymphatic surgery in both of these groups.
- 2) High-qualitative reconstructive lymphatic surgery procedures will be performed: a) Independent experts in reconstructive lymphatic surgery are involved in the Trial Steering Committee and have trained the surgeons of the 3 study centers; in this way, standardisation and quality of the surgical procedure is guaranteed; b) Advanced imaging techniques (i.e. ICG lymphofluoroscopy, lymph MRI, lymphoscintigraphy and CT angiography) are used to prepare the surgical procedure in the trial.
- 3) A comprehensive evaluation of the participants with lymphoedema will be performed: a lymphoedema-specific quality of life outcome is assessed, which is a self-reported outcome (= primary outcome) and limb volume and duration of wearing the compression garment as well, which are objective outcomes (= key secondary outcomes).
- 4) If reconstructive lymphatic surgery is found effective, detailed inventory of cost and quality of life will permit a cost-effectiveness analysis.
- 5) Besides a statistical plan (developed by statistician SF), also a monitoring plan, data management plan, communication plan and risk assessment plan has been set in place.

INTRODUCTION

Lymphoedema is a chronic and debilitating condition caused by lymphatic insufficiency. It leads to swelling of the limb/ midline region and an increased risk of infection. It can be classified as primary (congenital) or secondary (acquired) lymphoedema. Lymphoedema is very burdensome for the patient, often causing mental problems such as frustration and stress.¹ In addition, due to the increase in volume of the limb, patients may develop physical problems, such as pain, heaviness, loss of strength, as well as functional problems with household, mobility or social activities.² These mental, physical and functional problems have a negative impact on the quality of life and the ability to work.³

There is consensus that the first choice of treatment of lymphoedema is a conservative treatment, also called decongestive lymphatic therapy (DLT).^{4,5} In case of pitting oedema, this consists of an intensive daily treatment to maximally reduce the oedema volume. This phase consists of skin care, manual lymph drainage, multilayer bandaging and exercise therapy. Once that sufficient reduction of the pitting is obtained and the patients receive education to improve their self-management skills, the maintenance phase starts, which aims at stabilising the results obtained in the previous phase. During the maintenance phase, skin care, exercises and lymph drainage are continued but bandaging is replaced by low-stretch compression garments. Professional's involvement can be minimised in this phase.

Reconstructive lymphatic surgery is another treatment option, consisting of either lymphovenous anastomoses (LVA), lymph node transfer (LNT) or a combination of both. The choice can be based on the surgeons clinical judgement or on local algorithms, as the Barcelona Lymphoedema Algorithm.⁶ The objective of LVA is to redirect the lymph to the venous stream directly, bypassing areas of obstruction, and without going through the thoracic duct. LVA is applied if functional lymphatics can be localized, primarily by ICG lymphofluoroscopy and lymph MRI.⁷ With LNT, orthotopically placed lymph nodes act as a sponge to absorb lymphatic fluid and direct it into the vascular network. The transferred nodes induce lymphangiogenesis and if they are placed in the site of lymphadenectomy, scar tissue and adhesions are removed to improve vascularisation.^{5,8} Indications for LNT are a total occlusion of lymphatic transport visualised through lymphoscintigraphy and a stage 2 lymphoedema with repeated episodes of erysipelas. Only subjects who had a history of at least 6 to 12 months of conservative treatment with good decongestion of the limb are candidates for reconstructive lymphatic surgery.⁷

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3 Our hypothesis is that reconstructive lymphatic surgery partially restores the lymphatic transport
4 which leads to a decrease of the lymphoedema volume and as a result lowers the need for a
5 compression garment. This will probably improve lymphoedema-specific quality of life.
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9 Robust evidence on the effectiveness of reconstructive lymphatic surgery for lymphoedema has so
10 far not been procured. In 2019, a Cochrane systematic review of Markkula et al revealed that there is
11 not enough high-quality research investigating the effect of reconstructive lymphatic surgery on
12 lymphoedema.⁹ Only one RCT so far evaluated the effect of LNT. Dionyssiou et al randomised 36
13 patients with breast cancer related arm lymphoedema.¹⁰ After surgery/no surgery, all patients first
14 received for 6 months DLT and DLT was discontinued for the next 12 months. At 18 months follow-
15 up, mean limb volume reduction was superior in the group with LNT compared to no LNT (57% vs
16 18%, $p < 0.01$). In the group with LNT infections were less frequent and subjective symptoms
17 improved. An RCT evaluating the effect of LVA has not been performed yet.
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27 **Objectives**

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29 The main objective of this study is to investigate the added value of reconstructive lymphatic surgery
30 to decongestive lymphatic therapy (usual care) in patients with lymphoedema of the upper limb or
31 lower limb in terms of lymphoedema-specific QoL (primary outcome), limb volume and duration of
32 wearing the compression garment (key secondary outcomes) at 18 months and of other outcomes at
33 1, 3, 6, 12, 18, 24 and 36 months post-baseline (secondary outcomes; see table 1 for the outcomes).
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37 A secondary objective is to verify whether the rate of complications in participants receiving
38 reconstructive lymphatic surgery is acceptable and if so, whether these complications are reversible.
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40 We also verify in patients with lymphoedema due to cancer treatment, if reconstructive lymphatic
41 surgery causes higher cancer recurrence rates.
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46 A first exploratory objective is to compare the added value of the reconstructive surgery between
47 different subgroups (stage 1 vs stage 2; normal weight vs overweight; combination of LVA and LNT vs
48 one method). A second exploratory objective is to investigate predictive variables for lymphoedema-
49 specific QoL at 36 months.
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Table 1 Overview of assessment of descriptive variables and primary and secondary outcomes at each time interval

	A1	A2	A3	A4	A5	A6	A7	A8
Assessment	Randomisation	1M	3M	6M	12M	18M	24M	36M
Baseline								
DESCRIPTIVES								
Demographics	X							
Characteristics of lymphoedema and its treatment	X							
PRIMARY OUTCOME								
Self-reported questionnaire	X					X		
Lymphoedema-specific QoL								
SECONDARY OUTCOMES								
Self-reported questionnaires								
Lymphoedema-specific QoL	X	X	X	X	X		X	X
Duration (key secondary outcome) and experience of wearing compression garment	X	X	X	X	X	X	X	X
Health related QoL	X	X	X	X	X	X	X	X
Work capacity and ability	X	X	X	X	X	X	X	X
Physical activity level	X	X	X	X	X	X	X	X
Costs related to lymphoedema and its treatment*		X	X	X	X	X	X	X
Usual care & self-management*§, including need for intensive treatment		X	X	X	X	X	X	X

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3 Assessments
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5 Limb volume (key secondary
6 outcome) X X X X X X X X X
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9 Hand/ foot volume X X X X X X X X X
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12 Failure to reduce hours a day
13 of wearing compression X X X X
14 stocking
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17 Body weight X X X X X X X X X
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20 Infection previous 18 months X X X
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22 Recurrence of cancer X X
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25 Adverse events and
26 complications of surgery X X X X X X X X
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29 Lymphatic transport
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31 ICG fluoroscopy X X
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33 Lymphoscintigraphy X X
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36 * Information is collected on a monthly basis

37 § No secondary outcome
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43 **METHODS AND ANALYSIS**
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45 Described according to the SPIRIT guidelines.
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50 **Trial design and study setting**
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53 A multicentre, pragmatic randomised controlled trial is performed at three university hospitals in
54 Belgium: University Hospitals Leuven (UZ Leuven), Ghent University Hospital (UZ Gent) and CHU UCL
55 Namur.
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58 The general flow, starting from screening for eligibility, is shown in figure 1.
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3 Before the real screening (A0), a fast eligibility check is performed and Informed Consent Form is
4 signed. If the patient is eligible and confirms participation, he/ she is randomised. The interval
5 between screening (A0) and baseline assessment (A1) is ideally less than 3 months, but may be up to
6 6 months. The baseline assessments have to be performed shortly before the surgery, with a
7 maximal interval of 1 month.
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13 Figure 1. Flow diagram of SurLym trial
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16 **Patient and public involvement in the trial design**

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18 Four patients with arm lymphoedema and 3 patients with leg lymphoedema from the center for
19 lymphedema of UZ Leuven have completed a questionnaire about the study design and feasibility of
20 the SurLym study. All but one patient, found the primary outcome, assessment of lymphoedema-
21 specific QoL, a relevant and very important outcome. This patient preferred arm volume (which is a
22 key secondary outcome) as outcome measure. None of the patients objected to a technical
23 examination using an injection in the hand/ foot of the affected side (for imaging of the lymphatic
24 system). All patients found it feasible to come to the hospital for 8 study-visits during 36 months, well
25 aware that two of the visits take up to 6 hours. Three of seven patients were not keen to undergo
26 surgery at the affected limb. All patients declared having little problems performing usual care: only
27 one patient considered self-management difficult and another patient was afraid to reduce the hours
28 of wearing the compression garment.
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38 From the patients willing to be part of the trial's patient board (n=5), two patients were selected: one
39 patient with arm lymphoedema and one with leg lymphoedema. They are both member of the Trial
40 Steering Committee. The rationale and design of the trial was thoroughly discussed with them. They
41 will be invited to further participate during the future meetings of the Trial Steering Committee, to
42 advise us during the course of the trial and for the dissemination of the project results.
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49 **Eligibility criteria**

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51 Patients *eligible for inclusion* in the trial have to meet all of the following criteria:

- 52 1) Unilateral or bilateral, primary or secondary lymphoedema of the upper or lower limb;
 - 53 2) If cancer-related lymphoedema, approval for participation from the multidisciplinary oncological
54 board; participation only if estimated cancer-related survival is ≥ 3 years and no concerns on
55 oncological safety are raised;
 - 56 3) Lymphoedema stage 1 to 2b (according to staging 1-3 of International Society of Lymphology)⁵;
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- 4) Objective diagnosis of lymphoedema: $\geq 5\%$ volume difference OR ≥ 2 minor/ 1 major criteria on lymphoscintigraphy OR presence of ICG dermal backflow;
- 5) Total score or one of domain scores on Lymph-ICF questionnaire at screening: $\geq 25/ 100$ (= moderate level of problems in functioning related to the development of lymphoedema)¹¹;
- 6) History of at least 6 months of DLT until minimal pitting;
- 7) Age ≥ 18 years.

Following persons are *excluded*:

- 1) Persons with history of liposuction, LVA or LNT;
- 2) Persons who are pregnant or plan to become pregnant in the next 18 months;
- 3) Severely obese participants: BMI >35 ;
- 4) In case of lower limb lymphoedema: presence of chronic venous insufficiency C4, C5, C6; deep venous thrombosis; post-thrombotic syndrome;
- 5) Allergy for ICG, iodine; increased activity of thyroid gland; benign tumour in thyroid gland; heparin use and severe renal insufficiency

Recruitment, participant screening and consent

The recruitment of patients started in March 2022. One hundred eighty patients have to be recruited by the 3 hospitals. Initially a recruitment period of 24 months (= 7.5 pts/ month) was planned however difficulties in accessing operating theatres linked to COVID have caused delays. To make the recruitment period as short as possible, a competitive recruitment is applied. We estimate that around 20% of the patients screened for eligibility (A0, n=900) can be accepted for participation.

Identification of eligible patients will be performed by the (sub)investigators of the lymphoedema centres of the 3 hospitals (ST, BBH, AKH and ND for UZ Leuven; CM, CR, TD, VVB, MDS for UZ Gent; and TD, JF, MS, AB, PF for CHU UCL Namur), supported by the study coordinators. The consultation lists of the lymphoedema centres are screened before the consultation and the possible patients eligible for the trial are marked.

During the lymphoedema consultation, the clinician checks the eligibility criteria for which a measurement is not necessary; if the patient seems eligible and he/ she is interested to receive information about the trial, the trial is discussed using a study-specific recruitment document: this is a concise and well-organised document that clarifies the design of the study and provides information about side effects, costs and potential benefits and harms of participation. If a patient is interested to participate, he/ she receives the Informed Consent Form and the 'study at a glance

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3 (summary)' document. In addition, the patient receives an appointment for the screening (A0). Some
4 patients are informed about the trial through another way, e.g. by their oncologist. In that case, the
5 patient contacts the study coordinator by phone, who performs the fast eligibility check and
6 discusses the study during the phone call. If the patient is interested to participate, the Informed
7 Consent Form and the 'study at a glance' document is sent. In addition, the patient receives an
8 appointment for the screening (A0).
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13 During the *screening appointment (A0)*, patients receive all information and explanation they request
14 or need before signing the Informed Consent Form. Thereafter, the complete screening procedure is
15 executed to verify whether the participant fulfils all eligibility criteria.
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21 In order to optimally recruit patients with lymphoedema, the study is presented inside (at other
22 departments) as well as outside the hospitals of the study centers by lectures, posters and mailing.
23 Potential candidates with lymphoedema as well as their treating physicians, physical therapists and
24 other health care providers are informed about the trial (through social media, publication in local
25 journals and on websites).
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30 31 32 **Allocation and randomisation**

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34 Given the nature of the trial, *blinding* of participants and care providers (surgeon/ physical therapist/
35 compression specialist) is not feasible. Because the participants fill out different questionnaires to
36 determine the primary outcome and some of the secondary outcomes, detection bias may be a
37 potential risk. However, bias of the participants will be limited as much as possible because the study
38 will be explained by a neutral person (physical therapists ND, AKH, VVB, MDS, JF or physical medicine
39 & rehabilitation physician TD (hospital of Ghent), TD (hospital of CHU UCL)).
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45 The *randomisation* is computer generated. To obtain concealment of allocation, the randomisation
46 list is prepared by the trial's statistician (SF) and is incorporated in the data management tool
47 'REDCap'. Randomisation is performed by using varying block sizes. A 1:1 allocation ratio is applied. A
48 stratification is applied for study centre (UZ Leuven vs UZ gent vs CHU-UCL Namur) and for region of
49 lymphoedema (upper limb vs lower limb, with a ratio 1:1). At each participating site, only the chief
50 investigator (ND) and trial manager (TDV), investigators and study coordinators have access to the
51 randomisation tool in REDCap. After randomisation, the study coordinator of the specific study
52 centre plans the intervention if applicable (surgery), as well as the usual care and the follow-up
53 assessments.
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3 After all patients have finished the trial and the database is locked to analyse the data, the
4 randomisation code will be broken.
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9 **Intervention**

10 All participants are randomised to the intervention or control group. The intervention group is
11 treated with reconstructive lymphatic surgery in addition to conservative DLT (decongestive
12 lymphatic therapy; usual care). In the control group patients only receive conservative DLT (usual
13 care) without surgery (see figure 1).
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19 The researchers will follow the protocol as strictly as possible. However, since the pragmatic nature
20 of the trial, a deviation of the protocol is allowed if necessary. This protocol deviation has to be
21 registered in the protocol deviation log.
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27 *Reconstructive lymphatic surgery*

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29 The intervention treatment is reconstructive lymphatic surgery and is performed by the team of
30 vascular and/ or plastic surgeons from each study center (ST and KT of UZ Leuven; BDP and LD of
31 Ghent University Hospital; and MS, AB and PF of CHU UCL Namur). As reconstructive technique, a
32 lymphovenous anastomosis (LVA), lymph node transfer (LNT) or a combination of both is applied.
33 The choice of the technique is determined by the surgeons of the study centre. See table 2 for the
34 clinical reasoning for each procedure and the technical description of the reconstructive procedure.
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40 To obtain standardisation and to ascertain the quality of the reconstructive lymphatic surgery, all
41 surgeons received training in the Reconstructive Microsurgery European School (by JM and GP) in
42 May 2021. Moreover, to improve standardisation of the patient selection and the reconstructive
43 lymphatic procedure between the surgeons and between the centres, every patient that is planned
44 for surgery in the trial is discussed during a monthly meeting with at least one surgeon per centre
45 attending. A final quality control measure is that the first 10 surgical procedures are discussed with
46 the whole surgical team including the independent experts JM, GP, SS and KVL.
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Table 2. Overview of the procedure of the lymphovenous anastomosis (LVA) and lymph node transfer (LNT) with the clinical reasoning of the choice and the different steps (based on Chang et al)⁷

Timing		Lymphovenous anastomosis (LVA)	Lymph node transfer (LNT)
Before surgery	Clinical reasoning based on pre-surgical investigations (see figure 2 for example)	Presence of suitable lymphatic vessel(s), visualised through ICG lymphofluoroscopy and/ or lymph MRI.	Presence of fibrosis or adhesions due to surgery, lymph node dissection and/ or radiotherapy, known through inspection and visualisation of interruption of lymphatic transport by lymphoscintigraphy. Presence of a well-vascularised donor flap (CT angiography is performed if needed).
During week before surgery	Compression garment	Measured by the team of compression specialists of the specific center; Choice of the type of compression garment is made pragmatically, as performed in the real clinical situation.	
	Registration of compression garment	Compression specialist registers each time after delivery the type of compression material and cost for patient/ health insurance.	
Surgery	Material	Microsurgical equipment to make anastomoses of vessels with diameter of 0.3-0.8 mm (suture size 11 or 12), supermicro clips, fine bipolar.	Microsurgical equipment to perform vascularised lymph-tissue transfer, suturing vein and artery with suture size 9 or 10, micro clips, fine bipolar.
	Preparation	ICG is injected interdigitally and lymph transport is designed on skin and location(s) of anastomosis is indicated (confirmed by lymph MRI).	To check for the safety not developing limb oedema due to the dissection of lymph nodes, ^{99m} Tc nanocolloids or ICG

			are injected in 1 st web of both hands (in case the donor site is the axilla) or feet (in case the donor site is the groin).
	Anaesthesia	General or if wish of patient local	General
	Procedure	<ol style="list-style-type: none"> 1) Patent blue is injected distal of location of anastomosis. 2) 2-3 cm incision. 3) Functional lymphatic is dissected, lymphatic is kept wet and lumen is made open; picture is taken. 4) Lymphatic is anastomosed to vein. 5) Between 1 and 10 anastomoses are made. 5) With ICG camera is checked whether anastomosis is open. 6) Wound is covered and cotton wool and elastic bandages are applied around the whole limb. 	<ol style="list-style-type: none"> 1) ICG is injected interdigitally. 2) Patent blue is injected distal of donor side flap. 3) Donor site flap is resected (= lymph nodes and skin and tissue around): in most cases groin proximal of inguinal ligament, sometimes lateral trunk; picture is taken. 4) Donor site flap is transferred to recipient site (= region with fibrosis/ adhesion): a wide excision of scar tissue is made to ensure a healthy bed for lymphangiogenesis and to improve bridging of lymphatics; picture is made. 5) Wound is covered and cotton wool and elastic bandages are applied around the whole limb.
	Registration	<ol style="list-style-type: none"> 1) Duration of procedure (in minutes). 2) Description of procedure: LVA vs LNT vs combination; general vs local anaesthesia; per-operative ICG fluoroscopy or scintigraphy; injection patent blue and localisation; for LVA, number of anastomoses and location; for LNT, donor site and recipient site. 3) Material (amount): flacon ICG/ patent blue; surgical wire; wound dressing; bandaging material (cotton wool, non-elastic bandages, tubular bandage); other material 4) Personnel (number and duration of presence): surgeon(s); nurse(s); other personnel 	

1 2 3 4 5 6	Aftercare in hospital	Number of days	1 day or longer if necessary	2 days or longer if necessary
7 8 9 10 11 12		Medication	To prevent thrombosis, to stimulate vasodilation, to reduce pain, to prevent infection	
13 14 15 16 17 18 19		Inelastic bandage	In most of the patients (if risk of damaging LVA/ LNT by putting on compression garment; First tubular bandage and cotton wool covering whole limb, then non-elastic bandages, finally other tubular bandage over bandages (to keep everything together); keep it day and night	
20 21 22 23		Advise	As much as possible limb elevation and regularly muscle contractions	
24 25 26 27 28 29 30 31 32 33 34 35		Registration	1) Number of days of hospitalisation 2) Material (amount): bandaging material (cotton wool, non-elastic bandages, tubular bandage); other material 3) Medication (type and amount)	
36 37 38 39 40 41 42 43 44 45 46	Aftercare at home	Wound control	Once a week, inelastic bandage is removed, wound is cared and bandage is re-applied	
		Advise	As much as possible limb elevation and regularly muscle contractions	
		Compression garment	If wound is healed, new compression garment is applied and usual care protocol is started	
		Registration	1) Number of wound control visits and duration 2) Material (amount): bandaging material (cotton wool, non-elastic bandages, tubular bandage); wound care material; other material 3) Personnel (number and duration of presence): surgeon(s); nurse(s); other personnel	

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3 Figure 2 Woman, 57 years old, secondary lymphoedema right leg (> left leg) and midline, developed
4 after inguinal and pelvic lymph node dissection and radio-chemotherapy for vulvar cancer;

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6 Preoperative investigations: A) *lymphoscintigraphy in 3 phases*: 1. early phase after rest, 2.
7 early phase after activity (cycling), 3. late phase after activity (walking); demonstrating
8 dermal backflow at lower and upper leg (dotted arrow) and a lymph node in the groin (*); B)
9
10 *ICG lymphofluoroscopy*; 1. Picture of limb with markings of the superficial lymphatic
11 architecture; 2. Body diagram; demonstrating dermal backflow (dotted arrow) and two useful
12 lymph collectors at the level of the knee (full arrow), c) *lymph MRI*; confirming the presence
13 of two useful lymph collectors (full arrow);
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17 Based on preoperative investigations, choice of reconstructive lymphatic surgery: LVA at the
18 level of the knee; no LNT because of pelvic lymph node dissection and activity (working
19 lymph node) in the groin.
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28 Usual care

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30 All patients receive usual care. The patient's own (regular) physical therapist performs the usual care
31 in a pragmatic way consisting of exercises and skin care and manual lymph drainage (MLD) (i.e. the
32 maintenance phase of decongestive lymphatic therapy (DLT)). Moreover, the physical therapist
33 educates the patient to perform self-management, i.e. self-exercises, self-skin care, self-MLD, self-
34 bandaging and putting on and removing the compression garment. In all patients (of intervention
35 and control group), a new compression garment is measured by the compression specialist at
36 baseline. The schematic overview of the usual care is given in figure 1 and is divided into four
37 periods:
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44 1) M1-6: From week 3 (or, in the intervention group, after healing of the wounds) the patient sees
45 the home physical therapist twice per week and from week 5 once a week. The patient also performs
46 self-management.
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50 2) M7-12: The patient sees the own physical therapist once a week. The compression garment use is
51 gradually reduced from 16h/w (end of 6th month) to 0h/w (end of 12th month). The own physical
52 therapist performs circumference measurements of the limb weekly (i.e. with a perimeter provided
53 by the study team) to control for changes of the limb volume¹². The patient completes a digital
54 scoring form in REDCap weekly. The study investigator of the center checks the change of limb
55 volume every week: if the limb volume increases $\geq 5\%$ compared to baseline, the patient is planned
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3 for an intermediate checkup in the study center. The study investigator decides whether the hours a
4 day of wearing the compression garment has to be increased again.

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7 3) M13-18: The patient only performs self-management and does not see the own physical therapist
8 anymore. If possible, the patient does not wear the compression garment.

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11 4) M19-36: The patient may choose whether he/ she visits the own physical therapist or performs
12 self-management, or a combination.

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15 This scheme of usual care has to be followed as strictly as possible, except when the patient's clinical
16 situation deteriorates or risks to deteriorate. For example, a patient may visit the physical therapist
17 more often in case of more lymphoedema-related complaints due to warm weather. Or, if during the
18 follow-up, the clinical situation of the lymphoedema deteriorates unacceptably (e.g. there is
19 presence of pitting oedema in the limb or there is a wound), the study investigator may advise the
20 patient and physical therapist to perform an intensive treatment of the lymphoedema with
21 bandaging. This information has to be registered by the patient in the usual care questionnaire.

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24 To obtain standardisation of the usual care, the physical therapist of the patient receives a training
25 before the start of the study. During this training, instructions about the study protocol are given
26 orally. In addition, the physical therapist receives an informative leaflet explaining the aim and design
27 of the trial, the treatment in the intervention/ control group and the assessment of the patient. It
28 also clarifies what the study investigators expect from the patient's physical therapist and vice-versa.
29 Following information regarding the patient's physical therapist is collected: age and gender,
30 education level and experience with treating lymphoedema (number of years of experience and in
31 which modalities, type of lymphoedema education).

32 33 34 35 36 37 38 39 40 41 42 43 44 **Outcomes**

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46 The outcome measures were chosen based on input from patients with lymphoedema (see section
47 'patient and public involvement') and on input from the investigators of this trial who have
48 experience in evaluating and treating patients with lymphoedema. Moreover, recently, Chang et al
49 stated in their systematic review and meta-analysis about the surgical treatment of lymphoedema
50 that better designed studies are necessary: with objective reporting of outcomes using quantitative
51 methods for measuring fluid and both physiologic and immunologic function during longer follow-
52 up.¹³

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3 Assessments are performed at baseline (A1) and at 1 month (A2), 3 months (A3), 6 months (A4), 12
4 months (A5), 18 months (A6), 24 months (A7) and 36 months (A8) post-baseline. However, to limit
5 the burden for the patients, not all outcomes are assessed at each time interval. See table 1 for the
6 overview of the outcomes per time interval and see table 3 for the assessment method and the
7 description of the assessment per variable and outcome. Figure 1 gives an overview of the timing of
8 the baseline assessment related to the screening and to the surgery, and of the foreseen windows
9 for the follow-up assessments.
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15 The primary outcome is lymphoedema-specific QoL (= problems in functioning related to
16 development of lymphoedema) at 18 months, evaluated with the Dutch or French version of the
17 Lymph-ICF questionnaire for upper or lower limb lymphoedema.^{11 14-16} In addition, the
18 lymphoedema-specific QoL will be investigated at other time points in the short term (1, 3, 6, 12
19 months) and longer term (24 and 36 months) as a secondary outcome parameter.
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25 Other secondary outcomes are: duration of wearing the compression garment during one week (at
26 18 months' time-point = key secondary outcome) and experience of the compression garment,
27 health-related QoL, work capacity and ability, physical activity level, costs related to lymphoedema
28 and its treatment, need for intensive treatment, limb volume (at 18 months' time-point = key
29 secondary outcome) and hand/ foot volume, failure to reduce the hours a day of wearing the
30 compression garment, body weight, episodes of infection previous 18 months, recurrence of cancer
31 (in patients with history of cancer), adverse events and lymphatic transport.
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37 Complications of surgery (in the intervention group) and information regarding usual care and self-
38 management are collected during the trial period as well.
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41 There is also a follow-up contact by phone at 9M and 15M, respectively. During the phone call,
42 information is further collected about adverse events and complications of the surgery, about the
43 usual care & self-management (to check for the adherence of the patient) and about the costs
44 related to lymphoedema and its treatment.
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48 To guarantee standardisation of the assessments all assessors are trained before the start of the trial.
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Table 3 Overview of the different variables in the SurLym trial, the assessment method and the description of the method

Variable	Assessment method; description of method
Descriptives (15 min)	
Demographics	
Age (in years)	Medical file
Gender (man vs women), smoking status (smoking vs non-smoking), living status (alone vs together)	Interview
Body height (in m)	Stadiometer
Comorbidity (yes vs no)	Self-reported questionnaire developed by IDEWE (= external institute for prevention and protection at work); presence of wound by accident, of disease of musculoskeletal, circulatory, respiratory, neurological, digestive, urinary system, of disease of blood or skin, of mental or metabolic problems or of tumor (yes vs no)
Educational level (low vs high)	Interview; lower education = primary and secondary school, higher education = non-university higher and university
Anxiety and depression (0- 42)	Self-reported Hospital Anxiety and Depression Scale; ¹⁷ 14 statements regarding anxiety and depression with score 0-3

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Characteristics of
lymphoedema and its
treatment

Duration of lymphoedema
(in months)

Interview

Localisation of
lymphoedema (yes vs no)

Inspection; for upper limb lymphoedema: hand/ lower arm/ upper arm/ trunk or
for lower limb lymphoedema: foot/ lower leg/ upper leg/ pelvic/ genital region, unilateral/ bilateral, site of lymphoedema
followed in trial: left/ right

Pitting status (yes vs no)

Palpation; for upper limb lymphoedema: hand/ lower arm/ upper arm/ trunk or for lower limb lymphoedema: Foot/ lower
leg/ upper leg/ pelvic/ genital region

Stage of lymphoedema (1
vs 2a vs 2b)

Inspection en palpation; Stage 1= pitting oedema that disappears with limb elevation (= reversible), 2a= pitting oedema
that does not disappear completely with limb elevation, 2b= further decrease of pitting and accumulation of fat tissue

Primary or secondary
lymphoedema

Interview and medical file; Primary = congenital; secondary = acquired after cancer-treatment (and type of cancer),
trauma, surgery, infection

History of conservative
treatment

Self-reported questionnaire (developed by author); Information regarding 1) physical therapy: number of years, number of
sessions last month/ year, content, 2) intensive treatment: where, how often, 3) other care giver, 4) self-management

Primary outcome

Self-reported questionnaire

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3 (5 min)

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6 Lymphoedema-specific Lymph-ICF questionnaire Dutch or French version for upper or lower limb lymphoedema;^{11 14 15 18 28} and 29 questions on
7 QoL (0-100) 11-point scale between 0-10, total score between 0-100 (0= no problems in functioning related to the development of
8 lymphoedema)
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11 **Secondary outcomes**

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14 Self-reported questionnaires

15 (60 min)

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18 Lymphoedema-specific See primary outcome; in addition, score on 5 domains, i.e. physical function, mental function, household, mobility and life
19 QoL (0-100) and social life domain (0-100)
20

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22 Duration (key secondary
23 outcome) and experience ICC compression questionnaire ;¹⁹ Dosage (0-168 hours/ week), application/ removing compression (0-10), comfort (score
24 of wearing compression between 0-10), complication (score between 0-10), general experience (0-10)
25 garment
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29 Health related QoL EuroQoL-5D-5L;²⁰ 5 items about mobility, self-care, activity, pain and anxiety (each dimension has 5 levels: no problems,
30 slight problems, moderate problems, severe problems and extreme problems), range between -0.33 for situation '33333'
31 (severe problems on all items) and 1 for situation '11111' (complete healthy)
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35 Work capacity and ability Work Productivity and Activity Impairment questionnaire (WPAI-GH); Impairment while working due to health, overall
36 work impairment due to health, activity impairment due to health (%)
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39 QuickScan 18 – short version;²¹ Chance for successful socio-professional reintegration (score between 0 certainly not and 5
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3		certainly yes)
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5	Physical activity level	International Physical Activity Questionnaire; ²² 7 questions about hours a week of vigorous (8 MET), moderate (4 MET) and
6	(MET-hours a week)	walking activities (3.3 MET), and sitting time
7		
8	Costs related to	Study-specific questionnaire completed monthly by the patient; collection of patient and health care costs for material
9	lymphoedema and its	(such as compression or exercise material), medication, diagnostics or care giver (similar questionnaire as for Effort-BCRL
10	treatment (in euro)	trial) ²³
11	Usual care & self-	
12	management \$, including	Study-specific usual care & self-management questionnaire completed monthly by the patient; information regarding 1)
13	need for intensive	physical therapy: number of sessions, duration and content; 2) intensive treatment: where, number of sessions, content;
14	treatment	3) other care giver; 4) self-management: number of days of each modality
15		
16	Assessment (60 min)	
17		
18	Limb volume (key	Circumference measurements every 4 cm with perimeter; ^{12 24-26} limb volume is calculated with formula of truncated
19	secondary outcome)	cone, ^{24 26} in participants with upper limb lymphoedema: assessment of affected and non-affected arm; outcome is
20		excessive arm volume (%) = (volume _{AFFECTED ARM} - volume _{UNAFFECTED ARM} / volume _{UNAFFECTED ARM}) x 100, in participants with
21		lower limb lymphoedema: assessment of affected leg (= leg that is followed in trial); outcome is whole leg volume (in ml)
22		Water displacement method of hand or foot; ^{25 27} volume is the mass of the displaced water, in participants with upper
23	Hand/ foot volume	limb lymphoedema: assessment of affected and non-affected hand, outcome is excessive hand volume (%); in participants
24		with lower limb lymphoedema: assessment of affected foot, outcome is foot volume (in ml)
25		
26	Failure to reduce hours a	Assessor determines whether participant is able to reduce the hours a day of wearing the compression garment as stated
27	day of wearing	by the protocol (see figure 1, M7-12); Not able = excessive arm volume/ leg volume increased more than the smallest real
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3	compression stocking (yes,	difference, i.e. 5% or more compared to baseline ¹²
4	not able vs no, able)	
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7	Body weight (in kg)	Scale
8		
9	Infection previous 18	
10	months (number)	Interview
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12		
13	Recurrence of cancer (yes/	
14	no)	Interview and medical file; only collected in the group with history of cancer
15		
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17	Adverse events (whole	Interview and medical file; registration of adverse events related to pre-surgical or study-specific investigations: ICG
18	group) and complications	fluoroscopy, lymphoscintigraphy, lymph MRI, CT angiography, of complications of reconstructive lymphatic surgery: 1) in
19	of surgery (in intervention	general blue spot, wound healing problem, infection of wound, decrease of sensibility around wound, erysipelas of limb,
20	group) (yes/ no)	deep venous thrombosis, 2) LNT-specific seroma, lymphocele, donor site lymphoedema, loss of flap
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25	Costs related to	Study-specific questionnaire completed by the compression specialist after delivery of compression material; registration
26	lymphoedema and its	of company, compression product, region of compression, type, compression class, cost for health insurance/ patient
27	treatment (in euro)	Inter Mutuality Agency (IMA) database (= agency collecting data from different mutual health insurance companies),
28		based on national number of the study participant
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33	Lymphatic transport	
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35	ICG fluoroscopy (60 min)	ICG fluoroscopy; ²⁸ 0.2 ml dilution of ICG/ aqua/ NaCl is injected in 1 st and 4 th web of affected hand or foot; procedure
36		consist of 3 minutes of rest, 5 minutes of stimulation and registration of outcomes (=early phase) and a break until 90
37		minutes post-injection and again registration of outcomes (= late phase); registration of following outcomes: 1) transport
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out of injection sites (yes/ no), 2) dermal rerouting (no, splash, stardust and diffuse for predefined regions on arm/ leg), 3) transport out of dermal rerouting, 4) lymph nodes (yes/ no)

Lymphoscintigraphy (60 min)

Lymphoscintigraphy;²⁹ 55MBq ^{99m}Tc nanocolloids are injected in 1st web of both hands or feet; procedure consist of following steps: 25 minutes of rest, 5 minutes of arm/ leg cycling and acquiring images (= early phase); 60 minutes break; late phase acquisition; following images are made: before and after each step an image of injection sites (outcome: extraction out of injection sites in %), after each step a mini whole body (outcomes: number of lymph nodes, intensity of lymph collectors, intensity of dermal backflow, presence of lymph collaterals), during 25 minutes of rest dynamic images of axilla/ arm or groin/ leg (outcomes: arrival time and uptake in axilla/ inguinal region in %)

§ No secondary outcome

Sample size

The sample size is calculated to have at least 90% power to detect a difference between the intervention group receiving reconstructive surgery and the control group without surgery, on lymphoedema-specific QoL at 18 months, separately within patients with upper limb lymphoedema and within patients with lower limb lymphoedema. Both comparisons are considered as separate trials and therefore alpha has been set equal to 0.05.

The planned analysis to compare the groups is a constrained longitudinal data analysis (cLDA),³⁰ using the baseline measurement and the follow-up measurements after 1, 3, 6, 12 and 18 months as outcome. The primary analysis refers to the comparison after 18 months (based on a two-sided test with $\alpha=0.05$). The approach is similar in spirit as an analysis of covariance (ANCOVA) but does not exclude subjects with one or more missing measurements. The calculation of the required sample size is based on an approach presented by Stroup.³¹ Information with respect to variability of the lymphoedema-specific QoL score and the correlation between the timepoints was obtained from two retrospective series (130 patients with arm oedema and 83 patients with leg oedema).

The following assumptions have been made for the comparison of the lymphoedema-specific QoL:

- Standard deviation (SD) of the lymphoedema-specific QoL equal to 20
- Correlation between the baseline and each of the follow-up measurements equal to 0.50
- Drop-out of 5%, 10%, 15% and 20% after 1 and 3 months, 6 months, 12 months and 18, 24 and 36 months, respectively

To detect a difference of 15 points, which is a clinically important difference,^{11 15} 36 subjects are required per group ($2 \times 2 \times 36 = 144$ subjects in total for the two trials) to have at least 90% power. If the number of subjects would be reached before the end of the planned recruitment period of 24M, recruitment will continue up to 45 subjects per group (180 subjects for the whole study) to obtain more precise information, especially on the set of secondary outcomes. If the number is not attained, the recruitment period will be prolonged.

The sample size estimation heavily depends on estimates of variability of the lymphoedema-specific QoL and the correlation with the baseline measurement. Therefore, after inclusion of 40 subjects per group the already available information will be used to verify if the assumptions were plausible (note however that there will be no information yet at the moment of the primary endpoint). If the observed standard deviation and correlations deviate from the assumed values such that the desired power level of 90% is not guaranteed anymore, an increase of the planned sample size will be considered (if feasible). At the moment of this blinded interim analysis for sample size re-estimation,

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3 the assumed dropout rates will also be verified. No interim analyses are planned to stop the study
4 earlier for efficacy or futility, this to avoid loss of information on the secondary endpoints.
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9 **Data analyses**

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11 Statistical analysis will comply with the Consolidated Standards of Reporting Trials (CONSORT)
12 guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarised
13 using mean and SD or median and range values. Different analysis sets will be defined. The intent-to-
14 treat analysis set (ITT) contains all randomised patients, grouped according to the allocated
15 treatment. The modified intent-to-treat analysis set (mITT) contains all randomised patients grouped
16 according to the allocated treatment, but excluding patients who have withdrawn their consent to
17 the randomised procedure. The as-treated analysis set also contains all randomised patients but
18 grouping the patients according to their received treatment. The per-protocol analysis set contains
19 all randomised patients who received the allocated treatment. The main analyses will be performed
20 on the ITT analysis set. Results on the other analysis sets will be reported additionally.
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30 *Primary outcome*

- 31 • Lymphoedema specific QoL

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33 A constrained longitudinal data analysis (cLDA)³⁰ using the baseline measurement and the follow-up
34 measurements after 1 month, 3 months, 6 months, 12 months and 18 months as outcome will be
35 used to compare the mean lymphoedema specific QoL after 18 months based on a two-sided test
36 with $\alpha=0.05$. The choice of the covariance structure for the five measurements will be based on
37 the Aikake criterion. Study site is added as a fixed factor in this model. For patients with a recurrence
38 of cancer in the root of the limb, only observations before the recurrence are included.
39

40 Since the analysis is only valid under the missing at random (MAR) assumption (the probability of a
41 missing lymphoedema-specific QoL measurement does not depend on the unobserved value),
42 sensitivity analyses will be performed allowing a non-missing at random (NMAR) mechanism. More
43 specifically, starting from the MAR model, a jump-to-reference (JR) and tipping-point (TP) analysis
44 will be applied.³²
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54 *Key secondary outcomes*

- 55 • Change of limb volume:

56 For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be
57 calculated. A multivariate model for the longitudinal measured ratios (7 timepoints) will be used to
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3 compare (changes in) log-transformed ratios between both groups. A log transformation for the
4 ratios is used since intervals between units are not equidistant. For the leg/ foot volume, the same
5 model will be used but on the original measurements of the (most) affected limb instead of on the
6 (log-transformed) ratios versus the contralateral side (since also patients with bilateral leg volume
7 are included).

- Duration of wearing the compression garment:

The same modelling approach will be used as for the primary outcome.

Other secondary outcomes

Continuous outcomes will be analysed in a similar way as the primary outcome. Categorical (binary) data will be analysed using stratified χ^2 test and logistic regression models with general estimating equations (GEE) for repeatedly measured binary data. Adverse events and complications after surgery will be reported descriptively.

This study has been designed to permit *economic analysis* in a later phase. If reconstructive surgery is deemed superior to no surgery (i.e. is clinically effective), the next step is to investigate its cost-effectiveness by determining the incremental cost-effectiveness ratio (ICER). To determine the ICER, the costs from a healthcare payer's perspective and from a societal perspective will be considered, as well as the effectiveness by using the EQ-5D-5L questionnaire. If reconstructive surgery is proven cost-effective, the budget impact will be calculated from a reimburse perspective.

Exploratory analyses

Subgroup analyses for the primary outcome will be considered as a function of stage (stage 1 versus 2a/ 2b), primary vs secondary lymphoedema, weight (normal weight (BMI \leq 25) versus overweight (BMI $>$ 25)) and combination of reconstructive techniques (combination of LVA/ LNT versus only LVA or only LNT)

Moreover, a multivariable model will be constructed to predict the lymphoedema-specific QoL at 36 months based on 14 baseline variables. For subjects with a missing lymphoedema-specific QoL at 36 months, values will be imputed based on a multivariate longitudinal model for the lymphoedema-specific QoL measurements. A model reduction will be performed on a stacked dataset consisting of the multiple imputed data (at least 10 imputations), using a weighting scheme to account for the fraction of missing data in each covariate.³³ Considering the dropouts at 36 months, data for lymphoedema-specific QoL of 144 patients will be available.

Data security and management

A study-specific Data Management Plan has been developed by the data management team. Participant data are stored on a secure database in accordance with the General Data Protection Regulations (2018). Data are de-identified and a unique trial identification number is used on all source documents. These source documents are being checked for completeness and congruity before data entry into REDCap. All trial documentation and data will be archived for at least 20 years after completion of the trial.

A Risk Assessment Plan has also been made with a summary of the concerns in the trial, how they were mitigated, the probability that this will occur and its impact. This finally leads to a risk score (low, medium, high, critical). The concerns with highest risks are discussed during the meeting of the Trial Steering Committee (during recruitment period: once each 6M; thereafter: once a year).

Trial monitoring

A separate Monitoring plan has been constructed and will be conducted periodically by trial monitors (independent from trial staff). The first monitoring visit at each site will be conducted within 4-8 weeks following the baseline visit of the first study subject at that site. Thereafter, monitoring visits will be organized at mean intervals of 6 months during recruitment, and mean intervals of 12 months thereafter. The participating site will provide direct access to the trial data and to the corresponding source data and documents. The trial will be monitored to ensure that it is being conducted in compliance with GCP and current legislation, that written informed consent has been obtained correctly, that the trial procedures have been followed as shown in the protocol, and that the data have been recorded, for which the source data will be compared with the data recorded in REDCap.

ETHICS AND DISSEMINATION

The SurLym trial will be conducted in compliance with the principles of the Declaration of Helsinki, the principles of GCP and in accordance with all applicable regulatory requirements. Approval has been obtained for the study protocol, the informed consent forms and other related documents by the main Ethical Committee of UZ Leuven (S631212) and the local Ethical Committees of UZ Gent and CHU UCL Namur. Any subsequent protocol amendments will be submitted to the Ethical Committee.

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3 Furthermore, the study is approved by the Federal Agency for Medicines and Health Products
4 (EudraCT: 2021-000397-29).
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9 **Dissemination of results**

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11 The results of the study owned by the sponsor shall be disseminated as soon as possible after the
12 end of the trial, by disclosing them to the public by appropriate means, including publications in
13 peer-reviewed scientific journals and presentations at congresses and events. Open access will be
14 ensured to all peer-reviewed scientific publications relating to the results of the study.
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19 **Acknowledgements**

20
21 We are grateful to all medical doctors for referring potential participants for inclusion in the trial. We
22 also want to thank the data management team and the representative of the clinical trial center of
23 UZ Leuven for their support. Finally, we are thankful to the patients of the advisory board and to the
24 independent expert for their valuable advises in the preparation phase and during the course of the
25 trial.
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33 **Author contributions**

34
35 ND is the chief investigator of the SurLym trial. TDV is the trial manager. ND, CR, TD are the principle
36 investigators of the 3 study sites. SF is the statistician. LG is expert in occupational medicine and will
37 supervise the economic analysis (if executed). ND, AKH, ST, BBH, IF, VVB, TDC, MDS, CR, CM, JF, TD
38 will perform the recruitment of patients. ST, KS, PF, MS, AB, BDP, LD will perform the surgical
39 procedures and follow-up. AKH, JF, VVB, TDC, MDS are responsible for the clinical assessments
40 (including lymphofluoroscopy and lymphoscintigraphy). GM, FK, AF, DD are the radiologists
41 responsible for the lymph MRI an BK is a nuclear medicine physician responsible for the
42 lymphoscintigraphy. JM, SS, GP, KVL are the independent experts in reconstructive lymphatic surgery
43 and will verify the quality of the surgical procedures. ND drafted the manuscript. All authors
44 contributed to the establishment of the protocol, revised the manuscript and provided input
45 according to their area of expertise.
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59 **Funding statement**

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3 This study (KCE19-1245) is an independent research study funded by the Belgian Health Care
4 Knowledge Centre under the KCE Trials Programme. The views expressed in this publication are
5 those of the author(s) and not necessarily those of Belgian Health Care Knowledge Centre.
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10 11 **Data statement**

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13 Data will be available on reasonable request.
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16 17 18 **Competing interests**

19
20 None declared
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24 25 **Ethics approval**

26
27 Approval is obtained by the central Ethical Committee of the University Hospitals Leuven (S63212)
28 and by the local Ethical Committees of UZ Gent (BC-09711) and CHU UCL Namur (43/2021).
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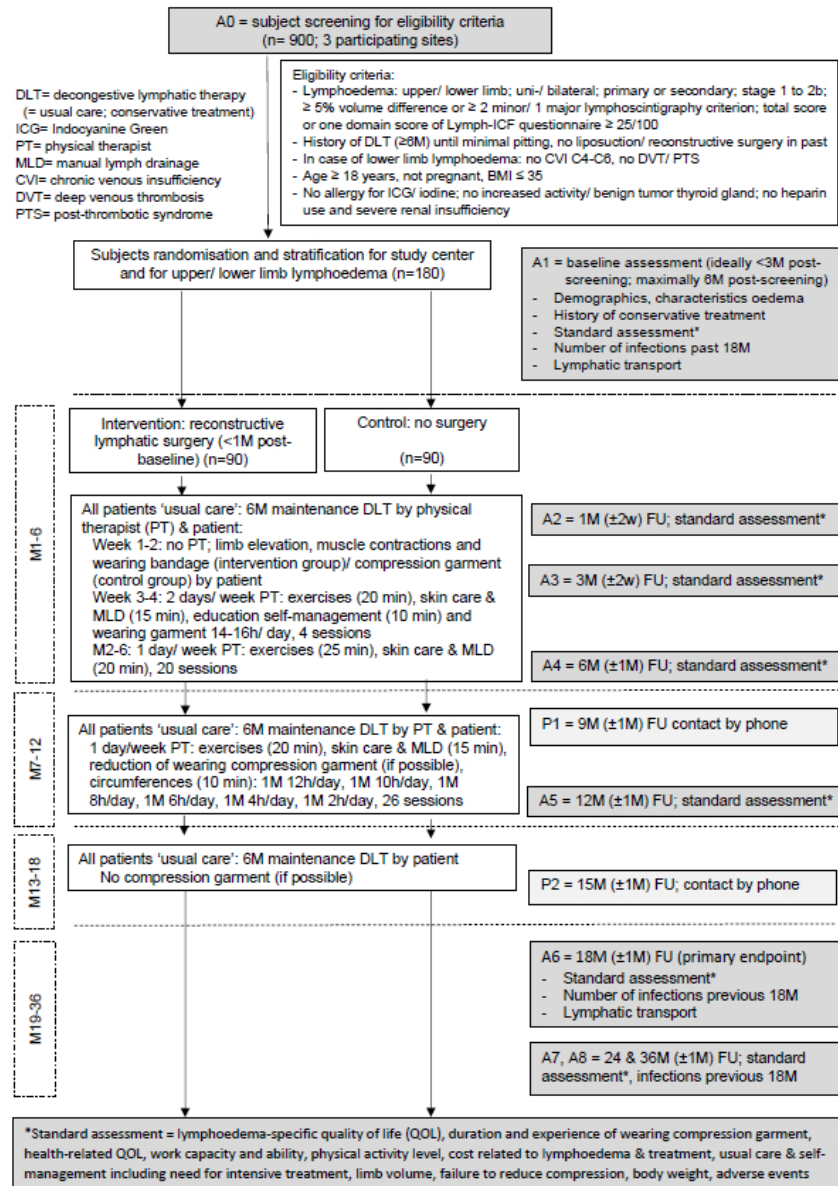


Figure 1. Flow diagram of SurLym trial

321x456mm (47 x 47 DPI)

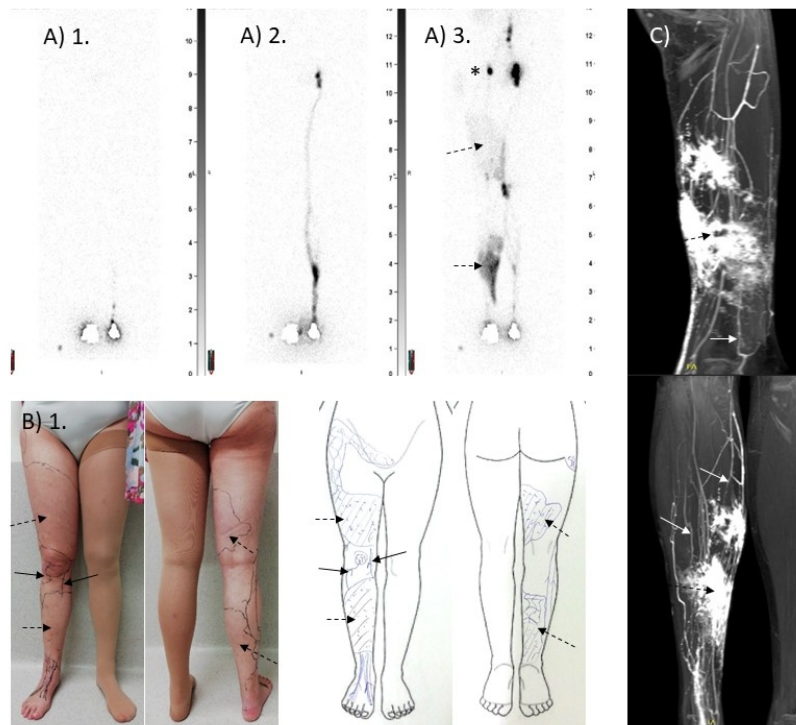


Figure 2 Woman, 57 years old, secondary lymphoedema right leg (> left leg) and midline, developed after inguinal and pelvic lymph node dissection and radio-chemotherapy for vulvar cancer; Preoperative investigations: A) lymphoscintigraphy in 3 phases: 1. early phase after rest, 2. early phase after activity (cycling), 3. late phase after activity (walking); demonstrating dermal backflow at lower and upper leg (dotted arrow) and a lymph node in the groin (*); B) ICG lymphofluoroscopy; 1. Picture of limb with markings of the superficial lymphatic architecture; 2. Body diagram; demonstrating dermal backflow (dotted arrow) and two useful lymph collectors at the level of the knee (full arrow), c) lymph MRI; confirming the presence of two useful lymph collectors (full arrow); Based on preoperative investigations, choice of reconstructive lymphatic surgery: LVA at the level of the knee; no LNT because of pelvic lymph node dissection and activity (working lymph node) in the groin.

254x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

Reporting Item

Page Number

Administrative information

Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Paper p1
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1	Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of	Paper p3
2			intended registry	
3				
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5				
6	Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data	Paper p3
7			Set	
8				
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11	Protocol version	#3	Date and version identifier	Paper p3
12				
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15	Funding	#4	Sources and types of financial, material, and other support	Paper p3, study
16				agreement KCE-UZ
17				Leuven
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22	Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	Paper p30
23	contributorship			
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28	Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	Paper p3
29	sponsor contact			
30				
31				
32	information			
33				
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36	Roles and responsibilities:	#5c	Role of study sponsor and funders, if any, in study design; collection,	Protocol v3.0 p9
37	sponsor and funder		management, analysis, and interpretation of data; writing of the	
38			report; and the decision to submit the report for publication, including	
39			whether they will have ultimate authority over any of these activities	
40				
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1 Roles and responsibilities: [#5d](#) Composition, roles, and responsibilities of the coordinating centre, Protocol v3.0 p10
 2 committees
 3 steering committee, endpoint adjudication committee, data
 4 management team, and other individuals or groups overseeing the
 5 trial, if applicable (see Item 21a for data monitoring committee)
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10 **Introduction**

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 14 Background and rationale [#6a](#) Description of research question and justification for undertaking the Paper p7
 15 trial, including summary of relevant studies (published and
 16 unpublished) examining benefits and harms for each intervention
 17
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 20

21
 22 Background and rationale: [#6b](#) Explanation for choice of comparators Paper p6
 23 choice of comparators
 24
 25

26
 27 Objectives [#7](#) Specific objectives or hypotheses Paper p7
 28
 29

30 Trial design [#8](#) Description of trial design including type of trial (eg, parallel group, Paper p9
 31 crossover, factorial, single group), allocation ratio, and framework
 32 (eg, superiority, equivalence, non-inferiority, exploratory)
 33
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38 **Methods: Participants,**
 39 **interventions, and**
 40 **outcomes**
 41
 42
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1	Study setting	#9	Description of study settings (eg, community clinic, academic	Paper p9
2			hospital) and list of countries where data will be collected. Reference	
3			to where list of study sites can be obtained	
4				
5				
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8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	Paper p10-11
9			eligibility criteria for study centres and individuals who will perform	
10			the interventions (eg, surgeons, psychotherapists)	
11				
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16	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication,	Paper p13-18
17			including how and when they will be administered	
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22	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a	Paper p13
23	modifications		given trial participant (eg, drug dose change in response to harms,	
24			participant request, or improving / worsening disease)	
25				
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28				
29	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any	Paper p19, Protocol v3.0
30			procedures for monitoring adherence (eg, drug tablet return;	p44
31			laboratory tests)	
32				
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37	Interventions: concomitant	#11d	Relevant concomitant care and interventions that are permitted or	Paper p18
38	care		prohibited during the trial	
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1	Outcomes	#12	Primary, secondary, and other outcomes, including the specific	Paper p19-25
2			measurement variable (eg, systolic blood pressure), analysis metric	
3			(eg, change from baseline, final value, time to event), method of	
4			aggregation (eg, median, proportion), and time point for each	
5			outcome. Explanation of the clinical relevance of chosen efficacy and	
6			harm outcomes is strongly recommended	
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16	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and	Paper figure1
17			washouts), assessments, and visits for participants. A schematic	
18			diagram is highly recommended (see Figure)	
19				
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23	Sample size	#14	Estimated number of participants needed to achieve study objectives	Paper p26
24			and how it was determined, including clinical and statistical	
25			assumptions supporting any sample size calculations	
26				
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31	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach	Paper p11-12
32			target sample size	
33				
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36	Methods: Assignment of			
37	interventions (for			
38	controlled trials)			
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1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-	Paper p12
2			generated random numbers), and list of any factors for stratification.	
3	generation		To reduce predictability of a random sequence, details of any	
4			planned restriction (eg, blocking) should be provided in a separate	
5			document that is unavailable to those who enrol participants or	
6			assign interventions	
7				
8	Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central	Paper p12
9	mechanism		telephone; sequentially numbered, opaque, sealed envelopes),	
10			describing any steps to conceal the sequence until interventions are	
11			assigned	
12				
13	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol	Paper p12
14			participants, and who will assign participants to interventions	
15				
16	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial	Paper p12
17			participants, care providers, outcome assessors, data analysts), and	
18			how	
19				
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and	N/A, no blinding
21	emergency unblinding		procedure for revealing a participant's allocated intervention during	
22			the trial	
23				

1 **Methods: Data collection,**
 2
 3 **management, and analysis**
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5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Data collection plan	#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	Data management plan v2.0
21 22 23 24 25 26 27 28	Data collection plan: retention	#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	Paper p29, Risk assessment plan v1 p8-9
29 30 31 32 33 34 35 36 37	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	Data management plan v2.0
38 39 40 41 42 43 44	Statistics: outcomes	#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	Paper p27-28

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	Paper p27-28
2				
3	analyses		analyses)	
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6	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence	Paper p27
7				
8	population and missing		(eg, as randomised analysis), and any statistical methods to handle	
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10	data		missing data (eg, multiple imputation)	
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14	Methods: Monitoring			
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16				
17	Data monitoring: formal	#21a	Composition of data monitoring committee (DMC); summary of its	Paper p29
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19	committee		role and reporting structure; statement of whether it is independent	
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29	Data monitoring: interim	#21b	Description of any interim analyses and stopping guidelines,	Paper p26
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31	analysis		including who will have access to these interim results and make the	
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37	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	Protocol v3.0 p46-47;
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1	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	Paper p29
2			whether the process will be independent from investigators and the	
3			sponsor	
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9	Ethics and dissemination			
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12	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review	Protocol v3.0 p57
13			board (REC / IRB) approval	
14				
15				
16				
17	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	Protocol v3.0 p57
18			changes to eligibility criteria, outcomes, analyses) to relevant parties	
19			(eg, investigators, REC / IRBs, trial participants, trial registries,	
20			journals, regulators)	
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27	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	Paper p11-12, Protocol
28			participants or authorised surrogates, and how (see Item 32)	v3.0 p33
29				
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32	Consent or assent:	#26b	Additional consent provisions for collection and use of participant	N/A
33	ancillary studies		data and biological specimens in ancillary studies, if applicable	
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38	Confidentiality	#27	How personal information about potential and enrolled participants	Paper p29, Data
39			will be collected, shared, and maintained in order to protect	Management Plan p6-7
40			confidentiality before, during, and after the trial	
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1	Declaration of interests	#28	Financial and other competing interests for principal investigators for	Paper p30
2			the overall trial and each study site	
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6	Data access	#29	Statement of who will have access to the final trial dataset, and	Data Management Plan
7			disclosure of contractual agreements that limit such access for	p3-4
8			investigators	
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14	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for	Not specified
15			compensation to those who suffer harm from trial participation	
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19	Dissemination policy: trial	#31a	Plans for investigators and sponsor to communicate trial results to	Paper p30, Protocol v3.0
20	results		participants, healthcare professionals, the public, and other relevant	p61
21			groups (eg, via publication, reporting in results databases, or other	
22			data sharing arrangements), including any publication restrictions	
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29	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional	Protocol v3.0 p61, study
30	authorship		writers	agreement sponsor-study
31				site
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37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	Protocol v3.0 p61
38	reproducible research		participant-level dataset, and statistical code	
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43	Appendices			
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1	Informed consent	#32	Model consent form and other related documentation given to	In TMF Informed Consent
2				
3	materials		participants and authorised surrogates	Form v6.0 in Dutch and
4				v5.0 in French
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8	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological	N/A
9			specimens for genetic or molecular analysis in the current trial and	
10			for future use in ancillary studies, if applicable	
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 19 collaboration with [Penelope.ai](#)
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BMJ Open

SurLym trial: Study protocol for a multicentre pragmatic randomised controlled trial on the added value of reconstructive lymphatic surgery to decongestive lymphatic therapy for the treatment of lymphoedema

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Surgery
Keywords:	Vascular medicine < INTERNAL MEDICINE, Plastic & reconstructive surgery < SURGERY, VASCULAR SURGERY

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Manuscripts

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3 SurLym trial: Study protocol for a multicentre pragmatic randomised controlled trial on the added
4 value of reconstructive lymphatic surgery to decongestive lymphatic therapy for the treatment of
5 lymphoedema
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42 Support statement: TDV is a post-doctoral research fellow of the Research Foundation – Flanders
43 (FWO).

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3 **Trial registration data set**
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Primary registry and trial identifying number	ClinicalTrials.gov Identifier: NCT05064176
Date of registration in primary registry	24-8-2021
Secondary identifying numbers	Ethical Committee UZ Leuven: S63212; EudraCT: 2021-000397-29
Source of monetary and material support	Belgian Health Care Knowledge Centre
Sponsor	University Hospitals Leuven, Clinical Trial center, Herestraat 49, 3000 Leuven, Belgium
Contact for public and scientific queries	Nele.devoogdt@uzleuven.be
Public title	Added value of reconstructive lymphatic surgery to usual care in lymphoedema
Scientific title	Comparison of reconstructive lymphatic surgery versus no surgery, additional to decongestive lymphatic therapy (usual care), for the treatment of lymphoedema , through a multicenter, pragmatic 3andomized controlled trial
Acronym	SurLym-trial
Protocol version	V3.0 19-4-2022
Country of recruitment	Belgium
Health condition studied	Primary or secondary upper or lower limb lymphoedema stage 1 to 2b
Intervention	Intervention group: Reconstructive lymphatic surgery (i.e. LVA or LNT or combination), added to usual care Control group: Only usual care (no surgery)
Key inclusion and exclusion criteria	-Lymphoedema: upper/ lower limb; uni-/ bilateral; primary or secondary; stage 1 to 2b; $\geq 5\%$ volume difference or ≥ 2 minor/ 1 major lymphoscintigraphy criterion; total score or one domain score of Lymph-ICF questionnaire $\geq 25/100$ -History of DLT ($\geq 6M$) until minimal pitting, no liposuction/ reconstructive surgery in past

	-In case of lower limb lymphoedema: no CVI C4-C6, no DVT/ PTS -Age \geq 18 years, not pregnant, BMI \leq 35 -No allergy for ICG/ iodine; no increased activity/ benign tumor thyroid gland; no heparin use and severe renal insufficiency
Study type	Multicentre, pragmatic randomised controlled trial
Date of first enrolment	March 2022
Target sample size	180
Recruitment status	Recruiting
Primary endpoint	Lymphoedema-specific QOL, at 18 months post-baseline
Key secondary endpoints	Limb volume, at 18 months post-baseline Duration of wearing the compression garment, at 18 months post-baseline
Treatment duration	18 months (usual care)
Follow up duration	36 months

Abstract

Introduction

Lymphoedema is a chronic condition caused by lymphatic insufficiency. It leads to swelling of the limb/ midline region and an increased risk of infection. Lymphoedema is often associated with mental and physical problems limiting quality of life. The first choice of treatment is a conservative treatment, consisting of exercises, skin care, lymph drainage and compression. Reconstructive lymphatic surgery is also often performed, i.e. lymphovenous anastomoses (LVA), lymph node transfer (LNT), or a combination. However, robust evidence on the effectiveness of reconstructive lymphatic surgery is missing. Therefore, the objective of this trial is to investigate the added value of reconstructive lymphatic surgery to the conservative treatment in patients with lymphoedema.

Methods and analysis

A multicentre randomised controlled and pragmatic trial was started since March 2022 in 3 Belgian university hospitals. Ninety patients with arm lymphoedema and 90 patients with leg lymphoedema will be included. All patients are randomised between conservative treatment alone (control group) or conservative treatment with reconstructive lymphatic surgery (intervention group). Assessments are performed at baseline and at 1, 3, 6, 12, 18, 24 and 36 months. The primary outcome is lymphoedema-specific quality of life at 18 months. Key secondary outcomes are limb volume and duration of wearing the compression garment at 18 months. The approach of reconstructive lymphatic surgery is based on pre-surgical investigations including clinical examination, lymphofluoroscopy, lymphoscintigraphy, lymph MRI or CT angiography (if needed). All patients receive conservative treatment during 36 months, which is applied by the patient's own physical therapist and by the patient self. From month 7-12, the hours a day of wearing the compression garment are gradually decreased.

Ethics and dissemination

The study has been approved by the ethical committees of University Hospitals Leuven, Ghent University Hospital and CHU UCL Namur. Results will be disseminated via peer-reviewed journals and presentations.

ClinicalTrials.gov Identifier: NCT05064176

Keywords: lymphedema, reconstructive surgery, surgical anastomosis, surgical flap

Word count: 4623 (up to data security and management), 5050 for all parts

Strengths and limitations of this study

- 1) This trial is stratified and powered for the effect of reconstructive lymphatic surgery in both arm and leg lymphoedema and will permit a conclusion regarding the effect of reconstructive lymphatic surgery in both groups.
- 2) As independent experts in reconstructive lymphatic surgery have trained the surgeons of the 3 study centers and advanced imaging techniques (i.e. ICG lymphofluoroscopy, lymph MRI, lymphoscintigraphy and CT angiography) are used to prepare the surgical procedure, high-qualitative reconstructive surgery procedures are guaranteed.
- 3) A comprehensive evaluation of the participants with lymphoedema will be performed by assessing lymphoedema-specific quality of life, which is a self-reported outcome, and by determining limb volume and duration of wearing the compression garment, which are objective outcomes.
- 4) If reconstructive lymphatic surgery is found effective, a detailed inventory of cost and quality of life will permit a cost-effectiveness analysis.
- 5) Besides a statistical plan, also a monitoring plan, data management plan, communication plan and risk assessment plan has been set in place.

INTRODUCTION

Lymphoedema is a chronic and debilitating condition caused by lymphatic insufficiency. It leads to swelling of the limb/ midline region and an increased risk of infection. It can be classified as primary (congenital) or secondary (acquired) lymphoedema. Lymphoedema is very burdensome for the patient, often causing mental problems such as frustration and stress.(1) In addition, due to the increase in volume of the limb, patients may develop physical problems, such as pain, heaviness, loss of strength, as well as functional problems with household, mobility or social activities.(2) These mental, physical and functional problems have a negative impact on the quality of life and the ability to work.(3)

There is consensus that the first choice of treatment of lymphoedema is a conservative treatment, also called decongestive lymphatic therapy (DLT).(4, 5) In case of pitting oedema, this consists of an intensive daily treatment to maximally reduce the oedema volume. This phase consists of skin care, manual lymph drainage, multilayer bandaging and exercise therapy. Once sufficient reduction of the pitting is obtained (i.e. there is no or minimal pitting) and the patients received education to improve their self-management skills, the maintenance phase starts, which aims at stabilising the results obtained in the previous phase. During the maintenance phase, skin care, exercises and lymph drainage are continued but bandaging is replaced by low-stretch compression garments. Professional's involvement can be minimised in this phase.

Reconstructive lymphatic surgery is another treatment option, consisting of either lymphovenous anastomoses (LVA), lymph node transfer (LNT) or a combination of both. The choice can be based on the surgeons clinical judgement or on local algorithms, as the Barcelona Lymphoedema Algorithm.(6) The objective of LVA is to redirect the lymph to the venous stream directly, bypassing areas of obstruction, and without going through the thoracic duct. LVA is applied if functional lymphatics can be localized, primarily by ICG lymphofluoroscopy and lymph MRI.(7) With LNT, orthotopically placed lymph nodes act as a sponge to absorb lymphatic fluid and direct it into the vascular network. The transferred nodes may also induce lymphangiogenesis and if they are placed in the site of lymphadenectomy, scar tissue and adhesions are removed, which may lower the pressure on the vein.(8) The lymphangiogenesis and the increase of the diameter of the vein as well may improve vascularisation.(5, 9) Indications for LNT are a total occlusion of lymphatic transport visualised through lymphoscintigraphy and a stage 2 lymphoedema with repeated episodes of erysipelas. Only subjects who had a history of at least 6 to 12 months of conservative treatment with good decongestion of the limb are candidates for reconstructive lymphatic surgery.(7)

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3 Our hypothesis is that reconstructive lymphatic surgery partially restores the lymphatic transport
4 which leads to a decrease of the lymphoedema volume and as a result lowers the need for a
5 compression garment. This will probably improve lymphoedema-specific quality of life.
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9 Robust evidence on the effectiveness of reconstructive lymphatic surgery for lymphoedema has so
10 far not been procured. In 2019, a Cochrane systematic review of Markkula et al revealed that there is
11 not enough high-quality research investigating the effect of reconstructive lymphatic surgery on
12 lymphoedema.(10) Only one RCT so far evaluated the effect of LNT. Dionyssiou et al randomised 36
13 patients with breast cancer related arm lymphoedema.(11) After surgery/no surgery, all patients first
14 received for 6 months DLT and DLT was discontinued for the next 12 months. At 18 months follow-
15 up, mean limb volume reduction was superior in the group with LNT compared to no LNT (57% vs
16 18%, $p < 0.01$). In the group with LNT infections were less frequent and subjective symptoms
17 improved. An RCT evaluating the effect of LVA has not been performed yet.
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27 **Objectives**

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29 The main objective of this study is to investigate the added value of reconstructive lymphatic surgery
30 to decongestive lymphatic therapy (usual care) in patients with lymphoedema of the upper limb or
31 lower limb in terms of lymphoedema-specific QoL (primary outcome), limb volume and duration of
32 wearing the compression garment (key secondary outcomes) at 18 months and of other outcomes at
33 1, 3, 6, 12, 18, 24 and 36 months post-baseline (secondary outcomes; see table 1 for the outcomes).
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37 A secondary objective is to verify whether the rate of complications in participants receiving
38 reconstructive lymphatic surgery is acceptable and if so, whether these complications are reversible.
39 We also verify in patients with lymphoedema due to cancer treatment, if reconstructive lymphatic
40 surgery causes higher cancer recurrence rates.
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46 A first exploratory objective is to compare the added value of the reconstructive surgery between
47 different subgroups (stage 1 vs stage 2; normal weight vs overweight; combination of LVA and LNT vs
48 one method). A second exploratory objective is to investigate predictive variables for lymphoedema-
49 specific QoL at 36 months.
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Table 1 Overview of the primary and secondary outcomes and the assessment method at each time interval

Outcome	Method	A1	A2, 3, 4	A5	A6	A7	A8
		Baseline	1, 3, 6M	12M	18M	24M	36M
Primary outcome							
Lymphoedema-specific QoL	Lymph-ICF questionnaire for upper or lower limb lymphoedema(12-15)	X			X		
Secondary outcomes							
Self-reported questionnaire							
Lymphoedema-specific QoL	See primary outcome	X	X	X		X	X
Duration (key secondary outcome) and experience of wearing compression garment	ICC compression questionnaire(16)	X	X	X	X	X	X
Health related QoL	EuroQoL-5D-5L(17)	X	X	X	X	X	X
Work capacity and ability	Work Productivity and Activity Impairment questionnaire;(18) QuickScan 18 (19)	X	X	X	X	X	X
Physical activity level	International Physical Activity Questionnaire(20)	X	X	X	X	X	X

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Costs related to lymphoedema and its treatment*	Study-specific questionnaire		X	X	X	X	X
Usual care & self-management*§, including need for intensive treatment	Study-specific questionnaire		X	X	X	X	X
Assessments							
Limb volume (key secondary outcome)	Circumference measurements every 4 cm with perimeter(21-24)	X	X	X	X	X	X
Hand/ foot volume	Water displacement method of hand or foot(22, 25)	X	X	X	X	X	X
Failure to reduce hours a day of wearing compression garment	Based on change of limb volume			X	X	X	X
Body weight	Scale	X	X	X	X	X	X
Infection previous 18 months	Interview	X			X		X
Recurrence of cancer	Interview and medical file				X		X
Adverse events and complications of surgery	Interview and medical file		X	X	X	X	X
Lymphatic transport	ICG fluoroscopy;(26) lymphoscintigraphy(27, 28)	X			X		

* Information is collected on a monthly basis; § No secondary outcome

METHODS AND ANALYSIS

Described according to the SPIRIT guidelines.(29)

Trial design and study setting

A multicentre, pragmatic randomised controlled trial is performed at three university hospitals in Belgium: University Hospitals Leuven (UZ Leuven), Ghent University Hospital (UZ Gent) and CHU UCL Namur.

The general flow, starting from screening for eligibility, is shown in figure 1.

Before the real screening (A0), a fast eligibility check is performed and Informed Consent Form is signed. If the patient is eligible and confirms participation, he/ she is randomised. The interval between screening (A0) and baseline assessment (A1) is ideally less than 3 months, but may be up to 6 months. The baseline assessments have to be performed shortly before the surgery, with a maximal interval of 1 month.

Figure 1. Flow diagram of the SurLym trial

Patient and public involvement in the trial design

Four patients with arm lymphoedema and 3 patients with leg lymphoedema from the center for lymphedema of UZ Leuven have completed a questionnaire about the study design and feasibility of the SurLym study. All but one patient, found the primary outcome, assessment of lymphoedema-specific QoL, a relevant and very important outcome. This patient preferred arm volume (which is a key secondary outcome) as outcome measure. None of the patients objected to a technical examination using an injection in the hand/ foot of the affected side (for imaging of the lymphatic system). All patients found it feasible to come to the hospital for 8 study-visits during 36 months, well aware that two of the visits take up to 6 hours. Three of seven patients were not keen to undergo surgery at the affected limb. All patients declared having little problems performing usual care: only one patient considered self-management difficult and another patient was afraid to reduce the hours of wearing the compression garment.

From the patients willing to be part of the trial's patient board (n=5), two patients were selected: one patient with arm lymphoedema and one with leg lymphoedema. They are both member of the Trial Steering Committee. The rationale and design of the trial was thoroughly discussed with them. They

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3 will be invited to further participate during future meetings of the Trial Steering Committee, to
4 advise us during the course of the trial and for the dissemination of the project results.
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9 **Eligibility criteria**

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11 Patients *eligible for inclusion* in the trial have to meet all of the following criteria:

- 12 1) Unilateral or bilateral, primary or secondary lymphoedema of the upper or lower limb;
- 13 2) If cancer-related lymphoedema, approval for participation from the multidisciplinary oncological
14 board; participation only if estimated cancer-related survival is ≥ 3 years and no concerns on
15 oncological safety are raised;
- 16 3) Lymphoedema stage 1 to 2 (according to staging 1-3 of International Society of Lymphology)(5);
- 17 4) Objective diagnosis of lymphoedema: $\geq 5\%$ volume difference OR ≥ 2 minor/ 1 major criteria on
18 lymphoscintigraphy OR presence of ICG dermal backflow;
- 19 5) Total score or one of domain scores on Lymph-ICF questionnaire at screening: $\geq 25/100$ (= moderate level of problems in functioning related to the development of lymphoedema)(14);
- 20 6) History of at least 6 months of DLT until minimal pitting;
- 21 7) Age ≥ 18 years.

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34 Following persons are *excluded*:

- 35 1) Persons with history of liposuction, LVA or LNT;
- 36 2) Persons who are pregnant or plan to become pregnant in the next 18 months;
- 37 3) Severely obese participants: BMI >35 ;
- 38 4) In case of lower limb lymphoedema: presence of chronic venous insufficiency C4, C5, C6; deep
39 venous thrombosis; post-thrombotic syndrome;
- 40 5) Allergy for ICG, iodine; increased activity of thyroid gland; benign tumour in thyroid gland; heparin
41 use and severe renal insufficiency
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49 **Recruitment, participant screening and consent**

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51 The recruitment of patients started in March 2022. One hundred eighty patients have to be recruited
52 by the 3 hospitals. Initially a recruitment period of 24 months (= 7.5 pts/ month) was planned
53 however difficulties in accessing operating theatres linked to COVID have caused delays. To make the
54 recruitment period as short as possible, a competitive recruitment is applied. We estimate that
55 around 20% of the patients screened for eligibility (A0, n=900) can be accepted for participation.
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3 Identification of eligible patients will be performed by the (sub)investigators of the lymphoedema
4 centres of the 3 hospitals (ST, BBH, AKH and ND for UZ Leuven; CM, CR, TD, VVB, MDS for UZ Gent;
5 and TD, JF, MS, AB, PF for CHU UCL Namur), supported by the study coordinators. The consultation
6 lists of the lymphoedema centres are screened before the consultation and the possible patients
7 eligible for the trial are marked.
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12 During the lymphoedema consultation, the clinician checks the eligibility criteria for which a
13 measurement is not necessary; if the patient seems eligible and he/ she is interested to receive
14 information about the trial, the trial is discussed using a study-specific recruitment document: this is
15 a concise and well-organised document that clarifies the design of the study and provides
16 information about side effects, costs and potential benefits and harms of participation. If a patient is
17 interested to participate, he/ she receives the Informed Consent Form and the 'study at a glance
18 (summary)' document. In addition, the patient receives an appointment for the screening (A0). Some
19 patients are informed about the trial through another way, e.g. by their oncologist. In that case, the
20 patient contacts the study coordinator by phone, who performs the fast eligibility check and
21 discusses the study during the phone call. If the patient is interested to participate, the Informed
22 Consent Form and the 'study at a glance' document is sent. In addition, the patient receives an
23 appointment for the screening (A0).
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32 During the *screening appointment (A0)*, patients receive all information and explanation they request
33 or need before signing the Informed Consent Form. Thereafter, the complete screening procedure is
34 executed to verify whether the participant fulfils all eligibility criteria.
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40 In order to optimally recruit patients with lymphoedema, the study is presented inside (at other
41 departments) as well as outside the hospitals of the study centers by lectures, posters and mailing.
42 Potential candidates with lymphoedema as well as their treating physicians, physical therapists and
43 other health care providers are informed about the trial (through social media, publication in local
44 journals and on websites).
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51 **Allocation and randomisation**

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53 Given the nature of the trial, *blinding* of participants and care providers (surgeon/ physical therapist/
54 compression specialist) is not feasible. Because the participants fill out different questionnaires to
55 determine the primary outcome and some of the secondary outcomes, detection bias may be a
56 potential risk. However, bias of the participants will be limited as much as possible because the study
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3 will be explained by a neutral person (physical therapists ND, AKH, VVB, MDS, JF or physical medicine
4 & rehabilitation physician TD (hospital of Ghent), TD (hospital of CHU UCL)).
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7 The *randomisation* is computer generated. To obtain concealment of allocation, the randomisation
8 list is prepared by the trial's statistician (SF) and is incorporated in the data management tool
9 'REDCap'. Randomisation is performed by using varying block sizes. A 1:1 allocation ratio is applied. A
10 stratification is applied for study centre (UZ Leuven vs UZ gent vs CHU-UCL Namur) and for region of
11 lymphoedema (upper limb vs lower limb, with a ratio 1:1). At each participating site, only the chief
12 investigator (ND) and trial manager (TDV), investigators and study coordinators have access to the
13 randomisation tool in REDCap. After randomisation, the study coordinator of the specific study
14 centre plans the intervention if applicable (surgery), as well as the usual care and the follow-up
15 assessments.
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22 After all patients have finished the trial and the database is locked to analyse the data, the
23 randomisation code will be broken.
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29 **Intervention**

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31 All participants are randomised to the intervention or control group. The intervention group is
32 treated with reconstructive lymphatic surgery in addition to conservative DLT (decongestive
33 lymphatic therapy; usual care). In the control group patients only receive conservative DLT (usual
34 care) without surgery (see figure 1).
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38 The researchers will follow the protocol as strictly as possible. However, since the pragmatic nature
39 of the trial, a deviation of the protocol is allowed if necessary. This protocol deviation has to be
40 registered in the protocol deviation log.
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47 *Reconstructive lymphatic surgery*

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49 The intervention treatment is reconstructive lymphatic surgery and is performed by the team of
50 vascular and/ or plastic surgeons from each study center (ST and KT of UZ Leuven; BDP and LD of
51 Ghent University Hospital; and MS, AB and PF of CHU UCL Namur). As reconstructive technique, a
52 lymphovenous anastomosis (LVA), lymph node transfer (LNT) or a combination of both is applied.
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54 The choice of the technique is determined by the surgeons of the study centre. See table 2 for the
55 overview of the preparation and for the technical description of the reconstructive procedure (which
56 is based on Chang et al).(7) In table 3 the aftercare is discussed.
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3 To obtain standardisation and to ascertain the quality of the reconstructive lymphatic surgery, all
4 surgeons received training in the Reconstructive Microsurgery European School (by JM and GP) in
5 May 2021. Moreover, to improve standardisation of the patient selection and the reconstructive
6 lymphatic procedure between the surgeons and between the centres, every patient that is planned
7 for surgery in the trial is discussed during a monthly meeting with at least one surgeon per centre
8 attending. A final quality control measure is that the first 10 surgical procedures are discussed with
9 the whole surgical team including the independent experts JM, GP, SS and KVL.
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For peer review only

Table 2. Overview of the preparation and procedure of LVA and LNT

Timing		Lymphovenous anastomosis (LVA)	Lymph node transfer (LNT)
Before surgery	Clinical reasoning based on pre-surgical investigations	Presence of suitable lymphatic vessel(s), visualised through ICG lymphofluoroscopy and/ or lymph MRI.	Presence of fibrosis or adhesions due to surgery, lymph node dissection and/ or radiotherapy, known through inspection and visualisation of interruption of lymphatic transport by lymphoscintigraphy. Presence of a well-vascularised donor flap (CT angiography is performed if needed).
Week before surgery	Compression garment	Measured by the team of compression specialists of the specific center; Choice of the type of compression garment is made pragmatically, as performed in the real clinical situation.	
	Registration of compression garment	Compression specialist registers each time after delivery the type of compression material and cost for patient/ health insurance.	
Surgery	Material	Microsurgical equipment to make anastomoses of vessels with diameter of 0.3-0.8 mm (suture size 11 or 12), supermicro clips, fine bipolar.	Microsurgical equipment to perform vascularised lymph-tissue transfer, suturing vein and artery with suture size 9 or 10, micro clips, fine bipolar.
	Preparation	ICG is injected interdigitally and lymph transport is designed on skin and location(s) of anastomosis is indicated (confirmed by lymph MRI).	To check for the safety not developing limb oedema due to the dissection of lymph nodes, ^{99m} Tc nanocolloids or ICG are injected in 1 st web of both hands (in case the donor site is the axilla) or feet (in case the donor site is the groin).
	Anaesthesia	General or if wish of patient local	General

	Procedure	<ol style="list-style-type: none"> 1) Patent blue is injected distal of location of anastomosis. 2) 2-3 cm incision. 3) Functional lymphatic is dissected, lymphatic is kept wet and lumen is made open; picture is taken. 4) Lymphatic is anastomosed to vein. 5) Between 1 and 10 anastomoses are made. 5) With ICG camera is checked whether anastomosis is open. 6) Wound is covered and cotton wool and elastic bandages are applied around the whole limb. 	<ol style="list-style-type: none"> 1) ICG is injected interdigitally. 2) Patent blue is injected distal of donor side flap. 3) Donor site flap is resected (= lymph nodes and skin and tissue around): in most cases groin proximal of inguinal ligament, sometimes lateral trunk; picture is taken. 4) Donor site flap is transferred to recipient site (= region with fibrosis/ adhesion): a wide excision of scar tissue is made to ensure a healthy bed for lymphangiogenesis and to improve bridging of lymphatics; picture is made. 5) Wound is covered and cotton wool and elastic bandages are applied around the whole limb.
	Registration	<ol style="list-style-type: none"> 1) Duration of procedure (in minutes). 2) Description of procedure: LVA vs LNT vs combination; general vs local anaesthesia; per-operative ICG fluoroscopy or scintigraphy; injection patent blue and localisation; for LVA, number of anastomoses and location; for LNT, donor site and recipient site. 3) Material (amount): flacon ICG/ patent blue; surgical wire; wound dressing; bandaging material (cotton wool, non-elastic bandages, tubular bandage); other material 4) Personnel (number and duration of presence): surgeon(s); nurse(s); other personnel 	

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Table 3. Overview of the after care in the hospital and at home following LVA and LNT.

Timing		Lymphovenous anastomosis (LVA)	Lymph node transfer (LNT)
Aftercare in hospital	Number of days	1 day or longer if necessary	2 days or longer if necessary
	Medication	To prevent thrombosis, to stimulate vasodilation, to reduce pain, to prevent infection	
	Inelastic bandage	In most of the patients (if risk of damaging LVA/ LNT by putting on compression garment; First tubular bandage and cotton wool covering whole limb, then non-elastic bandages, finally other tubular bandage over bandages (to keep everything together); keep it day and night	
	Advise	As much as possible limb elevation and regularly muscle contractions	
	Registration	1) Number of days of hospitalisation 2) Material (amount): bandaging material (cotton wool, non-elastic bandages, tubular bandage); other material 3) Medication (type and amount)	
Aftercare at home	Wound control	Once a week, inelastic bandage is removed, wound is cared and bandage is re-applied	
	Advise	As long as wound is not closed, as much as possible limb elevation and regularly muscle contractions	
	Compression garment	If wound is healed, new compression garment is applied and usual care protocol is started	
	Registration	1) Number of wound control visits and duration 2) Material (amount): bandaging material (cotton wool, non-elastic bandages, tubular bandage); wound care material; other material 3) Personnel (number and duration of presence): surgeon(s); nurse(s); other personnel	

Usual care

All patients receive usual care. The patient's own (regular) physical therapist performs the usual care in a pragmatic way consisting of exercises and skin care and manual lymph drainage (MLD) (i.e. the maintenance phase of decongestive lymphatic therapy (DLT)). Moreover, the physical therapist educates the patient to perform self-management, i.e. self-exercises, self-skin care, self-MLD, self-bandaging and putting on and removing the compression garment. In all patients (of intervention and control group), a new compression garment is measured by the compression specialist at baseline. The schematic overview of the usual care is given in figure 1 and is divided into four periods:

1) M1-6: From week 3 (or, in the intervention group, after healing of the wounds) the patient sees the home physical therapist twice per week and from week 5 once a week. The patient also performs self-management.

2) M7-12: The patient sees the own physical therapist once a week. The compression garment use is gradually reduced from 16h/d (end of 6th month) to 0h/d (end of 12th month). The own physical therapist performs circumference measurements of the limb weekly (i.e. with a perimeter provided by the study team) to control for changes of the limb volume(23). The patient completes a digital scoring form in REDCap weekly. The study investigator of the center checks the change of limb volume every week: if the limb volume increases $\geq 5\%$ compared to baseline, the patient is planned for an intermediate checkup in the study center. The study investigator decides whether the hours a day of wearing the compression garment has to be increased again.

3) M13-18: The patient only performs self-management and does not see the own physical therapist anymore. If possible, the patient does not wear the compression garment.

4) M19-36: The patient may choose whether he/ she visits the own physical therapist or performs self-management, or a combination.

This scheme of usual care has to be followed as strictly as possible, except when the patient's clinical situation deteriorates or risks to deteriorate. For example, a patient may visit the physical therapist more often in case of more lymphoedema-related complaints due to warm weather. Or, if during the follow-up, the clinical situation of the lymphoedema deteriorates unacceptably (e.g. there is presence of pitting oedema in the limb or there is a wound), the study investigator may advise the patient and physical therapist to perform an intensive treatment of the lymphoedema with bandaging. This information has to be registered by the patient in the usual care questionnaire.

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3 To obtain standardisation of the usual care, the physical therapist of the patient receives a training
4 before the start of the study. During this training, instructions about the study protocol are given
5 orally. In addition, the physical therapist receives an informative leaflet explaining the aim and design
6 of the trial, the treatment in the intervention/ control group and the assessment of the patient. It
7 also clarifies what the study investigators expect from the patient's physical therapist and vice-versa.
8 Following information regarding the patient's physical therapist is collected: age and gender,
9 education level and experience with treating lymphoedema (number of years of experience and in
10 which modalities, type of lymphoedema education).

19 **Outcomes**

21 The outcome measures were chosen based on input from patients with lymphoedema (see section
22 'patient and public involvement') and on input from the investigators of this trial who have
23 experience in evaluating and treating patients with lymphoedema. Patient-reported outcomes
24 provide essential information about the patient experience with the intervention that cannot be
25 reliably captured in another way, and are necessary for the complete evaluations of risks and
26 benefits and the value of the intervention. As a consequence, the trial's primary outcome is a
27 patient-reported outcome.⁽³⁰⁾ Moreover, recently, Chang et al stated in their systematic review and
28 meta-analysis about the surgical treatment of lymphoedema that better designed studies are
29 necessary: with objective reporting of outcomes using quantitative methods for measuring fluid and
30 both physiologic and immunologic function during longer follow-up.⁽³¹⁾

31 Assessments are performed at baseline (A1) and at 1 month (A2), 3 months (A3), 6 months (A4), 12
32 months (A5), 18 months (A6), 24 months (A7) and 36 months (A8) post-baseline. However, to limit
33 the burden for the patients, not all outcomes are assessed at each time interval. See table 1 for the
34 overview of the outcomes per time interval and see the Appendix for the assessment method and
35 the description of the assessment per variable and outcome. Figure 1 gives an overview of the timing
36 of the baseline assessment related to the screening and to the surgery, and of the foreseen windows
37 for the follow-up assessments.

38 At baseline, patient's demographics and information about the characteristics of the lymphoedema
39 and its treatment is collected.

40 The primary outcome is lymphoedema-specific QoL (= problems in functioning related to
41 development of lymphoedema) at 18 months, evaluated with the Dutch or French version of the
42 Lymph-ICF questionnaire for upper or lower limb lymphoedema.^(13-15, 32) Besides this patient-
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3 reported outcome, the trial contains also two key secondary outcomes at 18 months that are
4 objective outcomes. These are limb volume and failure to reduce the hours a day of wearing the
5 compression garment. In addition, these outcomes will be investigated at other time points in the
6 short term (1, 3, 6, 12 months) and longer term (24 and 36 months) as a secondary outcome
7 parameter. The outcome limb volume is determined differently in participants with upper and lower
8 limb lymphoedema. Since most of the patients with upper limb lymphoedema have unilateral
9 lymphoedema, limb volume is determined as the relative excessive arm volume. As too many
10 patients with lower limb lymphoedema have bilateral lymphoedema, limb volume is determined as
11 the leg volume.
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19 Other secondary outcomes are: duration of wearing the compression garment during one week and
20 experience of the compression garment, health-related QoL, work capacity and ability, physical
21 activity level, costs related to lymphoedema and its treatment, need for intensive treatment, hand/
22 foot volume, failure to reduce the hours a day of wearing the compression garment, body weight,
23 episodes of infection previous 18 months, recurrence of cancer (in patients with history of cancer),
24 adverse events and lymphatic transport.
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Complications of surgery (in the intervention group) and information regarding usual care and self-
management are collected during the trial period as well.

There is also a follow-up contact by phone at 9M and 15M, respectively. During the phone call,
information is further collected about adverse events and complications of the surgery, about the
usual care & self-management (to check for the adherence of the patient) and about the costs
related to lymphoedema and its treatment.

To guarantee standardisation of the assessments all assessors are trained before the start of the trial.

Sample size

The sample size is calculated to have at least 90% power to detect a difference between the
intervention group receiving reconstructive surgery and the control group without surgery, on
lymphoedema-specific QoL at 18 months, separately within patients with upper limb lymphoedema
and within patients with lower limb lymphoedema. Both comparisons are considered as separate
trials and therefore alpha has been set equal to 0.05.

The planned analysis to compare the groups is a constrained longitudinal data analysis (cLDA),(33)
using the baseline measurement and the follow-up measurements after 1, 3, 6, 12 and 18 months as
outcome. The primary analysis refers to the comparison after 18 months (based on a two-sided test

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3 with $\alpha=0.05$). The approach is similar in spirit as an analysis of covariance (ANCOVA) but does not
4 exclude subjects with one or more missing measurements. The calculation of the required sample
5 size is based on an approach presented by Stroup.⁽³⁴⁾ Information with respect to variability of the
6 lymphoedema-specific QoL score and the correlation between the timepoints was obtained from two
7 retrospective series (130 patients with arm oedema and 83 patients with leg oedema).

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10 The following assumptions have been made for the comparison of the lymphoedema-specific QoL:

- 11 - Standard deviation (SD) of the lymphoedema-specific QoL equal to 20
- 12 - Correlation between the baseline and each of the follow-up measurements equal to 0.50
- 13 - Drop-out of 5%, 10%, 15% and 20% after 1 and 3 months, 6 months, 12 months and 18, 24 and
14 36 months, respectively

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17 To detect a difference of 15 points, which is a clinically important difference,^(14, 15) 36 subjects are
18 required per group ($2 \times 2 \times 36 = 144$ subjects in total for the two trials) to have at least 90% power. If the
19 number of subjects would be reached before the end of the planned recruitment period of 24M,
20 recruitment will continue up to 45 subjects per group (180 subjects for the whole study) to obtain
21 more precise information, especially on the set of secondary outcomes. If the number is not attained,
22 the recruitment period will be prolonged.

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25 The sample size estimation heavily depends on estimates of variability of the lymphoedema-specific
26 QoL and the correlation with the baseline measurement. Therefore, after inclusion of 40 subjects per
27 group the already available information will be used to verify if the assumptions were plausible (note
28 however that there will be no information yet at the moment of the primary endpoint). If the
29 observed standard deviation and correlations deviate from the assumed values such that the desired
30 power level of 90% is not guaranteed anymore, an increase of the planned sample size will be
31 considered (if feasible). At the moment of this blinded interim analysis for sample size re-estimation,
32 the assumed dropout rates will also be verified. No interim analyses are planned to stop the study
33 earlier for efficacy or futility, this to avoid loss of information on the secondary endpoints.

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52 Statistical analysis will comply with the Consolidated Standards of Reporting Trials (CONSORT)
53 guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarised
54 using mean and SD and median and range values. Different analysis sets will be defined. The intent-
55 to-treat analysis set (ITT) contains all randomised patients, grouped according to the allocated
56 treatment. The modified intent-to-treat analysis set (mITT) contains all randomised patients grouped
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3 according to the allocated treatment, but excluding patients who have withdrawn their consent to
4 the randomised procedure. The as-treated analysis set also contains all randomised patients but
5 grouping the patients according to their received treatment. The per-protocol analysis set contains
6 all randomised patients who received the allocated treatment. The main analyses will be performed
7 on the ITT analysis set. Results on the other analysis sets will be reported additionally.
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13 *Primary outcome*

- 14 • Lymphoedema specific QoL

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16 A constrained longitudinal data analysis (cLDA)(33) using the baseline measurement and the follow-
17 up measurements after 1 month, 3 months, 6 months, 12 months and 18 months as outcome will be
18 used to compare the mean lymphoedema specific QoL after 18 months based on a two-sided test
19 with $\alpha=0.05$. The choice of the covariance structure for the five measurements will be based on
20 the Aikake criterion.(35) Study site is added as a fixed factor in this model. For patients with a
21 recurrence of cancer in the root of the limb, only observations before the recurrence are included.
22 Since the analysis is only valid under the missing at random (MAR) assumption (the probability of a
23 missing lymphoedema-specific QoL measurement does not depend on the unobserved value),
24 sensitivity analyses will be performed allowing a non-missing at random (NMAR) mechanism. More
25 specifically, starting from the MAR model, a jump-to-reference (JR) and tipping-point (TP) analysis
26 will be applied.(36)
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37 *Key secondary outcomes*

- 38 • Change of limb volume:

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40 For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be
41 calculated. A multivariate model for the longitudinal measured ratios (7 timepoints) will be used to
42 compare (changes in) log-transformed ratios between both groups. A log transformation for the
43 ratios is used since intervals between units are not equidistant. For the leg/ foot volume, the same
44 model will be used but on the original measurements of the (most) affected limb instead of on the
45 (log-transformed) ratios versus the contralateral side (since also patients with bilateral leg volume
46 are included).
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- 52 • Duration of wearing the compression garment:

53 The same modelling approach will be used as for the primary outcome.
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57 *Other secondary outcomes*

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3 Continuous outcomes will be analysed in a similar way as the primary outcome. Categorical (binary)
4 data will be analysed using stratified χ^2 test and logistic regression models with general estimating
5 equations (GEE) for repeatedly measured binary data. Adverse events and complications after
6 surgery will be reported descriptively.
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12 This study has been designed to permit *economic analysis* in a later phase. If reconstructive surgery is
13 deemed superior to no surgery (i.e. is clinically effective), the next step is to investigate its cost-
14 effectiveness by determining the incremental cost-effectiveness ratio (ICER). To determine the ICER,
15 the costs from a healthcare payer's perspective and from a societal perspective will be considered, as
16 well as the effectiveness by using the EQ-5D-5L questionnaire. If reconstructive surgery is proven
17 cost-effective, the budget impact will be calculated from a reimburse perspective.
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23 24 25 *Exploratory analyses*

26 Subgroup analyses for the primary outcome will be considered as a function of stage (stage 1 versus
27 2a/ 2b), primary vs secondary lymphoedema, weight (normal weight (BMI \leq 25) versus overweight
28 (BMI $>$ 25)) and combination of reconstructive techniques (combination of LVA/ LNT versus only LVA
29 or only LNT)
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34 Moreover, a multivariable model will be constructed to predict the lymphoedema-specific QoL at 36
35 months based on 14 baseline variables. For subjects with a missing lymphoedema-specific QoL at 36
36 months, values will be imputed based on a multivariate longitudinal model for the lymphoedema-
37 specific QoL measurements. A model reduction will be performed on a stacked dataset consisting of
38 the multiple imputed data (at least 10 imputations), using a weighting scheme to account for the
39 fraction of missing data in each covariate.⁽³⁷⁾ Considering the dropouts at 36 months, data for
40 lymphoedema-specific QoL of 144 patients will be available.
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49 **Data security and management**

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51 A study-specific Data Management Plan has been developed by the data management team.
52 Participant data are stored on a secure database in accordance with the General Data Protection
53 Regulations (2018). Data are de-identified and a unique trial identification number is used on all
54 source documents. These source documents are being checked for completeness and congruity
55 before data entry into REDCap. All trial documentation and data will be archived for at least 20 years
56 after completion of the trial.
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3 A Risk Assessment Plan has also been made with a summary of the concerns in the trial, how they
4 were mitigated, the probability that this will occur and its impact. This finally leads to a risk score
5 (low, medium, high, critical). The concerns with highest risks are discussed during the meeting of the
6 Trial Steering Committee (during recruitment period: once each 6M; thereafter: once a year).
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10 11 12 13 **Trial monitoring**

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15 A separate Monitoring plan has been constructed and will be conducted periodically by trial monitors
16 (independent from trial staff). The first monitoring visit at each site will be conducted within 4-8
17 weeks following the baseline visit of the first study subject at that site. Thereafter, monitoring visits
18 will be organized at mean intervals of 6 months during recruitment, and mean intervals of 12 months
19 thereafter. The participating site will provide direct access to the trial data and to the corresponding
20 source data and documents. The trial will be monitored to ensure that it is being conducted in
21 compliance with GCP and current legislation, that written informed consent has been obtained
22 correctly, that the trial procedures have been followed as shown in the protocol, and that the data
23 have been recorded, for which the source data will be compared with the data recorded in REDCap.
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33 **ETHICS AND DISSEMINATION**

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35 The SurLym trial will be conducted in compliance with the principles of the Declaration of Helsinki,
36 the principles of GCP and in accordance with all applicable regulatory requirements. Approval has
37 been obtained for the study protocol, the informed consent forms and other related documents by
38 the main Ethical Committee of UZ Leuven (S631212) and the local Ethical Committees of UZ Gent and
39 CHU UCL Namur. Any subsequent protocol amendments will be submitted to the Ethical Committee.
40 Furthermore, the study is approved by the Federal Agency for Medicines and Health Products
41 (EudraCT: 2021-000397-29).
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50 **Dissemination of results**

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52 The results of the study owned by the sponsor shall be disseminated as soon as possible after the
53 end of the trial, by disclosing them to the public by appropriate means, including publications in
54 peer-reviewed scientific journals and presentations at congresses and events. Open access will be
55 ensured to all peer-reviewed scientific publications relating to the results of the study.
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Author contributions

ND is the chief investigator of the SurLym trial. TDV is the trial manager. ND, CR, TD are the principle investigators of the 3 study sites. SF is the statistician. LG is expert in occupational medicine and will supervise the economic analysis (if executed). ND, AKH, ST, BBH, IF, VVB, TDC, MDS, CR, CM, JF, TD will perform the recruitment of patients. ST, KS, PF, MS, AB, BDP, LD will perform the surgical procedures and follow-up. AKH, JF, VVB, TDC, MDS are responsible for the clinical assessments (including lymphofluoroscopy and lymphoscintigraphy). GM, FK, AF, DD are the radiologists responsible for the lymph MRI an BK is a nuclear medicine physician responsible for the lymphoscintigraphy. JM, SS, GP, KVL are the independent experts in reconstructive lymphatic surgery and will verify the quality of the surgical procedures. ND drafted the manuscript. All authors contributed to the establishment of the protocol, revised the manuscript and provided input according to their area of expertise.

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Data statement

Data will be available on reasonable request.

Competing interests

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3 None declared
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8 **Ethics approval**

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10 Approval is obtained by the central Ethical Committee of the University Hospitals Leuven (S63212)
11 and by the local Ethical Committees of UZ Gent (BC-09711) and CHU UCL Namur (43/2021).
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16 **Figure legend**

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18 Figure 1 Flow diagram of the SurLym trial.
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23 **Supplemental material**

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25 Appendix Overview of the different variables and outcomes in the SurLym trial, the assessment
26 method and the description of the method
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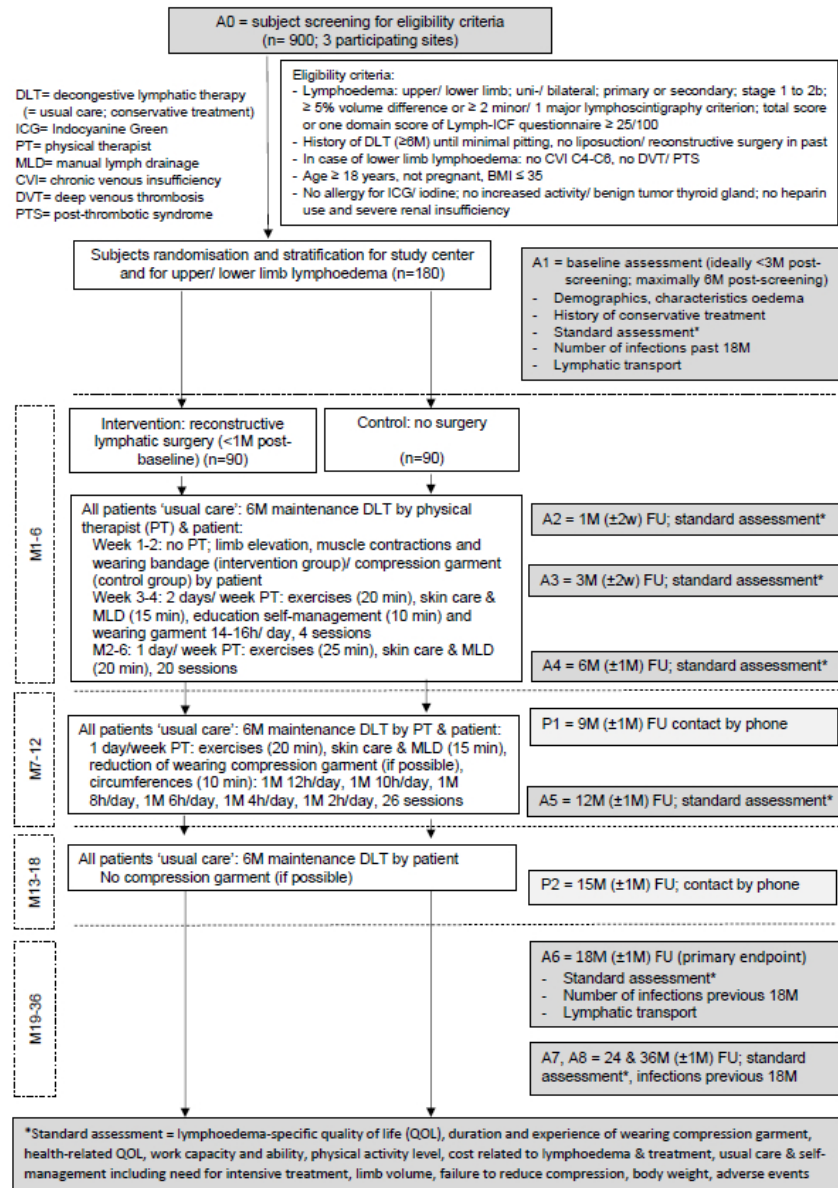


Figure 1. Flow diagram of SurLym trial

321x456mm (47 x 47 DPI)

Appendix Overview of the different variables and outcomes in the SurLym trial, the assessment method and the description of the method

Variable	Assessment method; description of method
Descriptives (15 min)	
Demographics	
Age (in years)	Medical file
Gender (man vs women), smoking status (smoking vs non-smoking), living status (alone vs together)	Interview
Body height (in m)	Stadiometer
Comorbidity (yes vs no)	Self-reported questionnaire developed by IDEWE (= external institute for prevention and protection at work); presence of wound by accident, of disease of musculoskeletal, circulatory, respiratory, neurological, digestive, urinary system, of disease of blood or skin, of mental or metabolic problems or of tumor (yes vs no)
Educational level (low vs high)	Interview; lower education = primary and secondary school, higher education = non-university higher and university
Anxiety and depression (0- 42)	Self-reported Hospital Anxiety and Depression Scale; 14 statements regarding anxiety and depression with score 0-3

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Characteristics of
lymphoedema and its
treatment

Duration of lymphoedema
(in months)

Interview

Localisation of
lymphoedema (yes vs no)

Inspection; for upper limb lymphoedema: hand/ lower arm/ upper arm/ trunk or
for lower limb lymphoedema: foot/ lower leg/ upper leg/ pelvic/ genital region, unilateral/ bilateral, site of lymphoedema
followed in trial: left/ right

Pitting status (yes vs no)

Palpation; for upper limb lymphoedema: hand/ lower arm/ upper arm/ trunk or for lower limb lymphoedema: Foot/ lower
leg/ upper leg/ pelvic/ genital region

Stage of lymphoedema (1
vs 2a vs 2b)

Inspection en palpation; Stage 1= pitting oedema that disappears with limb elevation (= reversible), 2a= pitting oedema
that does not disappear completely with limb elevation, 2b= further decrease of pitting and accumulation of fat tissue

Primary or secondary
lymphoedema

Interview and medical file; Primary = congenital; secondary = acquired after cancer-treatment (and type of cancer),
trauma, surgery, infection

History of conservative
treatment

Self-reported questionnaire (developed by author); Information regarding 1) physical therapy: number of years, number of
sessions last month/ year, content, 2) intensive treatment: where, how often, 3) other care giver, 4) self-management

Primary outcome

 Self-reported questionnaire

(5 min)

 Lymphoedema-specific
 QoL (0-100)

 Lymph-ICF questionnaire Dutch or French version for upper or lower limb lymphoedema;(12-15) 28 and 29 questions on
 11-point scale between 0-10, total score between 0-100 (0= no problems in functioning related to the development of
 lymphoedema)

Secondary outcomes

Self-reported questionnaires

(60 min)

 Lymphoedema-specific
 QoL (0-100)

 See primary outcome; in addition, score on 5 domains, i.e. physical function, mental function, household, mobility and life
 and social life domain (0-100)

 Duration (key secondary
 outcome) and experience
 of wearing compression
 garment

 ICC compression questionnaire;(16) Dosage (0-168 hours/ week), application/ removing compression (0-10), comfort
 (score between 0-10), complication (score between 0-10), general experience (0-10)

Health related QoL

 EuroQoL-5D-5L;(17) 5 items about mobility, self-care, activity, pain and anxiety (each dimension has 5 levels: no problems,
 slight problems, moderate problems, severe problems and extreme problems), range between -0.33 for situation '33333'
 (severe problems on all items) and 1 for situation '11111' (complete healthy)

Work capacity and ability

 Work Productivity and Activity Impairment questionnaire (WPAI-GH);(18) Impairment while working due to health, overall
 work impairment due to health, activity impairment due to health (%)

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3		QuickScan 18 – short version;(19) Chance for successful socio-professional reintegration (score between 0 certainly not
4		and 5 certainly yes)
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7	Physical activity level	International Physical Activity Questionnaire;(20) 7 questions about hours a week of vigorous (8 MET), moderate (4 MET)
8	(MET-hours a week)	and walking activities (3.3 MET), and sitting time
9		
10		
11	Costs related to	Study-specific questionnaire completed monthly by the patient; collection of patient and health care costs for material
12	lymphoedema and its	(such as compression or exercise material), medication, diagnostics or care giver (similar questionnaire as for Effort-BCRL
13	treatment (in euro)	trial)
14		
15		
16	Usual care & self-	
17	management §, including	Study-specific usual care & self-management questionnaire completed monthly by the patient; information regarding 1)
18	need for intensive	physical therapy: number of sessions, duration and content; 2) intensive treatment: where, number of sessions, content;
19	treatment	3) other care giver; 4) self-management: number of days of each modality
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24	Assessment (60 min)	
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27		Circumference measurements every 4 cm with perimeter;(21-24) limb volume is calculated with formula of truncated
28	Limb volume (key	cone, in participants with upper limb lymphoedema: assessment of affected and non-affected arm; outcome is excessive
29	secondary outcome)	arm volume (%) = (volume _{AFFECTED ARM} – volume _{UNAFFECTED ARM} / volume _{UNAFFECTED ARM}) x 100, in participants with lower limb
30		lymphoedema: assessment of affected leg (= leg that is followed in trial); outcome is whole leg volume (in ml)
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33		Water displacement method of hand or foot;(22, 25) volume is the mass of the displaced water, in participants with upper
34		limb lymphoedema: assessment of affected and non-affected hand, outcome is excessive hand volume (%); in participants
35	Hand/ foot volume	with lower limb lymphoedema: assessment of affected foot, outcome is foot volume (in ml)
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3	Failure to reduce hours a	
4	day of wearing	Assessor determines whether participant is able to reduce the hours a day of wearing the compression garment as stated
5	compression stocking (yes,	by the protocol (see figure 1, M7-12); Not able = excessive arm volume/ leg volume increased more than the smallest real
6	not able vs no, able)	difference, i.e. 5% or more compared to baseline(14)
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10	Body weight (in kg)	Scale
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12	Infection previous 18	
13	months (number)	Interview
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15	Recurrence of cancer (yes/	
16	no)	Interview and medical file; only collected in the group with history of cancer
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21	Adverse events (whole	Interview and medical file; registration of adverse events related to pre-surgical or study-specific investigations: ICG
22	group) and complications	fluoroscopy, lymphoscintigraphy, lymph MRI, CT angiography, of complications of reconstructive lymphatic surgery: 1) in
23	of surgery (in intervention	general blue spot, wound healing problem, infection of wound, decrease of sensibility around wound, erysipelas of limb,
24	group) (yes/ no)	deep venous thrombosis, 2) LNT-specific seroma, lymphocele, donor site lymphoedema, loss of flap
25		
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27		
28		Study-specific questionnaire completed by the compression specialist after delivery of compression material; registration
29	Costs related to	of company, compression product, region of compression, type, compression class, cost for health insurance/ patient
30	lymphoedema and its	
31	treatment (in euro)	Inter Mutuality Agency (IMA) database (= agency collecting data from different mutual health insurance companies),
32		based on national number of the study participant
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36	Lymphatic transport	
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6 ICG fluoroscopy (60 min)
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ICG fluoroscopy;(26) 0.2 ml dilution of ICG/ aqua/ NaCl is injected intradermally in 1st and 4th web of affected hand or foot; procedure consist of 3 minutes of rest, 5 minutes of stimulation and registration of outcomes (=early phase) and a break until 90 minutes post-injection and again registration of outcomes (= late phase); registration of following outcomes: 1) transport out of injection sites (yes/ no), 2) dermal rerouting (no, splash, stardust and diffuse for predefined regions on arm/ leg), 3) transport out of dermal rerouting, 4) lymph nodes (yes/ no)

Lymphoscintigraphy (60 min)

Lymphoscintigraphy;(27, 28) 55MBq ^{99m}Tc nanocolloids are injected intradermally in 1st web of both hands or feet; procedure consist of following steps: 1) 25 minutes of rest, 2) 5 minutes of arm/ leg cycling and 3) early phase acquisition; 4) 60 minutes break; 5) late phase acquisition; following images are made: before and after rest an image of injection sites and at the end (outcome: extraction out of injection sites in %), after rest, cycling and at the end a mini whole body (outcomes: number of lymph nodes, intensity of lymph collectors, intensity of dermal backflow, presence of lymph collaterals), during 25 minutes of rest dynamic images of axilla/ arm or groin/ leg (outcomes: arrival time and uptake in axilla/ inguinal region in %); in addition transport index is determined, based on transport kinetics, distribution of tracer, time to visualize lymph nodes and visualization of lymph nodes/ vessels

§ No secondary outcome

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item

Page Number

Administrative information

Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Paper p1
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For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of	Paper p3
2			intended registry	
3				
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6	Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data	Paper p3
7			Set	
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11	Protocol version	#3	Date and version identifier	Paper p3
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15	Funding	#4	Sources and types of financial, material, and other support	Paper p3, study
16				agreement KCE-UZ
17				Leuven
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22	Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	Paper p30
23	contributorship			
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28	Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	Paper p3
29	sponsor contact			
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32	information			
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36	Roles and responsibilities:	#5c	Role of study sponsor and funders, if any, in study design; collection,	Protocol v3.0 p9
37	sponsor and funder		management, analysis, and interpretation of data; writing of the	
38			report; and the decision to submit the report for publication, including	
39			whether they will have ultimate authority over any of these activities	
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1 Roles and responsibilities: [#5d](#) Composition, roles, and responsibilities of the coordinating centre, Protocol v3.0 p10
2 committees
3 steering committee, endpoint adjudication committee, data
4 management team, and other individuals or groups overseeing the
5 trial, if applicable (see Item 21a for data monitoring committee)
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10 Introduction

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14 Background and rationale [#6a](#) Description of research question and justification for undertaking the Paper p7
15 trial, including summary of relevant studies (published and
16 unpublished) examining benefits and harms for each intervention
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22 Background and rationale: [#6b](#) Explanation for choice of comparators Paper p6
23 choice of comparators
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27 Objectives [#7](#) Specific objectives or hypotheses Paper p7
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30 Trial design [#8](#) Description of trial design including type of trial (eg, parallel group, Paper p9
31 crossover, factorial, single group), allocation ratio, and framework
32 (eg, superiority, equivalence, non-inferiority, exploratory)
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38 **Methods: Participants,**
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40 **interventions, and**
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42 **outcomes**
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1	Study setting	#9	Description of study settings (eg, community clinic, academic	Paper p9
2			hospital) and list of countries where data will be collected. Reference	
3			to where list of study sites can be obtained	
4				
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8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	Paper p10-11
9			eligibility criteria for study centres and individuals who will perform	
10			the interventions (eg, surgeons, psychotherapists)	
11				
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16	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication,	Paper p13-18
17			including how and when they will be administered	
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22	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a	Paper p13
23	modifications		given trial participant (eg, drug dose change in response to harms,	
24			participant request, or improving / worsening disease)	
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29	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any	Paper p19, Protocol v3.0
30			procedures for monitoring adherence (eg, drug tablet return;	p44
31			laboratory tests)	
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37	Interventions: concomitant	#11d	Relevant concomitant care and interventions that are permitted or	Paper p18
38	care		prohibited during the trial	
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1	Outcomes	#12	Primary, secondary, and other outcomes, including the specific	Paper p19-25
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4			measurement variable (eg, systolic blood pressure), analysis metric	
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6			(eg, change from baseline, final value, time to event), method of	
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8			aggregation (eg, median, proportion), and time point for each	
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10			outcome. Explanation of the clinical relevance of chosen efficacy and	
11				
12			harm outcomes is strongly recommended	
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16	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and	Paper figure1
17			washouts), assessments, and visits for participants. A schematic	
18			diagram is highly recommended (see Figure)	
19				
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23	Sample size	#14	Estimated number of participants needed to achieve study objectives	Paper p26
24			and how it was determined, including clinical and statistical	
25			assumptions supporting any sample size calculations	
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31	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach	Paper p11-12
32			target sample size	
33				
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36 **Methods: Assignment of**
37
38 **interventions (for**
39
40 **controlled trials)**
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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	Paper p12
16 17 18 19 20 21 22 23 24	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	Paper p12
26 27 28 29 30	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Paper p12
31 32 33 34 35 36 37	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Paper p12
39 40 41 42 43 44	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial	N/A, no blinding

1 **Methods: Data collection,**
 2
 3 **management, and analysis**
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5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Data collection plan	#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	Data management plan v2.0
21 22 23 24 25 26 27 28	Data collection plan: retention	#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	Paper p29, Risk assessment plan v1 p8-9
29 30 31 32 33 34 35 36 37	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	Data management plan v2.0
38 39 40 41 42 43 44	Statistics: outcomes	#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	Paper p27-28

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	Paper p27-28
2				
3	analyses		analyses)	
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6	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence	Paper p27
7				
8	population and missing		(eg, as randomised analysis), and any statistical methods to handle	
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10	data		missing data (eg, multiple imputation)	
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14	Methods: Monitoring			
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17	Data monitoring: formal	#21a	Composition of data monitoring committee (DMC); summary of its	Paper p29
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19	committee		role and reporting structure; statement of whether it is independent	
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29	Data monitoring: interim	#21b	Description of any interim analyses and stopping guidelines,	Paper p26
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31	analysis		including who will have access to these interim results and make the	
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37	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	Protocol v3.0 p46-47;
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1	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Paper p29
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9	Ethics and dissemination			
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12	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Protocol v3.0 p57
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17	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)	Protocol v3.0 p57
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27	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Paper p11-12, Protocol v3.0 p33
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32	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
33	ancillary studies			
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38	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	Paper p29, Data Management Plan p6-7
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1	Declaration of interests	#28	Financial and other competing interests for principal investigators for	Paper p30
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3			the overall trial and each study site	
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6	Data access	#29	Statement of who will have access to the final trial dataset, and	Data Management Plan
7				
8			disclosure of contractual agreements that limit such access for	p3-4
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10			investigators	
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14	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for	Not specified
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16			compensation to those who suffer harm from trial participation	
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18				
19	Dissemination policy: trial	#31a	Plans for investigators and sponsor to communicate trial results to	Paper p30, Protocol v3.0
20				
21	results		participants, healthcare professionals, the public, and other relevant	p61
22				
23			groups (eg, via publication, reporting in results databases, or other	
24				
25			data sharing arrangements), including any publication restrictions	
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29	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional	Protocol v3.0 p61, study
30				
31	authorship		writers	agreement sponsor-study
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37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	Protocol v3.0 p61
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39	reproducible research		participant-level dataset, and statistical code	
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43	Appendices			
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1 2 3 4 5 6 7	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	In TMF Informed Consent Form v6.0 in Dutch and v5.0 in French
8 9 10 11 12 13 14 15	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	N/A

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BMJ Open

SurLym trial: Study protocol for a multicentre pragmatic randomised controlled trial on the added value of reconstructive lymphatic surgery to decongestive lymphatic therapy for the treatment of lymphoedema

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Surgery
Keywords:	Vascular medicine < INTERNAL MEDICINE, Plastic & reconstructive surgery < SURGERY, VASCULAR SURGERY

SCHOLARONE™
Manuscripts

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3 SurLym trial: Study protocol for a multicentre pragmatic randomised controlled trial on the added
4 value of reconstructive lymphatic surgery to decongestive lymphatic therapy for the treatment of
5 lymphoedema
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43 (FWO).

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3 **Trial registration data set**
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Primary registry and trial identifying number	ClinicalTrials.gov Identifier: NCT05064176
Date of registration in primary registry	24-8-2021
Secondary identifying numbers	Ethical Committee UZ Leuven: S63212; EudraCT: 2021-000397-29
Source of monetary and material support	Belgian Health Care Knowledge Centre
Sponsor	University Hospitals Leuven, Clinical Trial center, Herestraat 49, 3000 Leuven, Belgium
Contact for public and scientific queries	Nele.devoogdt@uzleuven.be
Public title	Added value of reconstructive lymphatic surgery to usual care in lymphoedema
Scientific title	Comparison of reconstructive lymphatic surgery versus no surgery, additional to decongestive lymphatic therapy (usual care), for the treatment of lymphoedema , through a multicenter, pragmatic 3andomized controlled trial
Acronym	SurLym-trial
Protocol version	V3.0 19-4-2022
Country of recruitment	Belgium
Health condition studied	Primary or secondary upper or lower limb lymphoedema stage 1 to 2b
Intervention	Intervention group: Reconstructive lymphatic surgery (i.e. LVA or LNT or combination), added to usual care Control group: Only usual care (no surgery)
Key inclusion and exclusion criteria	-Lymphoedema: upper/ lower limb; uni-/ bilateral; primary or secondary; stage 1 to 2b; $\geq 5\%$ volume difference or ≥ 2 minor/ 1 major lymphoscintigraphy criterion; total score or one domain score of Lymph-ICF questionnaire $\geq 25/100$ -History of DLT ($\geq 6M$) until minimal pitting, no liposuction/ reconstructive surgery in past

	-In case of lower limb lymphoedema: no CVI C4-C6, no DVT/ PTS -Age \geq 18 years, not pregnant, BMI \leq 35 -No allergy for ICG/ iodine; no increased activity/ benign tumor thyroid gland; no heparin use and severe renal insufficiency
Study type	Multicentre, pragmatic randomised controlled trial
Date of first enrolment	March 2022
Target sample size	180
Recruitment status	Recruiting
Primary endpoint	Lymphoedema-specific QOL, at 18 months post-baseline
Key secondary endpoints	Limb volume, at 18 months post-baseline Duration of wearing the compression garment, at 18 months post-baseline
Treatment duration	18 months (usual care)
Follow up duration	36 months

Abstract

Introduction

Lymphoedema is a chronic condition caused by lymphatic insufficiency. It leads to swelling of the limb/ midline region and an increased risk of infection. Lymphoedema is often associated with mental and physical problems limiting quality of life. The first choice of treatment is a conservative treatment, consisting of exercises, skin care, lymph drainage and compression. Reconstructive lymphatic surgery is also often performed, i.e. lymphovenous anastomoses (LVA), lymph node transfer (LNT), or a combination. However, robust evidence on the effectiveness of reconstructive lymphatic surgery is missing. Therefore, the objective of this trial is to investigate the added value of reconstructive lymphatic surgery to the conservative treatment in patients with lymphoedema.

Methods and analysis

A multicentre randomised controlled and pragmatic trial was started since March 2022 in 3 Belgian university hospitals. Ninety patients with arm lymphoedema and 90 patients with leg lymphoedema will be included. All patients are randomised between conservative treatment alone (control group) or conservative treatment with reconstructive lymphatic surgery (intervention group). Assessments are performed at baseline and at 1, 3, 6, 12, 18, 24 and 36 months. The primary outcome is lymphoedema-specific quality of life at 18 months. Key secondary outcomes are limb volume and duration of wearing the compression garment at 18 months. The approach of reconstructive lymphatic surgery is based on pre-surgical investigations including clinical examination, lymphofluoroscopy, lymphoscintigraphy, lymph MRI or CT angiography (if needed). All patients receive conservative treatment during 36 months, which is applied by the patient's own physical therapist and by the patient self. From month 7-12, the hours a day of wearing the compression garment are gradually decreased.

Ethics and dissemination

The study has been approved by the ethical committees of University Hospitals Leuven, Ghent University Hospital and CHU UCL Namur. Results will be disseminated via peer-reviewed journals and presentations.

ClinicalTrials.gov Identifier: NCT05064176

Keywords: lymphedema, reconstructive surgery, surgical anastomosis, surgical flap

Word count: 4623 (up to data security and management), 5050 for all parts

Strengths and limitations of this study

- 1) This trial is stratified and powered for the effect of reconstructive lymphatic surgery in both arm and leg lymphoedema and will permit a conclusion regarding the effect of reconstructive lymphatic surgery in both groups.
- 2) As independent experts in reconstructive lymphatic surgery have trained the surgeons of the 3 study centers and advanced imaging techniques (i.e. ICG lymphofluoroscopy, lymph MRI, lymphoscintigraphy and CT angiography) are used to prepare the surgical procedure, high-qualitative reconstructive surgery procedures are guaranteed.
- 3) A comprehensive evaluation of the participants with lymphoedema will be performed by assessing lymphoedema-specific quality of life, which is a self-reported outcome, and by determining limb volume and duration of wearing the compression garment, which are objective outcomes.
- 4) If reconstructive lymphatic surgery is found effective, a detailed inventory of cost and quality of life will permit a cost-effectiveness analysis.
- 5) Besides a statistical plan, also a monitoring plan, data management plan, communication plan and risk assessment plan has been set in place.

INTRODUCTION

Lymphoedema is a chronic and debilitating condition caused by lymphatic insufficiency. It leads to swelling of the limb/ midline region and an increased risk of infection. It can be classified as primary (congenital) or secondary (acquired) lymphoedema. Lymphoedema is very burdensome for the patient, often causing mental problems such as frustration and stress.(1) In addition, due to the increase in volume of the limb, patients may develop physical problems, such as pain, heaviness, loss of strength, as well as functional problems with household, mobility or social activities.(2) These mental, physical and functional problems have a negative impact on the quality of life and the ability to work.(3)

There is consensus that the first choice of treatment of lymphoedema is a conservative treatment, also called decongestive lymphatic therapy (DLT).(4, 5) In case of pitting oedema, this consists of an intensive daily treatment to maximally reduce the oedema volume. This phase consists of skin care, manual lymph drainage, multilayer bandaging and exercise therapy. Once sufficient reduction of the pitting is obtained (i.e. there is no or minimal pitting) and the patients received education to improve their self-management skills, the maintenance phase starts, which aims at stabilising the results obtained in the previous phase. During the maintenance phase, skin care, exercises and lymph drainage are continued but bandaging is replaced by low-stretch compression garments. Professional's involvement can be minimised in this phase.

Reconstructive lymphatic surgery is another treatment option, consisting of either lymphovenous anastomoses (LVA), lymph node transfer (LNT) or a combination of both. The choice can be based on the surgeons clinical judgement or on local algorithms, as the Barcelona Lymphoedema Algorithm.(6) The objective of LVA is to redirect the lymph to the venous stream directly, bypassing areas of obstruction, and without going through the thoracic duct. LVA is applied if functional lymphatics can be localized, primarily by ICG lymphofluoroscopy and lymph MRI.(7) With LNT, orthotopically placed lymph nodes act as a sponge to absorb lymphatic fluid and direct it into the vascular network. The transferred nodes may also induce lymphangiogenesis and if they are placed in the site of lymphadenectomy, scar tissue and adhesions are removed, which may lower the pressure on the vein.(8) The lymphangiogenesis and the increase of the diameter of the vein as well may improve vascularisation.(5, 9) Indications for LNT are a total occlusion of lymphatic transport visualised through lymphoscintigraphy and a stage 2 lymphoedema with repeated episodes of erysipelas. Only subjects who had a history of at least 6 to 12 months of conservative treatment with good decongestion of the limb are candidates for reconstructive lymphatic surgery.(7)

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3 Our hypothesis is that reconstructive lymphatic surgery partially restores the lymphatic transport
4 which leads to a decrease of the lymphoedema volume and as a result lowers the need for a
5 compression garment. This will probably improve lymphoedema-specific quality of life.
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9 Robust evidence on the effectiveness of reconstructive lymphatic surgery for lymphoedema has so
10 far not been procured. In 2019, a Cochrane systematic review of Markkula et al revealed that there is
11 not enough high-quality research investigating the effect of reconstructive lymphatic surgery on
12 lymphoedema.(10) Only one RCT so far evaluated the effect of LNT. Dionyssiou et al randomised 36
13 patients with breast cancer related arm lymphoedema.(11) After surgery/no surgery, all patients first
14 received for 6 months DLT and DLT was discontinued for the next 12 months. At 18 months follow-
15 up, mean limb volume reduction was superior in the group with LNT compared to no LNT (57% vs
16 18%, $p<0.01$). In the group with LNT infections were less frequent and subjective symptoms
17 improved. An RCT evaluating the effect of LVA has not been performed yet.
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27 **Objectives**

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29 The main objective of this study is to investigate the added value of reconstructive lymphatic surgery
30 to decongestive lymphatic therapy (usual care) in patients with lymphoedema of the upper limb or
31 lower limb in terms of lymphoedema-specific QoL (primary outcome), limb volume and duration of
32 wearing the compression garment (key secondary outcomes) at 18 months and of other outcomes at
33 1, 3, 6, 12, 18, 24 and 36 months post-baseline (secondary outcomes; see table 1 for the outcomes).
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37 A secondary objective is to verify whether the rate of complications in participants receiving
38 reconstructive lymphatic surgery is acceptable and if so, whether these complications are reversible.
39 We also verify in patients with lymphoedema due to cancer treatment, if reconstructive lymphatic
40 surgery causes higher cancer recurrence rates.
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46 A first exploratory objective is to compare the added value of the reconstructive surgery between
47 different subgroups (stage 1 vs stage 2; normal weight vs overweight; combination of LVA and LNT vs
48 one method). A second exploratory objective is to investigate predictive variables for lymphoedema-
49 specific QoL at 36 months.
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Table 1 Overview of the primary and secondary outcomes and the assessment method at each time interval

Outcome	Method	A1	A2, 3, 4	A5	A6	A7	A8
		Baseline	1, 3, 6M	12M	18M	24M	36M
Primary outcome							
Lymphoedema-specific QoL	Lymph-ICF questionnaire for upper or lower limb lymphoedema(12-15)	X			X		
Secondary outcomes							
Self-reported questionnaire							
Lymphoedema-specific QoL	See primary outcome	X	X	X		X	X
Duration (key secondary outcome) and experience of wearing compression garment	ICC compression questionnaire(16)	X	X	X	X	X	X
Health related QoL	EuroQoL-5D-5L(17)	X	X	X	X	X	X
Work capacity and ability	Work Productivity and Activity Impairment questionnaire;(18) QuickScan 18 (19)	X	X	X	X	X	X
Physical activity level	International Physical Activity Questionnaire(20)	X	X	X	X	X	X

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Costs related to lymphoedema and its treatment*	Study-specific questionnaire		X	X	X	X	X
Usual care & self-management*§, including need for intensive treatment	Study-specific questionnaire		X	X	X	X	X
Assessments							
Limb volume (key secondary outcome)	Circumference measurements every 4 cm with perimeter(21-24)	X	X	X	X	X	X
Hand/ foot volume	Water displacement method of hand or foot(22, 25)	X	X	X	X	X	X
Failure to reduce hours a day of wearing compression garment	Based on change of limb volume			X	X	X	X
Body weight	Scale	X	X	X	X	X	X
Infection previous 18 months	Interview	X			X		X
Recurrence of cancer	Interview and medical file				X		X
Adverse events and complications of surgery	Interview and medical file		X	X	X	X	X
Lymphatic transport	ICG fluoroscopy;(26) lymphoscintigraphy(27, 28)	X			X		

* Information is collected on a monthly basis; § No secondary outcome

METHODS AND ANALYSIS

Described according to the SPIRIT guidelines.(29)

Trial design and study setting

A multicentre, pragmatic randomised controlled trial is performed at three university hospitals in Belgium: University Hospitals Leuven (UZ Leuven), Ghent University Hospital (UZ Gent) and CHU UCL Namur.

The general flow, starting from screening for eligibility, is shown in figure 1.

Before the real screening (A0), a fast eligibility check is performed and Informed Consent Form is signed. If the patient is eligible and confirms participation, he/ she is randomised. The interval between screening (A0) and baseline assessment (A1) is ideally less than 3 months, but may be up to 6 months. The baseline assessments have to be performed shortly before the surgery, with a maximal interval of 1 month.

Figure 1. Flow diagram of the SurLym trial

Patient and public involvement in the trial design

Four patients with arm lymphoedema and 3 patients with leg lymphoedema from the center for lymphedema of UZ Leuven have completed a questionnaire about the study design and feasibility of the SurLym study. All but one patient, found the primary outcome, assessment of lymphoedema-specific QoL, a relevant and very important outcome. This patient preferred arm volume (which is a key secondary outcome) as outcome measure. None of the patients objected to a technical examination using an injection in the hand/ foot of the affected side (for imaging of the lymphatic system). All patients found it feasible to come to the hospital for 8 study-visits during 36 months, well aware that two of the visits take up to 6 hours. Three of seven patients were not keen to undergo surgery at the affected limb. All patients declared having little problems performing usual care: only one patient considered self-management difficult and another patient was afraid to reduce the hours of wearing the compression garment.

From the patients willing to be part of the trial's patient board (n=5), two patients were selected: one patient with arm lymphoedema and one with leg lymphoedema. They are both member of the Trial Steering Committee. The rationale and design of the trial was thoroughly discussed with them. They

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3 will be invited to further participate during future meetings of the Trial Steering Committee, to
4 advise us during the course of the trial and for the dissemination of the project results.
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9 **Eligibility criteria**

10 Patients *eligible for inclusion* in the trial have to meet all of the following criteria:

- 11 1) Unilateral or bilateral, primary or secondary lymphoedema of the upper or lower limb;
- 12 2) If cancer-related lymphoedema, approval for participation from the multidisciplinary oncological
- 13 board; participation only if estimated cancer-related survival is ≥ 3 years and no concerns on
- 14 oncological safety are raised;
- 15 3) Lymphoedema stage 1 to 2 (according to staging 1-3 of International Society of Lymphology)(5);
- 16 4) Objective diagnosis of lymphoedema: $\geq 5\%$ volume difference OR ≥ 2 minor/ 1 major criteria on
- 17 lymphoscintigraphy OR presence of ICG dermal backflow;
- 18 5) Total score or one of domain scores on Lymph-ICF questionnaire at screening: $\geq 25/100$ (=
- 19 moderate level of problems in functioning related to the development of lymphoedema)(14);
- 20 6) History of at least 6 months of DLT until minimal pitting (sustained thumb pressure on the skin is
- 21 performed during 5 seconds; after removing the thumb, indentation of tissue is evaluated and is
- 22 scored as 0 = no clinical pitting, 1 = slight/doubtful pitting and 2 = noticeably pitting; a patient with
- 23 score 2 may not participate)(30);
- 24 7) Age ≥ 18 years.

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39 Following persons are *excluded*:

- 40 1) Persons with history of liposuction, LVA or LNT;
- 41 2) Persons who are pregnant or plan to become pregnant in the next 18 months;
- 42 3) Severely obese participants: BMI >35 ;
- 43 4) In case of lower limb lymphoedema: presence of chronic venous insufficiency C4, C5, C6; deep
- 44 venous thrombosis; post-thrombotic syndrome;
- 45 5) Allergy for ICG, iodine; increased activity of thyroid gland; benign tumour in thyroid gland; heparin
- 46 use and severe renal insufficiency
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54 **Recruitment, participant screening and consent**

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56 The recruitment of patients started in March 2022. One hundred eighty patients have to be recruited
57 by the 3 hospitals. Initially a recruitment period of 24 months (= 7.5 pts/ month) was planned
58 however difficulties in accessing operating theatres linked to COVID have caused delays. To make the
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3 recruitment period as short as possible, a competitive recruitment is applied. We estimate that
4 around 20% of the patients screened for eligibility (A0, n=900) can be accepted for participation.
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7 Identification of eligible patients will be performed by the (sub)investigators of the lymphoedema
8 centres of the 3 hospitals (ST, BBH, AKH and ND for UZ Leuven; CM, CR, TD, VVB, MDS for UZ Gent;
9 and TD, JF, MS, AB, PF for CHU UCL Namur), supported by the study coordinators. The consultation
10 lists of the lymphoedema centres are screened before the consultation and the possible patients
11 eligible for the trial are marked.
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16 During the lymphoedema consultation, the clinician checks the eligibility criteria for which a
17 measurement is not necessary; if the patient seems eligible and he/ she is interested to receive
18 information about the trial, the trial is discussed using a study-specific recruitment document: this is
19 a concise and well-organised document that clarifies the design of the study and provides
20 information about side effects, costs and potential benefits and harms of participation. If a patient is
21 interested to participate, he/ she receives the Informed Consent Form and the 'study at a glance
22 (summary)' document. In addition, the patient receives an appointment for the screening (A0). Some
23 patients are informed about the trial through another way, e.g. by their oncologist. In that case, the
24 patient contacts the study coordinator by phone, who performs the fast eligibility check and
25 discusses the study during the phone call. If the patient is interested to participate, the Informed
26 Consent Form and the 'study at a glance' document is sent. In addition, the patient receives an
27 appointment for the screening (A0).
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36 During the *screening appointment (A0)*, patients receive all information and explanation they request
37 or need before signing the Informed Consent Form. Thereafter, the complete screening procedure is
38 executed to verify whether the participant fulfils all eligibility criteria.
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44 In order to optimally recruit patients with lymphoedema, the study is presented inside (at other
45 departments) as well as outside the hospitals of the study centers by lectures, posters and mailing.
46 Potential candidates with lymphoedema as well as their treating physicians, physical therapists and
47 other health care providers are informed about the trial (through social media, publication in local
48 journals and on websites).
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55 **Allocation and randomisation**

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57 Given the nature of the trial, *blinding* of participants and care providers (surgeon/ physical therapist/
58 compression specialist) is not feasible. Because the participants fill out different questionnaires to
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3 determine the primary outcome and some of the secondary outcomes, detection bias may be a
4 potential risk. However, bias of the participants will be limited as much as possible because the study
5 will be explained by a neutral person (physical therapists ND, AKH, VVB, MDS, JF or physical medicine
6 & rehabilitation physician TD (hospital of Ghent), TD (hospital of CHU UCL)).
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10 The *randomisation* is computer generated. To obtain concealment of allocation, the randomisation
11 list is prepared by the trial's statistician (SF) and is incorporated in the data management tool
12 'REDCap'. Randomisation is performed by using varying block sizes. A 1:1 allocation ratio is applied. A
13 stratification is applied for study centre (UZ Leuven vs UZ gent vs CHU-UCL Namur) and for region of
14 lymphoedema (upper limb vs lower limb, with a ratio 1:1). At each participating site, only the chief
15 investigator (ND) and trial manager (TDV), investigators and study coordinators have access to the
16 randomisation tool in REDCap. After randomisation, the study coordinator of the specific study
17 centre plans the intervention if applicable (surgery), as well as the usual care and the follow-up
18 assessments.
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26 After all patients have finished the trial and the database is locked to analyse the data, the
27 randomisation code will be broken.
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32 **Intervention**

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34 All participants are randomised to the intervention or control group. The intervention group is
35 treated with reconstructive lymphatic surgery in addition to conservative DLT (decongestive
36 lymphatic therapy; usual care). In the control group patients only receive conservative DLT (usual
37 care) without surgery (see figure 1).
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42 The researchers will follow the protocol as strictly as possible. However, since the pragmatic nature
43 of the trial, a deviation of the protocol is allowed if necessary. This protocol deviation has to be
44 registered in the protocol deviation log.
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50 *Reconstructive lymphatic surgery*

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52 The intervention treatment is reconstructive lymphatic surgery and is performed by the team of
53 vascular and/ or plastic surgeons from each study center (ST and KT of UZ Leuven; BDP and LD of
54 Ghent University Hospital; and MS, AB and PF of CHU UCL Namur). As reconstructive technique, a
55 lymphovenous anastomosis (LVA), lymph node transfer (LNT) or a combination of both is applied.
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59 The choice of the technique is determined by the surgeons of the study centre. See table 2 for the
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3 overview of the preparation and for the technical description of the reconstructive procedure (which
4 is based on Chang et al).(7) In table 3 the aftercare is discussed.
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7 To obtain standardisation and to ascertain the quality of the reconstructive lymphatic surgery, all
8 surgeons received training in the Reconstructive Microsurgery European School (by JM and GP) in
9 May 2021. Moreover, to improve standardisation of the patient selection and the reconstructive
10 lymphatic procedure between the surgeons and between the centres, every patient that is planned
11 for surgery in the trial is discussed during a monthly meeting with at least one surgeon per centre
12 attending. A final quality control measure is that the first 10 surgical procedures are discussed with
13 the whole surgical team including the independent experts JM, GP, SS and KVL.
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Table 2. Overview of the preparation and procedure of LVA and LNT

Timing		Lymphovenous anastomosis (LVA)	Lymph node transfer (LNT)
Before surgery	Clinical reasoning based on pre-surgical investigations	Presence of suitable lymphatic vessel(s), visualised through ICG lymphofluoroscopy and/ or lymph MRI.	Presence of fibrosis or adhesions due to surgery, lymph node dissection and/ or radiotherapy, known through inspection and visualisation of interruption of lymphatic transport by lymphoscintigraphy. Presence of a well-vascularised donor flap (CT angiography is performed if needed).
Week before surgery	Compression garment	Measured by the team of compression specialists of the specific center; Choice of the type of compression garment is made pragmatically, as performed in the real clinical situation. So, length, options, compression class, type (flat/round-knitted, standard/custom-made) of the compression garment is determined patient-specific.	
	Registration of compression garment	Compression specialist registers each time after delivery the type of compression material and cost for patient/ health insurance.	
Surgery	Material	Microsurgical equipment to make anastomoses of vessels with diameter of 0.3-0.8 mm (suture size 11 or 12), supermicro clips, fine bipolar.	Microsurgical equipment to perform vascularised lymph-tissue transfer, suturing vein and artery with suture size 9 or 10, micro clips, fine bipolar.
	Preparation	ICG is injected interdigitally and lymph transport is designed on skin and location(s) of anastomosis is indicated (confirmed by lymph MRI).	To check for the safety not developing limb oedema due to the dissection of lymph nodes, ^{99m} Tc nanocolloids or ICG

			are injected in 1 st web of both hands (in case the donor site is the axilla) or feet (in case the donor site is the groin).
	Anaesthesia	General or if wish of patient local	General
	Procedure	<ol style="list-style-type: none"> 1) Patent blue is injected distal of location of anastomosis. 2) 2-3 cm incision. 3) Functional lymphatic is dissected, lymphatic is kept wet and lumen is made open; picture is taken. 4) Lymphatic is anastomosed to vein. 5) Between 1 and 10 anastomoses are made. 5) With ICG camera is checked whether anastomosis is open. 6) Wound is covered and cotton wool and elastic bandages are applied around the whole limb. 	<ol style="list-style-type: none"> 1) ICG is injected interdigitally. 2) Patent blue is injected distal of donor side flap. 3) Donor site flap is resected (= lymph nodes and skin and tissue around): in most cases groin proximal of inguinal ligament, sometimes lateral trunk; picture is taken. 4) Donor site flap is transferred to recipient site (= region with fibrosis/ adhesion): a wide excision of scar tissue is made to ensure a healthy bed for lymphangiogenesis and to improve bridging of lymphatics; picture is made. 5) Wound is covered and cotton wool and elastic bandages are applied around the whole limb.
	Registration	<ol style="list-style-type: none"> 1) Duration of procedure (in minutes). 2) Description of procedure: LVA vs LNT vs combination; general vs local anaesthesia; per-operative ICG fluoroscopy or scintigraphy; injection patent blue and localisation; for LVA, number of anastomoses and location; for LNT, donor site and recipient site. 3) Material (amount): flacon ICG/ patent blue; surgical wire; wound dressing; bandaging material (cotton wool, non-elastic bandages, tubular bandage); other material 4) Personnel (number and duration of presence): surgeon(s); nurse(s); other personnel 	

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Table 3. Overview of the after care in the hospital and at home following LVA and LNT.

Timing		Lymphovenous anastomosis (LVA)	Lymph node transfer (LNT)
Aftercare in hospital	Number of days	1 day or longer if necessary	2 days or longer if necessary
	Medication	To prevent thrombosis, to stimulate vasodilation, to reduce pain, to prevent infection	
	Inelastic bandage	In most of the patients (if risk of damaging LVA/ LNT by putting on compression garment; First tubular bandage and cotton wool covering whole limb, then non-elastic bandages, finally other tubular bandage over bandages (to keep everything together); keep it day and night	
	Advise	As much as possible limb elevation and regularly muscle contractions	
	Registration	1) Number of days of hospitalisation 2) Material (amount): bandaging material (cotton wool, non-elastic bandages, tubular bandage); other material 3) Medication (type and amount)	
Aftercare at home	Wound control	Once a week, inelastic bandage is removed, wound is cared and bandage is re-applied	
	Advise	As long as wound is not closed, as much as possible limb elevation and regularly muscle contractions	
	Compression garment	If wound is healed, new compression garment is applied and usual care protocol is started	
	Registration	1) Number of wound control visits and duration 2) Material (amount): bandaging material (cotton wool, non-elastic bandages, tubular bandage); wound care material; other material 3) Personnel (number and duration of presence): surgeon(s); nurse(s); other personnel	

Usual care

All patients receive usual care. The patient's own (regular) physical therapist performs the usual care in a pragmatic way consisting of exercises and skin care and manual lymph drainage (MLD) (i.e. the maintenance phase of decongestive lymphatic therapy (DLT)). Nevertheless, MLD is not an evidence-based treatment modality for lymphoedema, it was added to the usual care as it stimulates lymph flow through functional lymphatics (31). Many surgeons specialised in performing reconstructive lymphatic surgery believe that performing MLD after LVA is important to keep the anastomosis open. Moreover, the physical therapist educates the patient to perform self-management, i.e. self-exercises, self-skin care, self-MLD, self-bandaging and putting on and removing the compression garment. In all patients (of intervention and control group), a new compression garment is measured by the compression specialist at baseline. The schematic overview of the usual care is given in figure 1 and is divided into four periods:

1) M1-6: From week 3 (or, in the intervention group, after healing of the wounds) the patient sees the home physical therapist twice per week and from week 5 once a week. The patient also performs self-management.

2) M7-12: The patient sees the own physical therapist once a week. The compression garment use is gradually reduced from 16h/d (end of 6th month) to 0h/d (end of 12th month). The own physical therapist performs circumference measurements of the limb weekly (i.e. with a perimeter provided by the study team) to control for changes of the limb volume(23). The patient completes a digital scoring form in REDCap weekly. The study investigator of the center checks the change of limb volume every week: if the limb volume increases $\geq 5\%$ compared to baseline, the patient is planned for an intermediate checkup in the study center. The study investigator decides whether the hours a day of wearing the compression garment has to be increased again.

3) M13-18: The patient only performs self-management and does not see the own physical therapist anymore. If possible, the patient does not wear the compression garment.

4) M19-36: The patient may choose whether he/ she visits the own physical therapist or performs self-management, or a combination.

This scheme of usual care has to be followed as strictly as possible, except when the patient's clinical situation deteriorates or risks to deteriorate. For example, a patient may visit the physical therapist more often in case of more lymphoedema-related complaints due to warm weather. Or, if during the follow-up, the clinical situation of the lymphoedema deteriorates unacceptably (e.g. there is presence of pitting oedema in the limb or there is a wound), the study investigator may advise the

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3 patient and physical therapist to perform an intensive treatment of the lymphoedema with
4 bandaging. This information has to be registered by the patient in the usual care questionnaire.
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7 To obtain standardisation of the usual care, the physical therapist of the patient receives a training
8 before the start of the study. During this training, instructions about the study protocol are given
9 orally. In addition, the physical therapist receives an informative leaflet explaining the aim and design
10 of the trial, the treatment in the intervention/ control group and the assessment of the patient. It
11 also clarifies what the study investigators expect from the patient's physical therapist and vice-versa.
12 Following information regarding the patient's physical therapist is collected: age and gender,
13 education level and experience with treating lymphoedema (number of years of experience and in
14 which modalities, type of lymphoedema education).
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23 **Outcomes**

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26 The outcome measures were chosen based on input from patients with lymphoedema (see section
27 'patient and public involvement') and on input from the investigators of this trial who have
28 experience in evaluating and treating patients with lymphoedema. Patient-reported outcomes
29 provide essential information about the patient experience with the intervention that cannot be
30 reliably captured in another way, and are necessary for the complete evaluations of risks and
31 benefits and the value of the intervention. As a consequence, the trial's primary outcome is a
32 patient-reported outcome.⁽³²⁾ Moreover, recently, Chang et al stated in their systematic review and
33 meta-analysis about the surgical treatment of lymphoedema that better designed studies are
34 necessary: with objective reporting of outcomes using quantitative methods for measuring fluid and
35 both physiologic and immunologic function during longer follow-up.⁽³³⁾
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43 Assessments are performed at baseline (A1) and at 1 month (A2), 3 months (A3), 6 months (A4), 12
44 months (A5), 18 months (A6), 24 months (A7) and 36 months (A8) post-baseline. However, to limit
45 the burden for the patients, not all outcomes are assessed at each time interval. See table 1 for the
46 overview of the outcomes per time interval and see the Appendix for the assessment method and
47 the description of the assessment per variable and outcome. Figure 1 gives an overview of the timing
48 of the baseline assessment related to the screening and to the surgery, and of the foreseen windows
49 for the follow-up assessments.
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55 At baseline, patient's demographics and information about the characteristics of the lymphoedema
56 and its treatment is collected.
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3 The primary outcome is lymphoedema-specific QoL (= problems in functioning related to
4 development of lymphoedema) at 18 months, evaluated with the Dutch or French version of the
5 Lymph-ICF questionnaire for upper or lower limb lymphoedema.(13-15, 34) Besides this patient-
6 reported outcome, the trial contains also two key secondary outcomes at 18 months that are
7 objective outcomes. These are limb volume and failure to reduce the hours a day of wearing the
8 compression garment. In addition, these outcomes will be investigated at other time points in the
9 short term (1, 3, 6, 12 months) and longer term (24 and 36 months) as a secondary outcome
10 parameter. The outcome limb volume is determined differently in participants with upper and lower
11 limb lymphoedema. Since most of the patients with upper limb lymphoedema have unilateral
12 lymphoedema, limb volume is determined as the relative excessive arm volume. As too many
13 patients with lower limb lymphoedema have bilateral lymphoedema, limb volume is determined as
14 the leg volume.

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24 Other secondary outcomes are: duration of wearing the compression garment during one week and
25 experience of the compression garment, health-related QoL, work capacity and ability, physical
26 activity level, costs related to lymphoedema and its treatment, need for intensive treatment, hand/
27 foot volume, failure to reduce the hours a day of wearing the compression garment, body weight,
28 episodes of infection previous 18 months, recurrence of cancer (in patients with history of cancer),
29 adverse events and lymphatic transport.

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Complications of surgery (in the intervention group) and information regarding usual care and self-
management are collected during the trial period as well.

There is also a follow-up contact by phone at 9M and 15M, respectively. During the phone call,
information is further collected about adverse events and complications of the surgery, about the
usual care & self-management (to check for the adherence of the patient) and about the costs
related to lymphoedema and its treatment.

To guarantee standardisation of the assessments all assessors are trained before the start of the trial.

Sample size

The sample size is calculated to have at least 90% power to detect a difference between the
intervention group receiving reconstructive surgery and the control group without surgery, on
lymphoedema-specific QoL at 18 months, separately within patients with upper limb lymphoedema
and within patients with lower limb lymphoedema. Both comparisons are considered as separate
trials and therefore alpha has been set equal to 0.05.

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3 The planned analysis to compare the groups is a constrained longitudinal data analysis (cLDA),(35)
4 using the baseline measurement and the follow-up measurements after 1, 3, 6, 12 and 18 months as
5 outcome. The primary analysis refers to the comparison after 18 months (based on a two-sided test
6 with $\alpha=0.05$). The approach is similar in spirit as an analysis of covariance (ANCOVA) but does not
7 exclude subjects with one or more missing measurements. The calculation of the required sample
8 size is based on an approach presented by Stroup.(36) Information with respect to variability of the
9 lymphoedema-specific QoL score and the correlation between the timepoints was obtained from two
10 retrospective series (130 patients with arm oedema and 83 patients with leg oedema).

11 The following assumptions have been made for the comparison of the lymphoedema-specific QoL:

- 12 - Standard deviation (SD) of the lymphoedema-specific QOL equal to 20
- 13 - Correlation between the baseline and each of the follow-up measurements equal to 0.50
- 14 - Drop-out of 5%, 10%, 15% and 20% after 1 and 3 months, 6 months, 12 months and 18, 24 and
15 36 months, respectively

16 To detect a difference of 15 points, which is a clinical important difference,(14, 15) 36 subjects are
17 required per group ($2 \times 2 \times 36 = 144$ subjects in total for the two trials) to have at least 90% power. If the
18 number of subjects would be reached before the end of the planned recruitment period of 24M,
19 recruitment will continue up to 45 subjects per group (180 subjects for the whole study) to obtain
20 more precise information, especially on the set of secondary outcomes. If the number is not attained,
21 the recruitment period will be prolonged.

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37 The sample size estimation heavily depends on estimates of variability of the lymphoedema-specific
38 QoL and the correlation with the baseline measurement. Therefore, after inclusion of 40 subjects per
39 group the already available information will be used to verify if the assumptions were plausible (note
40 however that there will be no information yet at the moment of the primary endpoint). If the
41 observed standard deviation and correlations deviate from the assumed values such that the desired
42 power level of 90% is not guaranteed anymore, an increase of the planned sample size will be
43 considered (if feasible). At the moment of this blinded interim analysis for sample size re-estimation,
44 the assumed dropout rates will also be verified. No interim analyses are planned to stop the study
45 earlier for efficacy or futility, this to avoid loss of information on the secondary endpoints.

56 Data analyses

57 Statistical analysis will comply with the Consolidated Standards of Reporting Trials (CONSORT)
58 guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarised
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3 using mean and SD and median and range values. Different analysis sets will be defined. The intent-
4 to-treat analysis set (ITT) contains all randomised patients, grouped according to the allocated
5 treatment. The modified intent-to-treat analysis set (mITT) contains all randomised patients grouped
6 according to the allocated treatment, but excluding patients who have withdrawn their consent to
7 the randomised procedure. The as-treated analysis set also contains all randomised patients but
8 grouping the patients according to their received treatment. The per-protocol analysis set contains
9 all randomised patients who received the allocated treatment. The main analyses will be performed
10 on the ITT analysis set. Results on the other analysis sets will be reported additionally.
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18 *Primary outcome*

- 19 • Lymphoedema specific QoL

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21 A constrained longitudinal data analysis (cLDA)(35) using the baseline measurement and the follow-
22 up measurements after 1 month, 3 months, 6 months, 12 months and 18 months as outcome will be
23 used to compare the mean lymphoedema specific QoL after 18 months based on a two-sided test
24 with $\alpha=0.05$. The choice of the covariance structure for the five measurements will be based on
25 the Aikake criterion.(37) Study site is added as a fixed factor in this model. For patients with a
26 recurrence of cancer in the root of the limb, only observations before the recurrence are included.
27 Since the analysis is only valid under the missing at random (MAR) assumption (the probability of a
28 missing lymphoedema-specific QoL measurement does not depend on the unobserved value),
29 sensitivity analyses will be performed allowing a non-missing at random (NMAR) mechanism. More
30 specifically, starting from the MAR model, a jump-to-reference (JR) and tipping-point (TP) analysis
31 will be applied.(38)
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42 *Key secondary outcomes*

- 43 • Change of limb volume:

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45 For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be
46 calculated. A multivariate model for the longitudinal measured ratios (7 timepoints) will be used to
47 compare (changes in) log-transformed ratios between both groups. A log transformation for the
48 ratios is used since intervals between units are not equidistant. For the leg/ foot volume, the same
49 model will be used but on the original measurements of the (most) affected limb instead of on the
50 (log-transformed) ratios versus the contralateral side (since also patients with bilateral leg volume
51 are included).
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- 57 • Duration of wearing the compression garment:

58 The same modelling approach will be used as for the primary outcome.
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Other secondary outcomes

Continuous outcomes will be analysed in a similar way as the primary outcome. Categorical (binary) data will be analysed using stratified χ^2 test and logistic regression models with general estimating equations (GEE) for repeatedly measured binary data. Adverse events and complications after surgery will be reported descriptively.

This study has been designed to permit *economic analysis* in a later phase. If reconstructive surgery is deemed superior to no surgery (i.e. is clinically effective), the next step is to investigate its cost-effectiveness by determining the incremental cost-effectiveness ratio (ICER). To determine the ICER, the costs from a healthcare payer's perspective and from a societal perspective will be considered, as well as the effectiveness by using the EQ-5D-5L questionnaire. If reconstructive surgery is proven cost-effective, the budget impact will be calculated from a reimburse perspective.

Exploratory analyses

Subgroup analyses for the primary outcome will be considered as a function of stage (stage 1 versus 2a/ 2b), primary vs secondary lymphoedema, weight (normal weight (BMI \leq 25) versus overweight (BMI $>$ 25)) and combination of reconstructive techniques (combination of LVA/ LNT versus only LVA or only LNT)

Moreover, a multivariable model will be constructed to predict the lymphoedema-specific QoL at 36 months based on 14 baseline variables. For subjects with a missing lymphoedema-specific QoL at 36 months, values will be imputed based on a multivariate longitudinal model for the lymphoedema-specific QoL measurements. A model reduction will be performed on a stacked dataset consisting of the multiple imputed data (at least 10 imputations), using a weighting scheme to account for the fraction of missing data in each covariate.⁽³⁹⁾ Considering the dropouts at 36 months, data for lymphoedema-specific QoL of 144 patients will be available.

Data security and management

A study-specific Data Management Plan has been developed by the data management team. Participant data are stored on a secure database in accordance with the General Data Protection Regulations (2018). Data are de-identified and a unique trial identification number is used on all source documents. These source documents are being checked for completeness and congruity

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3 before data entry into REDCap. All trial documentation and data will be archived for at least 20 years
4 after completion of the trial.
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7 A Risk Assessment Plan has also been made with a summary of the concerns in the trial, how they
8 were mitigated, the probability that this will occur and its impact. This finally leads to a risk score
9 (low, medium, high, critical). The concerns with highest risks are discussed during the meeting of the
10 Trial Steering Committee (during recruitment period: once each 6M; thereafter: once a year).
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17 **Trial monitoring**

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19 A separate Monitoring plan has been constructed and will be conducted periodically by trial monitors
20 (independent from trial staff). The first monitoring visit at each site will be conducted within 4-8
21 weeks following the baseline visit of the first study subject at that site. Thereafter, monitoring visits
22 will be organized at mean intervals of 6 months during recruitment, and mean intervals of 12 months
23 thereafter. The participating site will provide direct access to the trial data and to the corresponding
24 source data and documents. The trial will be monitored to ensure that it is being conducted in
25 compliance with GCP and current legislation, that written informed consent has been obtained
26 correctly, that the trial procedures have been followed as shown in the protocol, and that the data
27 have been recorded, for which the source data will be compared with the data recorded in REDCap.
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37 **ETHICS AND DISSEMINATION**

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39 The SurLym trial will be conducted in compliance with the principles of the Declaration of Helsinki,
40 the principles of GCP and in accordance with all applicable regulatory requirements. Approval has
41 been obtained for the study protocol, the informed consent forms and other related documents by
42 the main Ethical Committee of UZ Leuven (S631212) and the local Ethical Committees of UZ Gent and
43 CHU UCL Namur. Any subsequent protocol amendments will be submitted to the Ethical Committee.
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45 Furthermore, the study is approved by the Federal Agency for Medicines and Health Products
46 (EudraCT: 2021-000397-29).
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54 **Dissemination of results**

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56 The results of the study owned by the sponsor shall be disseminated as soon as possible after the
57 end of the trial, by disclosing them to the public by appropriate means, including publications in
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3 peer-reviewed scientific journals and presentations at congresses and events. Open access will be
4 ensured to all peer-reviewed scientific publications relating to the results of the study.
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9 **Acknowledgements**

10
11 We are grateful to all medical doctors for referring potential participants for inclusion in the trial. We
12 also want to thank the data management team and the representative of the clinical trial center of
13 UZ Leuven for their support. Finally, we are thankful to the patients of the advisory board and to the
14 independent expert for their valuable advises in the preparation phase and during the course of the
15 trial.
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20 **Author contributions**

21
22 ND is the chief investigator of the SurLym trial. TDV is the trial manager. ND, CR, TD are the principle
23 investigators of the 3 study sites. SF is the statistician. LG is expert in occupational medicine and will
24 supervise the economic analysis (if executed). ND, AKH, ST, BBH, IF, VVB, TDC, MDS, CR, CM, JF, TD
25 will perform the recruitment of patients. ST, KS, PF, MS, AB, BDP, LD will perform the surgical
26 procedures and follow-up. AKH, JF, VVB, TDC, MDS are responsible for the clinical assessments
27 (including lymphofluoroscopy and lymphoscintigraphy). GM, FK, AF, DD are the radiologists
28 responsible for the lymph MRI an BK is a nuclear medicine physician responsible for the
29 lymphoscintigraphy. JM, SS, GP, KVL are the independent experts in reconstructive lymphatic surgery
30 and will verify the quality of the surgical procedures. ND drafted the manuscript. All authors
31 contributed to the establishment of the protocol, revised the manuscript and provided input
32 according to their area of expertise.
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47 **Funding statement**

48
49 This study (KCE19-1245) is an independent research study funded by the Belgian Health Care
50 Knowledge Centre under the KCE Trials Programme. The views expressed in this publication are
51 those of the author(s) and not necessarily those of Belgian Health Care Knowledge Centre.
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56 **Data statement**

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58 Data will be available on reasonable request.
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Competing interests

None declared

Ethics approval

Approval is obtained by the central Ethical Committee of the University Hospitals Leuven (S63212) and by the local Ethical Committees of UZ Gent (BC-09711) and CHU UCL Namur (43/2021).

Figure legend

Figure 1 Flow diagram of the SurLym trial.

Supplemental material

Appendix Overview of the different variables and outcomes in the SurLym trial, the assessment method and the description of the method

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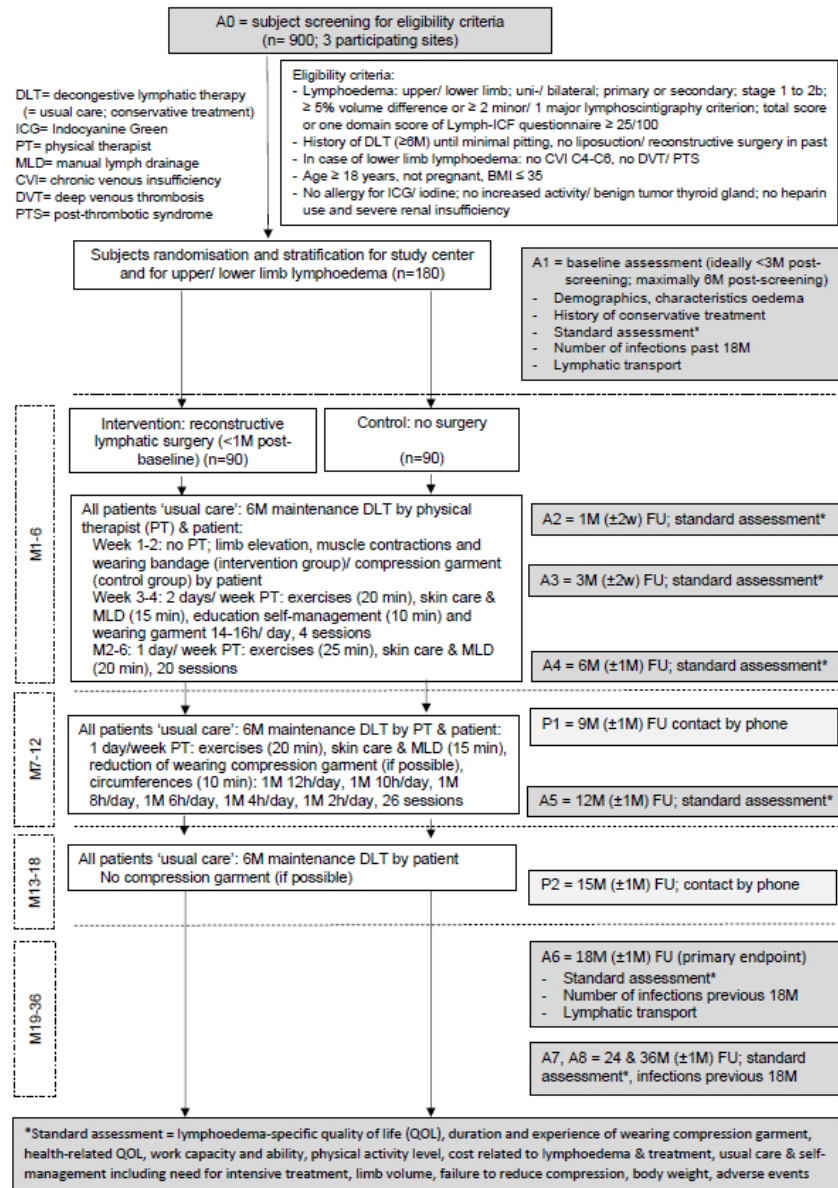


Figure 1. Flow diagram of SurLym trial

321x456mm (47 x 47 DPI)

Appendix Overview of the different variables and outcomes in the SurLym trial, the assessment method and the description of the method

Variable	Assessment method; description of method
Descriptives (15 min)	
Demographics	
Age (in years)	Medical file
Gender (man vs women), smoking status (smoking vs non-smoking), living status (alone vs together)	Interview
Body height (in m)	Stadiometer
Comorbidity (yes vs no)	Self-reported questionnaire developed by IDEWE (= external institute for prevention and protection at work); presence of wound by accident, of disease of musculoskeletal, circulatory, respiratory, neurological, digestive, urinary system, of disease of blood or skin, of mental or metabolic problems or of tumor (yes vs no)
Educational level (low vs high)	Interview; lower education = primary and secondary school, higher education = non-university higher and university
Anxiety and depression (0- 42)	Self-reported Hospital Anxiety and Depression Scale; 14 statements regarding anxiety and depression with score 0-3

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3 Characteristics of
4 lymphoedema and its
5 treatment
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9 Duration of lymphoedema
10 (in months)
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Interview

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14 Localisation of
15 lymphoedema (yes vs no)
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Inspection; for upper limb lymphoedema: hand/ lower arm/ upper arm/ trunk or

for lower limb lymphoedema: foot/ lower leg/ upper leg/ pelvic/ genital region, unilateral/ bilateral, site of lymphoedema
followed in trial: left/ right

18
19
20 Pitting status (yes vs no)
21
22

Palpation; for upper limb lymphoedema: hand/ lower arm/ upper arm/ trunk or for lower limb lymphoedema: Foot/ lower
leg/ upper leg/ pelvic/ genital region

23
24 Stage of lymphoedema (1
25 vs 2a vs 2b)
26

Inspection en palpation; Stage 1= pitting oedema that disappears with limb elevation (= reversible), 2a= pitting oedema
that does not disappear completely with limb elevation, 2b= further decrease of pitting and accumulation of fat tissue

27
28 Primary or secondary
29 lymphoedema
30

Interview and medical file; Primary = congenital; secondary = acquired after cancer-treatment (and type of cancer),
trauma, surgery, infection

31
32 History of conservative
33 treatment
34

Self-reported questionnaire (developed by author); Information regarding 1) physical therapy: number of years, number of
sessions last month/ year, content, 2) intensive treatment: where, how often, 3) other care giver, 4) self-management

35 **Primary outcome**
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 Self-reported questionnaire

(5 min)

 Lymphoedema-specific
 QoL (0-100)

 Lymph-ICF questionnaire Dutch or French version for upper or lower limb lymphoedema;(12-15) 28 and 29 questions on
 11-point scale between 0-10, total score between 0-100 (0= no problems in functioning related to the development of
 lymphoedema)

Secondary outcomes

Self-reported questionnaires

(60 min)

 Lymphoedema-specific
 QoL (0-100)

 See primary outcome; in addition, score on 5 domains, i.e. physical function, mental function, household, mobility and life
 and social life domain (0-100)

 Duration (key secondary
 outcome) and experience
 of wearing compression
 garment

 ICC compression questionnaire;(16) Dosage (0-168 hours/ week), application/ removing compression (0-10), comfort
 (score between 0-10), complication (score between 0-10), general experience (0-10)

Health related QoL

 EuroQoL-5D-5L;(17) 5 items about mobility, self-care, activity, pain and anxiety (each dimension has 5 levels: no problems,
 slight problems, moderate problems, severe problems and extreme problems), range between -0.33 for situation '33333'
 (severe problems on all items) and 1 for situation '11111' (complete healthy)

Work capacity and ability

 Work Productivity and Activity Impairment questionnaire (WPAI-GH);(18) Impairment while working due to health, overall
 work impairment due to health, activity impairment due to health (%)

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3		QuickScan 18 – short version;(19) Chance for successful socio-professional reintegration (score between 0 certainly not
4		and 5 certainly yes)
5		
6		
7	Physical activity level	International Physical Activity Questionnaire;(20) 7 questions about hours a week of vigorous (8 MET), moderate (4 MET)
8	(MET-hours a week)	and walking activities (3.3 MET), and sitting time
9		
10		
11	Costs related to	Study-specific questionnaire completed monthly by the patient; collection of patient and health care costs for material
12	lymphoedema and its	(such as compression or exercise material), medication, diagnostics or care giver (similar questionnaire as for Effort-BCRL
13	treatment (in euro)	trial)
14		
15		
16	Usual care & self-	
17	management §, including	Study-specific usual care & self-management questionnaire completed monthly by the patient; information regarding 1)
18	need for intensive	physical therapy: number of sessions, duration and content; 2) intensive treatment: where, number of sessions, content;
19	treatment	3) other care giver; 4) self-management: number of days of each modality
20		
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24	Assessment (60 min)	
25		
26		
27		Circumference measurements every 4 cm with perimeter;(21-24) limb volume is calculated with formula of truncated
28	Limb volume (key	cone, in participants with upper limb lymphoedema: assessment of affected and non-affected arm; outcome is excessive
29	secondary outcome)	arm volume (%) = $(\text{volume}_{\text{AFFECTED ARM}} - \text{volume}_{\text{UNAFFECTED ARM}} / \text{volume}_{\text{UNAFFECTED ARM}}) \times 100$, in participants with lower limb
30		lymphoedema: assessment of affected leg (= leg that is followed in trial); outcome is whole leg volume (in ml)
31		
32		
33		Water displacement method of hand or foot;(22, 25) volume is the mass of the displaced water, in participants with upper
34		limb lymphoedema: assessment of affected and non-affected hand, outcome is excessive hand volume (%); in participants
35	Hand/ foot volume	with lower limb lymphoedema: assessment of affected foot, outcome is foot volume (in ml)
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3	Failure to reduce hours a	
4	day of wearing	Assessor determines whether participant is able to reduce the hours a day of wearing the compression garment as stated
5	compression stocking (yes,	by the protocol (see figure 1, M7-12); Not able = excessive arm volume/ leg volume increased more than the smallest real
6	not able vs no, able)	difference, i.e. 5% or more compared to baseline(14)
7		
8		
9		
10	Body weight (in kg)	Scale
11		
12	Infection previous 18	
13	months (number)	Interview
14		
15	Recurrence of cancer (yes/	
16	no)	Interview and medical file; only collected in the group with history of cancer
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20		
21	Adverse events (whole	Interview and medical file; registration of adverse events related to pre-surgical or study-specific investigations: ICG
22	group) and complications	fluoroscopy, lymphoscintigraphy, lymph MRI, CT angiography, of complications of reconstructive lymphatic surgery: 1) in
23	of surgery (in intervention	general blue spot, wound healing problem, infection of wound, decrease of sensibility around wound, erysipelas of limb,
24	group) (yes/ no)	deep venous thrombosis, 2) LNT-specific seroma, lymphocele, donor site lymphoedema, loss of flap
25		
26		
27		
28		Study-specific questionnaire completed by the compression specialist after delivery of compression material; registration
29	Costs related to	of company, compression product, region of compression, type, compression class, cost for health insurance/ patient
30	lymphoedema and its	
31	treatment (in euro)	Inter Mutuality Agency (IMA) database (= agency collecting data from different mutual health insurance companies),
32		based on national number of the study participant
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36	Lymphatic transport	
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6 ICG fluoroscopy (60 min)
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ICG fluoroscopy;(26) 0.2 ml dilution of ICG/ aqua/ NaCl is injected intradermally in 1st and 4th web of affected hand or foot; procedure consist of 3 minutes of rest, 5 minutes of stimulation and registration of outcomes (=early phase) and a break until 90 minutes post-injection and again registration of outcomes (= late phase); registration of following outcomes: 1) transport out of injection sites (yes/ no), 2) dermal rerouting (no, splash, stardust and diffuse for predefined regions on arm/ leg), 3) transport out of dermal rerouting, 4) lymph nodes (yes/ no)

Lymphoscintigraphy (60 min)

Lymphoscintigraphy;(27, 28) 55MBq ^{99m}Tc nanocolloids are injected intradermally in 1st web of both hands or feet; procedure consist of following steps: 1) 25 minutes of rest, 2) 5 minutes of arm/ leg cycling and 3) early phase acquisition; 4) 60 minutes break; 5) late phase acquisition; following images are made: before and after rest an image of injection sites and at the end (outcome: extraction out of injection sites in %), after rest, cycling and at the end a mini whole body (outcomes: number of lymph nodes, intensity of lymph collectors, intensity of dermal backflow, presence of lymph collaterals), during 25 minutes of rest dynamic images of axilla/ arm or groin/ leg (outcomes: arrival time and uptake in axilla/ inguinal region in %); in addition transport index is determined, based on transport kinetics, distribution of tracer, time to visualize lymph nodes and visualization of lymph nodes/ vessels

§ No secondary outcome

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item

Page Number

Administrative information

Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Paper p1
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For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of	Paper p3
2			intended registry	
3				
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6	Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data	Paper p3
7			Set	
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11	Protocol version	#3	Date and version identifier	Paper p3
12				
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15	Funding	#4	Sources and types of financial, material, and other support	Paper p3, study
16				agreement KCE-UZ
17				Leuven
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21				
22	Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	Paper p30
23	contributorship			
24				
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28	Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	Paper p3
29	sponsor contact			
30				
31				
32	information			
33				
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35				
36	Roles and responsibilities:	#5c	Role of study sponsor and funders, if any, in study design; collection,	Protocol v3.0 p9
37	sponsor and funder		management, analysis, and interpretation of data; writing of the	
38			report; and the decision to submit the report for publication, including	
39			whether they will have ultimate authority over any of these activities	
40				
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1 Roles and responsibilities: [#5d](#) Composition, roles, and responsibilities of the coordinating centre, Protocol v3.0 p10
2 committees
3 steering committee, endpoint adjudication committee, data
4 management team, and other individuals or groups overseeing the
5 trial, if applicable (see Item 21a for data monitoring committee)
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10 Introduction

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14 Background and rationale [#6a](#) Description of research question and justification for undertaking the Paper p7
15 trial, including summary of relevant studies (published and
16 unpublished) examining benefits and harms for each intervention
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22 Background and rationale: [#6b](#) Explanation for choice of comparators Paper p6
23 choice of comparators
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27 Objectives [#7](#) Specific objectives or hypotheses Paper p7
28
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30 Trial design [#8](#) Description of trial design including type of trial (eg, parallel group, Paper p9
31 crossover, factorial, single group), allocation ratio, and framework
32 (eg, superiority, equivalence, non-inferiority, exploratory)
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38 **Methods: Participants,**
39
40 **interventions, and**
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42 **outcomes**
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1	Study setting	#9	Description of study settings (eg, community clinic, academic	Paper p9
2			hospital) and list of countries where data will be collected. Reference	
3			to where list of study sites can be obtained	
4				
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8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	Paper p10-11
9			eligibility criteria for study centres and individuals who will perform	
10			the interventions (eg, surgeons, psychotherapists)	
11				
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16	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication,	Paper p13-18
17			including how and when they will be administered	
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22	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a	Paper p13
23	modifications		given trial participant (eg, drug dose change in response to harms,	
24			participant request, or improving / worsening disease)	
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29	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any	Paper p19, Protocol v3.0
30			procedures for monitoring adherence (eg, drug tablet return;	p44
31			laboratory tests)	
32				
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37	Interventions: concomitant	#11d	Relevant concomitant care and interventions that are permitted or	Paper p18
38	care		prohibited during the trial	
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1	Outcomes	#12	Primary, secondary, and other outcomes, including the specific	Paper p19-25
2			measurement variable (eg, systolic blood pressure), analysis metric	
3			(eg, change from baseline, final value, time to event), method of	
4			aggregation (eg, median, proportion), and time point for each	
5			outcome. Explanation of the clinical relevance of chosen efficacy and	
6			harm outcomes is strongly recommended	
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15	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and	Paper figure1
16			washouts), assessments, and visits for participants. A schematic	
17			diagram is highly recommended (see Figure)	
18				
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23	Sample size	#14	Estimated number of participants needed to achieve study objectives	Paper p26
24			and how it was determined, including clinical and statistical	
25			assumptions supporting any sample size calculations	
26				
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31	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach	Paper p11-12
32			target sample size	
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36 **Methods: Assignment of**
37 **interventions (for**
38 **controlled trials)**
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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	Paper p12
16 17 18 19 20 21 22 23 24	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	Paper p12
26 27 28 29 30	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Paper p12
31 32 33 34 35 36 37	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Paper p12
39 40 41 42 43 44	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial	N/A, no blinding

1 **Methods: Data collection,**
 2
 3 **management, and analysis**
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5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Data collection plan	#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	Data management plan v2.0
21 22 23 24 25 26 27 28	Data collection plan: retention	#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	Paper p29, Risk assessment plan v1 p8-9
29 30 31 32 33 34 35 36 37	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	Data management plan v2.0
38 39 40 41 42 43 44	Statistics: outcomes	#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	Paper p27-28

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	Paper p27-28
2				
3	analyses		analyses)	
4				
5				
6	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence	Paper p27
7				
8	population and missing		(eg, as randomised analysis), and any statistical methods to handle	
9				
10	data		missing data (eg, multiple imputation)	
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14	Methods: Monitoring			
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16				
17	Data monitoring: formal	#21a	Composition of data monitoring committee (DMC); summary of its	Paper p29
18				
19	committee		role and reporting structure; statement of whether it is independent	
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29	Data monitoring: interim	#21b	Description of any interim analyses and stopping guidelines,	Paper p26
30				
31	analysis		including who will have access to these interim results and make the	
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37	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	Protocol v3.0 p46-47;
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1	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Paper p29
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9	Ethics and dissemination			
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12	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Protocol v3.0 p57
13				
14				
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16				
17	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)	Protocol v3.0 p57
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27	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Paper p11-12, Protocol v3.0 p33
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32	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
33	ancillary studies			
34				
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38	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	Paper p29, Data Management Plan p6-7
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1	Declaration of interests	#28	Financial and other competing interests for principal investigators for	Paper p30
2				
3			the overall trial and each study site	
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6	Data access	#29	Statement of who will have access to the final trial dataset, and	Data Management Plan
7				
8			disclosure of contractual agreements that limit such access for	p3-4
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10			investigators	
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14	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for	Not specified
15				
16			compensation to those who suffer harm from trial participation	
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18				
19	Dissemination policy: trial	#31a	Plans for investigators and sponsor to communicate trial results to	Paper p30, Protocol v3.0
20				
21	results		participants, healthcare professionals, the public, and other relevant	p61
22				
23			groups (eg, via publication, reporting in results databases, or other	
24				
25			data sharing arrangements), including any publication restrictions	
26				
27				
28				
29	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional	Protocol v3.0 p61, study
30				
31	authorship		writers	agreement sponsor-study
32				
33				site
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36				
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	Protocol v3.0 p61
38				
39	reproducible research		participant-level dataset, and statistical code	
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43	Appendices			
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1 2 3 4 5 6 7	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	In TMF Informed Consent Form v6.0 in Dutch and v5.0 in French
8 9 10 11 12 13 14 15	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	N/A

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