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Complete List of Authors:	Devoogdt, Nele; KU Leuven, Rehabilitation Sciences; KU Leuven University Hospitals Leuven, Center for lymphedema De Vrieze, Tessa; KU Leuven, Department of Rehabilitation Sciences Heroes, An-Kathleen; KU Leuven, Department of rehabilitation sciences; KU Leuven University Hospitals Leuven, Center for lymphedema Bechter-Hugl, Beate; KU Leuven University Hospitals Leuven, Vascular Surgery Fieuws, Steffen; Katholieke Universiteit Leuven, Biostats Godderis, Lode; KU Leuven, Centre for Environment and Health of KU Leuven Segers, Katarina; KU Leuven University Hospitals Leuven, Department of plastic and reconstructive surgery Maleux, Geert; KU Leuven University Hospitals Leuven, Department of radiology Deltombe, Thierry; CHU UCL Namur, Centre de Reference du Lymphoedème, Frippiat, Jacqueline; CHU UCL Namur, Centre de Reference du Lymphoedème, Servaes, Maxime; CHU UCL Namur Berners, Aline; CHU UCL Namur Fosseprez, Philippe; CHU UCL Namur Krug, Bruno; CHU UCL Namur Kayser, Francoise; CHU UCL Namur Falticeanu, Ana; CHU UCL Namur Randon, Caren; UZ Gent, Department of Thoracic and Vascular Surgery Monten, Chris; UZ Gent, Department of Radiotherapy Van Landuyt, Koen; UZ Gent De Pypere, Bernard; UZ Gent, Department of plastic and reconstructive surgery Degraeve, Liesl; UZ Gent, Department of plastic and reconstructive surgery Decorte, Tina; UZ Gent, Department of Physical Medicine and Rehabilitation De Schryver, Mieke; UZ Gent Van Besien, Vickie; UZ Gent Devos, Daniel; UZ Gent Suominen, Sinikka; Helsinki University Central Hospital Ayala, Jaume Masia; Universitat Internacional de Catalunya,

	Pons, Gemma; Hospital de la Santa Creu i Sant Pau, Department of plastic surgery Fourneau, Inge; KU Leuven University Hospitals Leuven, Vascular Surgery thomis, sarah; KU Leuven University Hospitals Leuven, Vascular Surgery
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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

Nele Devoogdt[1,2], Tessa De Vrieze[2], An-Kathleen Heroes[1,2], Beate Bechter-Hugl[1], Steffen Fieuws[3], Lode Godderis[4], Katarina Segers[5], Geert Maleux[6], Thierry Deltombe[7], Jacqueline Frippiat[7], Maxime Servaes[8], Aline Berners[8], Philippe Fosseprez[8], Bruno Krug[9], Francoise Kayser[9], Ana Falticeanu[10], Caren Randon[11], Chris Monten[12], Koen Van Landuyt[13], Bernard De Pypere[13], Liesl Degraeve[13], Tina Decorte[14], Mieke De Schryver[14], Vickie Van Besien[14], Daniel Devos[15], Sinikka Suominen[16], Jaume Masia[17], Gemma Pons[17], Inge Fourneau[1, ¥], Sarah Thomis[1, ¥]

[¥] Contributed equally as last author to the SurLym trial

[1]University Hospitals Leuven, Department of Vascular Surgery, Centre for Lymphedema, Leuven, Belgium

[2]KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

[3]KU Leuven – University of Leuven, Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat), Leuven, Belgium

[4]KU Leuven – University of Leuven, Centre for Environment and Health, Leuven, Flanders, Belgium

[5]University Hospitals Leuven, Department of Plastic and Reconstructive Surgery, Leuven, Belgium

[6]University Hospitals Leuven, Department of Radiology, Leuven, Belgium

[7]CHU UCL Namur – Site Godinne, Department of Physical Medicine and Rehabilitation, Centre de Reference du Lymphoedème, Yvoir, Belgium

[8]CHU UCL Namur – Site St-Elisabeth, Department of Plastic and Reconstructive Surgery, Namur, Belgium

[9]CHU UCL Namur – Site Godinne, Nuclear Medicine Department, Université catholique de Louvain, Yvoir, Belgium

[10]CHU UCL Namur – Site Godinne, Department of Radiology, Yvoir, Belgium

[11]Ghent University Hospital, Department of Thoracic and Vascular Surgery, Lymphedema Clinic, Ghent, Belgium

[12]Ghent University Hospital, Department of Radiotherapy, Lymphedema Clinic, Ghent, Belgium

[13]Ghent University Hospital, Department of Plastic and Reconstructive Surgery, Lymphedema Clinic, Ghent, Belgium

[14]Ghent University Hospital, Department of Physical Medicine and Rehabilitation, Lymphedema Clinic, Ghent, Belgium

[15]Ghent University Hospital, Department of Radiology, Ghent, Belgium

[16]Helsinki University and Helsinki University Hospital, Department of Plastic Surgery, Helsinki, Finland

[17]Hospital de la Santa Creu i Sant Pau and the Hospital del Mar of Barcelona, Department of Plastic Surgery, Barcelona, Spain

Correspondence to:

Prof. Nele Devoogdt

UZ Leuven, centre for lymphedema, Weligerveld 1, 3212 Pellenberg, Belgium

00 32 16 34 25 15

nele.devoogdt@kuleuven.be

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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 **sur**gery versus no surgery, additional to decongestive lymphatic therapy (usual care), for the treatment of **lym**phoedema, 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; ≥ 5% volume difference or ≥ 2 minor/ 1 major lymphoscintigraphy criterion; total score or one domain score of Lymph-ICF questionnaire ≥ 25/100 -History of DLT (≥6M) until minimal pitting, no liposuction/ reconstructive surgery in past

	-In case of lower limb lymphoedema: no CVI C4-C6, no DVT/ PTS -Age ≥ 18 years, not pregnant, BMI ≤ 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 a 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]

Our hypothesis is that reconstructive lymphatic surgery partially restores the lymphatic transport which leads to a decrease of the lymphoedema volume and as a result lowers the need for a compression garment. This will probably improve lymphoedema-specific quality of life.

Robust evidence on the effectiveness of reconstructive lymphatic surgery for lymphoedema has so far not been procured. In 2019, a Cochrane systematic review of Markkula et al revealed that there is not enough high-quality research investigating the effect of reconstructive lymphatic surgery on lymphoedema.[9] Only one RCT so far evaluated the effect of LNT. Dionyssiou et al randomised 36 patients with breast cancer related arm lymphoedema.[10] After surgery/no surgery, all patients first received for 6 months DLT and DLT was discontinued for the next 12 months. At 18 months follow-up, mean limb volume reduction was superior in the group with LNT compared to no LNT (57% vs 18%, $p<0.01$). In the group with LNT infections were less frequent and subjective symptoms improved. An RCT evaluating the effect of LVA has not been performed yet.

Objectives

The main objective of this study is to investigate the added value of reconstructive lymphatic surgery to decongestive lymphatic therapy (usual care) in patients with lymphoedema of the upper limb or lower limb in terms of lymphoedema-specific QoL (primary outcome), limb volume and duration of wearing the compression garment (key secondary outcomes) at 18 months and of other outcomes at 1, 3, 6, 12, 18, 24 and 36 months post-baseline (secondary outcomes; see table 1 for the outcomes).

A secondary objective is to verify whether the rate of complications in participants receiving reconstructive lymphatic surgery is acceptable and if so, whether these complications are reversible. We also verify in patients with lymphoedema due to cancer treatment, if reconstructive lymphatic surgery causes higher cancer recurrence rates.

A first exploratory objective is to compare the added value of the reconstructive surgery between different subgroups (stage 1 vs stage 2; normal weight vs overweight; combination of LVA and LNT vs one method). A second exploratory objective is to investigate predictive variables for lymphoedema-specific QoL at 36 months.

Table 1 Overview of assessment of descriptive variables and primary and secondary outcomes at each time interval

Assessment	A1 Randomisation Baseline	A2 1M	A3 3M	A4 6M	A5 12M	A6 18M	A7 24M	A8 36M
DESCRIPTIVES								
Demographics	X							
Characteristics of lymphoedema and its treatment	X							
PRIMARY OUTCOME								
Self-reported questionnaire Lymphoedema-specific QoL	X					X		
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

Assessments								
Limb volume (key secondary outcome)	X	X	X	X	X	X	X	X
Hand/ foot volume	X	X	X	X	X	X	X	X
Failure to reduce hours a day of wearing compression stocking					X	X	X	X
Body weight	X	X	X	X	X	X	X	X
Infection previous 18 months	X					X		X
Recurrence of cancer						X		X
Adverse events and complications of surgery		X	X	X	X	X	X	X
Lymphatic transport								
ICG fluoroscopy	X					X		
Lymphoscintigraphy	X					X		

* Information is collected on a monthly basis

§ No secondary outcome

METHODS AND ANALYSIS

Described according to the SPIRIT guidelines.

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

Eligibility criteria

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

1) Unilateral or bilateral, primary or secondary lymphoedema of the upper or lower limb;

2) If cancer-related lymphoedema, approval for participation from the multidisciplinary oncological board; participation only if estimated cancer-related survival is ≥3 years and no concerns on oncological safety are raised;

3) Lymphoedema stage 1 to 2b (according to staging 1-3 of International Society of Lymphology)[5];

4) Objective diagnosis of lymphoedema: ≥ 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: ≥ 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

(summary)' document. In addition, the patient receives an appointment for the screening (A0). Some patients are informed about the trial through another way, e.g. by their oncologist. In that case, the patient contacts the study coordinator by phone, who performs the fast eligibility check and discusses the study during the phone call. If the patient is interested to participate, the Informed Consent Form and the 'study at a glance' document is sent. In addition, the patient receives an appointment for the screening (A0).

During the *screening appointment* (A0), patients receive all information and explanation they request or need before signing the Informed Consent Form. Thereafter, the complete screening procedure is executed to verify whether the participant fulfils all eligibility criteria.

In order to optimally recruit patients with lymphoedema, the study is presented inside (at other departments) as well as outside the hospitals of the study centers by lectures, posters and mailing. Potential candidates with lymphoedema as well as their treating physicians, physical therapists and other health care providers are informed about the trial (through social media, publication in local journals and on websites).

Allocation and randomisation

Given the nature of the trial, *blinding* of participants and care providers (surgeon/ physical therapist/ compression specialist) is not feasible. Because the participants fill out different questionnaires to determine the primary outcome and some of the secondary outcomes, detection bias may be a potential risk. However, bias of the participants will be limited as much as possible because the study will be explained by a neutral person (physical therapists ND, AKH, VVB, MDS, JF or physical medicine & rehabilitation physician TD (hospital of Ghent), TD (hospital of CHU UCL)).

The *randomisation* is computer generated. To obtain concealment of allocation, the randomisation list is prepared by the trial's statistician (SF) and is incorporated in the data management tool 'REDCap'. Randomisation is performed by using varying block sizes. A 1:1 allocation ratio is applied. A stratification is applied for study centre (UZ Leuven vs UZ gent vs CHU-UCL Namur) and for region of lymphoedema (upper limb vs lower limb, with a ratio 1:1). At each participating site, only the chief investigator (ND) and trial manager (TDV), investigators and study coordinators have access to the randomisation tool in REDCap. After randomisation, the study coordinator of the specific study centre plans the intervention if applicable (surgery), as well as the usual care and the follow-up assessments.

After all patients have finished the trial and the database is locked to analyse the data, the randomisation code will be broken.

Intervention

All participants are randomised to the intervention or control group. The intervention group is treated with reconstructive lymphatic surgery in addition to conservative DLT (decongestive lymphatic therapy; usual care). In the control group patients only receive conservative DLT (usual care) without surgery (see figure 1).

The researchers will follow the protocol as strictly as possible. However, since the pragmatic nature of the trial, a deviation of the protocol is allowed if necessary. This protocol deviation has to be registered in the protocol deviation log.

Reconstructive lymphatic surgery

The intervention treatment is reconstructive lymphatic surgery and is performed by the team of vascular and/ or plastic surgeons from each study center (ST and KT of UZ Leuven; BDP and LD of Ghent University Hospital; and MS, AB and PF of CHU UCL Namur). As reconstructive technique, a lymphovenous anastomosis (LVA), lymph node transfer (LNT) or a combination of both is applied. The choice of the technique is determined by the surgeons of the study centre. See table 2 for the clinical reasoning for each procedure and the technical description of the reconstructive procedure.

To obtain standardisation and to ascertain the quality of the reconstructive lymphatic surgery, all surgeons received training in the Reconstructive Microsurgery European School (by JM and GP) in May 2021. Moreover, to improve standardisation of the patient selection and the reconstructive lymphatic procedure between the surgeons and between the centres, every patient that is planned for surgery in the trial is discussed during a monthly meeting with at least one surgeon per centre attending. A final quality control measure is that the first 10 surgical procedures are discussed with the whole surgical team including the independent experts JM, GP, SS and KVL.

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 1st 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	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.	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	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	

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 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	

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.

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/w (end of 6th month) to 0h/w (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[12]. 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 ≥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.

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

Outcomes

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

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

The primary outcome is lymphoedema-specific QoL (= problems in functioning related to development of lymphoedema) at 18 months, evaluated with the Dutch or French version of the Lymph-ICF questionnaire for upper or lower limb lymphoedema.[11 14-16] In addition, the lymphoedema-specific QoL will be investigated at other time points in the short term (1, 3, 6, 12 months) and longer term (24 and 36 months) as a secondary outcome parameter.

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

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.

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

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;[11 14 15 18] 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 ;[19] 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;[20] 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); Impairment while working due to health, overall work impairment due to health, activity impairment due to health (%)
	QuickScan 18 – short version;[21] Chance for successful socio-professional reintegration (score between 0 certainly not and 5

	certainly yes)
Physical activity level (MET-hours a week)	International Physical Activity Questionnaire;[22] 7 questions about hours a week of vigorous (8 MET), moderate (4 MET) and walking activities (3.3 MET), and sitting time
Costs related to lymphoedema and its treatment (in euro)	Study-specific questionnaire completed monthly by the patient; collection of patient and health care costs for material (such as compression or exercise material), medication, diagnostics or care giver (similar questionnaire as for Effort-BCRL trial)[23]
Usual care & self-management §, including need for intensive treatment	Study-specific usual care & self-management questionnaire completed monthly by the patient; information regarding 1) physical therapy: number of sessions, duration and content; 2) intensive treatment: where, number of sessions, content; 3) other care giver; 4) self-management: number of days of each modality
Assessment (60 min)	
Limb volume (key secondary outcome)	Circumference measurements every 4 cm with perimeter;[12 24-26] limb volume is calculated with formula of truncated cone,[24 26] in participants with upper limb lymphoedema: assessment of affected and non-affected arm; outcome is excessive arm volume (%) = (volume $_{\text{AFFECTED ARM}}$ – volume $_{\text{UNAFFECTED ARM}}$/ volume $_{\text{UNAFFECTED ARM}}$) x 100, in participants with lower limb lymphoedema: assessment of affected leg (= leg that is followed in trial); outcome is whole leg volume (in ml)
Hand/ foot volume	Water displacement method of hand or foot;[25 27] volume is the mass of the displaced water, in participants with upper limb lymphoedema: assessment of affected and non-affected hand, outcome is excessive hand volume (%); in participants with lower limb lymphoedema: assessment of affected foot, outcome is foot volume (in ml)
Failure to reduce hours a day of wearing	Assessor determines whether participant is able to reduce the hours a day of wearing the compression garment as stated by the protocol (see figure 1, M7-12); Not able = excessive arm volume/ leg volume increased more than the smallest real

compression stocking (yes, not able vs no, able)	difference, i.e. 5% or more compared to baseline[12]
Body weight (in kg)	Scale
Infection previous 18 months (number)	Interview
Recurrence of cancer (yes/ no)	Interview and medical file; only collected in the group with history of cancer
Adverse events (whole group) and complications of surgery (in intervention group) (yes/ no)	Interview and medical file; registration of adverse events related to pre-surgical or study-specific investigations: ICG fluoroscopy, lymphoscintigraphy, lymph MRI, CT angiography, of complications of reconstructive lymphatic surgery: 1) in general blue spot, wound healing problem, infection of wound, decrease of sensibility around wound, erysipelas of limb, deep venous thrombosis, 2) LNT-specific seroma, lymphocele, donor site lymphoedema, loss of flap
Costs related to lymphoedema and its treatment (in euro)	Study-specific questionnaire completed by the compression specialist after delivery of compression material; registration of company, compression product, region of compression, type, compression class, cost for health insurance/ patient Inter Mutuality Agency (IMA) database (= agency collecting data from different mutual health insurance companies), based on national number of the study participant
Lymphatic transport	
ICG fluoroscopy (60 min)	ICG fluoroscopy;[28] 0.2 ml dilution of ICG/ aqua/ NaCl is injected 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;[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 clinical important difference,[11 15] 36 subjects are required per group (2x2x36=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,

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

Data analyses

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

Primary outcome

- Lymphoedema specific QoL

A constrained longitudinal data analysis (cLDA)[30] using the baseline measurement and the follow-up measurements after 1 month, 3 months, 6 months, 12 months and 18 months as outcome will be used to compare the mean lymphoedema specific QoL after 18 months based on a two-sided test with alpha=0.05. The choice of the covariance structure for the five measurements will be based on the Aikake criterion. Study site is added as a fixed factor in this model. For patients with a recurrence of cancer in the root of the limb, only observations before the recurrence are included.
Since the analysis is only valid under the missing at random (MAR) assumption (the probability of a missing lymphoedema-specific QoL measurement does not depend on the unobserved value), sensitivity analyses will be performed allowing a non-missing at random (NMAR) mechanism. More specifically, starting from the MAR model, a jump-to-reference (JR) and tipping-point (TP) analysis will be applied.[32]

Key secondary outcomes

- Change of limb volume:

For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be calculated. A multivariate model for the longitudinal measured ratios (7 timepoints) will be used to

compare (changes in) log-transformed ratios between both groups. A log transformation for the ratios is used since intervals between units are not equidistant. For the leg/ foot volume, the same model will be used but on the original measurements of the (most) affected limb instead of on the (log-transformed) ratios versus the contralateral side (since also patients with bilateral leg volume 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 ≤ 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.

Furthermore, the study is approved by the Federal Agency for Medicines and Health Products (EudraCT: 2021-000397-29).

Dissemination of results

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

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).

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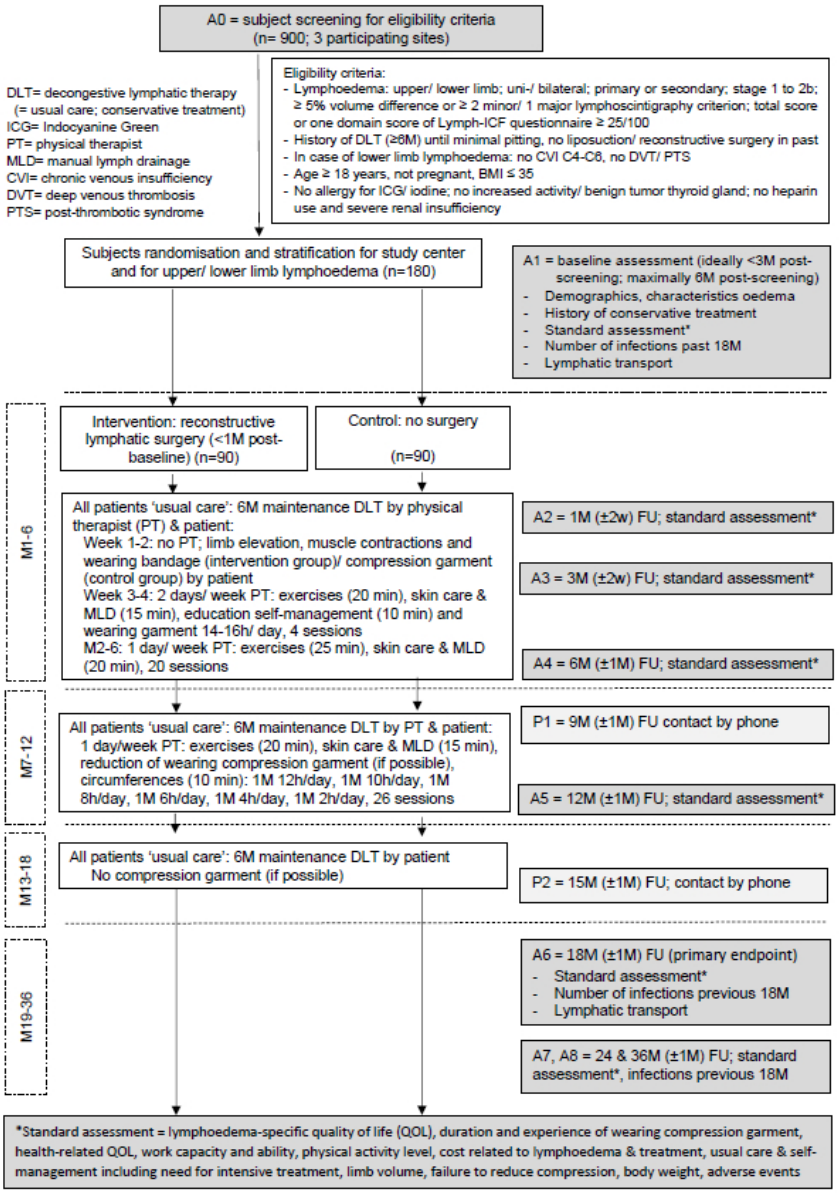

Figure 1. Flow diagram of SurLym trial

321x456mm (47 x 47 DPI)

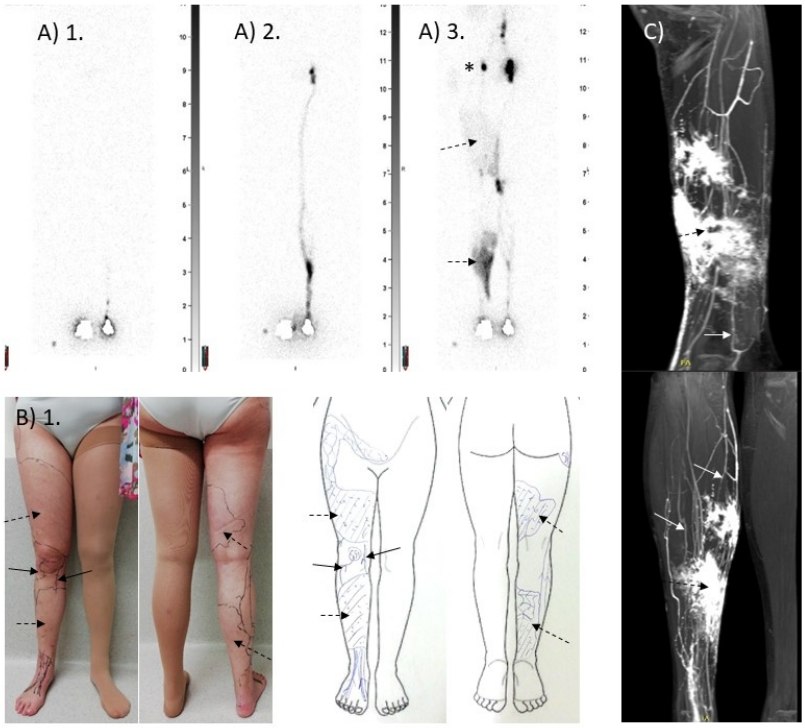

Figure 2 Woman, 57 years old, secondary lymphoedema right leg (> left leg) and midline, developed after inguinal and pelvic lymph node dissection and radio-chemotherapy for vulvar cancer;
Preoperative investigations: A) lymphoscintigraphy in 3 phases: 1. early phase after rest, 2. early phase after activity (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.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Paper p1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Paper p3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Paper p3
Protocol version	#3	Date and version identifier	Paper p3
Funding	#4	Sources and types of financial, material, and other support	Paper p3, study agreement KCE-UZ Leuven
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Paper p30
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Paper p3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Protocol v3.0 p9

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol v3.0 p10
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Paper p7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Paper p6
Objectives	#7	Specific objectives or hypotheses	Paper p7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Paper p9
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Paper p9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Paper p10-11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Paper p13-18
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Paper p13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Paper p19, Protocol v3.0 p44
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Paper p18

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Paper p19-25
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Paper figure1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Paper p26
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Paper p11-12
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Paper p12
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
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Paper p12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Paper p12
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

Methods: Data collection, management, and analysis			
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
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
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
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

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Paper p27-28
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Paper p27
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Paper p29
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Paper p26
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Protocol v3.0 p46-47; manual adverse events

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
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Protocol v3.0 p57
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
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
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Paper p30
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data Management Plan p3-4
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not specified
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Paper p30, Protocol v3.0 p61
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol v3.0 p61, study agreement sponsor-study site
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol v3.0 p61

Appendices

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
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

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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Complete List of Authors:	Devoogdt, Nele; KU Leuven, Rehabilitation Sciences; KU Leuven University Hospitals Leuven, Center for lymphedema De Vrieze, Tessa; KU Leuven, Department of Rehabilitation Sciences Heroes, An-Kathleen; KU Leuven, Department of rehabilitation sciences; KU Leuven University Hospitals Leuven, Center for lymphedema Bechter-Hugl, Beate; KU Leuven University Hospitals Leuven, Vascular Surgery Fieuws, Steffen; Katholieke Universiteit Leuven, Biostats Godderis, Lode; KU Leuven, Centre for Environment and Health of KU Leuven Segers, Katarina; KU Leuven University Hospitals Leuven, Department of plastic and reconstructive surgery Maleux, Geert; KU Leuven University Hospitals Leuven, Department of radiology Deltombe, Thierry; CHU UCL Namur, Centre de Reference du Lymphoedème, Frippiat, Jacqueline; CHU UCL Namur, Centre de Reference du Lymphoedème, Servaes, Maxime; CHU UCL Namur Berners, Aline; CHU UCL Namur Fosseprez, Philippe; CHU UCL Namur Krug, Bruno; CHU UCL Namur Kayser, Francoise; CHU UCL Namur Falticeanu, Ana; CHU UCL Namur Randon, Caren; UZ Gent, Department of Thoracic and Vascular Surgery Monten, Chris; UZ Gent, Department of Radiotherapy Van Landuyt, Koen; UZ Gent De Pypere, Bernard; UZ Gent, Department of plastic and reconstructive surgery Degraeve, Liesl; UZ Gent, Department of plastic and reconstructive surgery Decorte, Tina; UZ Gent, Department of Physical Medicine and Rehabilitation De Schryver, Mieke; UZ Gent Van Besien, Vickie; UZ Gent Devos, Daniel; UZ Gent Suominen, Sinikka; Helsinki University Central Hospital Ayala, Jaume Masia; Universitat Internacional de Catalunya,

	Pons, Gemma; Hospital de la Santa Creu i Sant Pau, Department of plastic surgery Fourneau, Inge; KU Leuven University Hospitals Leuven, Vascular Surgery thomis, sarah; KU Leuven University Hospitals Leuven, Vascular Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Surgery
Keywords:	Vascular medicine < INTERNAL MEDICINE, Plastic & reconstructive surgery < SURGERY, VASCULAR SURGERY

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

Nele Devoogdt[1,2], Tessa De Vrieze[2], An-Kathleen Heroes[1,2], Beate Bechter-Hugl[1], Steffen Fieuws[3], Lode Godderis[4], Katarina Segers[5], Geert Maleux[6], Thierry Deltombe[7], Jacqueline Frippiat[7], Maxime Servaes[8], Aline Berners[8], Philippe Fosseprez[8], Bruno Krug[9], Francoise Kayser[9], Ana Falticeanu[10], Caren Randon[11], Chris Monten[12], Koen Van Landuyt[13], Bernard De Pypere[13], Liesl Degraeve[13], Tina Decorte[14], Mieke De Schryver[14], Vickie Van Besien[14], Daniel Devos[15], Sinikka Suominen[16], Jaume Masia[17], Gemma Pons[17], Inge Fourneau[1, ¥], Sarah Thomis[1, ¥]

[¥] Contributed equally as last author to the SurLym trial

[1]University Hospitals Leuven, Department of Vascular Surgery, Centre for Lymphedema, Leuven, Belgium

[2]KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

[3]KU Leuven – University of Leuven, Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat), Leuven, Belgium

[4]KU Leuven – University of Leuven, Centre for Environment and Health, Leuven, Flanders, Belgium

[5]University Hospitals Leuven, Department of Plastic and Reconstructive Surgery, Leuven, Belgium

[6]University Hospitals Leuven, Department of Radiology, Leuven, Belgium

[7]CHU UCL Namur – Site Godinne, Department of Physical Medicine and Rehabilitation, Centre de Reference du Lymphoedème, Yvoir, Belgium

[8]CHU UCL Namur – Site St-Elisabeth, Department of Plastic and Reconstructive Surgery, Namur, Belgium

[9]CHU UCL Namur – Site Godinne, Nuclear Medicine Department, Université catholique de Louvain, Yvoir, Belgium

[10]CHU UCL Namur – Site Godinne, Department of Radiology, Yvoir, Belgium

[11]Ghent University Hospital, Department of Thoracic and Vascular Surgery, Lymphedema Clinic, Ghent, Belgium

[12]Ghent University Hospital, Department of Radiotherapy, Lymphedema Clinic, Ghent, Belgium

[13]Ghent University Hospital, Department of Plastic and Reconstructive Surgery, Lymphedema Clinic, Ghent, Belgium

[14]Ghent University Hospital, Department of Physical Medicine and Rehabilitation, Lymphedema Clinic, Ghent, Belgium

[15]Ghent University Hospital, Department of Radiology, Ghent, Belgium

[16]Helsinki University and Helsinki University Hospital, Department of Plastic Surgery, Helsinki, Finland

[17]Hospital de la Santa Creu i Sant Pau and the Hospital del Mar of Barcelona, Department of Plastic Surgery, Barcelona, Spain

Correspondence to:

Prof. Nele Devoogdt

UZ Leuven, centre for lymphedema, Weligerveld 1, 3212 Pellenberg, Belgium

00 32 16 34 25 15

nele.devoogdt@kuleuven.be

Support statement: TDV is a post-doctoral research fellow of the Research Foundation – Flanders (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 **sur**gery versus no surgery, additional to decongestive lymphatic therapy (usual care), for the treatment of **lym**phoedema, 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; ≥ 5% volume difference or ≥ 2 minor/ 1 major lymphoscintigraphy criterion; total score or one domain score of Lymph-ICF questionnaire ≥ 25/100 -History of DLT (≥6M) until minimal pitting, no liposuction/ reconstructive surgery in past

	-In case of lower limb lymphoedema: no CVI C4-C6, no DVT/ PTS -Age ≥ 18 years, not pregnant, BMI ≤ 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 a 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)

Our hypothesis is that reconstructive lymphatic surgery partially restores the lymphatic transport which leads to a decrease of the lymphoedema volume and as a result lowers the need for a compression garment. This will probably improve lymphoedema-specific quality of life.

Robust evidence on the effectiveness of reconstructive lymphatic surgery for lymphoedema has so far not been procured. In 2019, a Cochrane systematic review of Markkula et al revealed that there is not enough high-quality research investigating the effect of reconstructive lymphatic surgery on lymphoedema.(10) Only one RCT so far evaluated the effect of LNT. Dionyssiou et al randomised 36 patients with breast cancer related arm lymphoedema.(11) After surgery/no surgery, all patients first received for 6 months DLT and DLT was discontinued for the next 12 months. At 18 months follow-up, mean limb volume reduction was superior in the group with LNT compared to no LNT (57% vs 18%, $p<0.01$). In the group with LNT infections were less frequent and subjective symptoms improved. An RCT evaluating the effect of LVA has not been performed yet.

Objectives

The main objective of this study is to investigate the added value of reconstructive lymphatic surgery to decongestive lymphatic therapy (usual care) in patients with lymphoedema of the upper limb or lower limb in terms of lymphoedema-specific QoL (primary outcome), limb volume and duration of wearing the compression garment (key secondary outcomes) at 18 months and of other outcomes at 1, 3, 6, 12, 18, 24 and 36 months post-baseline (secondary outcomes; see table 1 for the outcomes).

A secondary objective is to verify whether the rate of complications in participants receiving reconstructive lymphatic surgery is acceptable and if so, whether these complications are reversible. We also verify in patients with lymphoedema due to cancer treatment, if reconstructive lymphatic surgery causes higher cancer recurrence rates.

A first exploratory objective is to compare the added value of the reconstructive surgery between different subgroups (stage 1 vs stage 2; normal weight vs overweight; combination of LVA and LNT vs one method). A second exploratory objective is to investigate predictive variables for lymphoedema-specific QoL at 36 months.

Table 1 Overview of the primary and secondary outcomes and the assessment method at each time interval

Outcome	Method	A1 Baseline	A2, 3, 4 1, 3, 6M	A5 12M	A6 18M	A7 24M	A8 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

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

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

Eligibility criteria

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

1) Unilateral or bilateral, primary or secondary lymphoedema of the upper or lower limb;

2) If cancer-related lymphoedema, approval for participation from the multidisciplinary oncological board; participation only if estimated cancer-related survival is ≥3 years and no concerns on oncological safety are raised;

3) Lymphoedema stage 1 to 2 (according to staging 1-3 of International Society of Lymphology)(5);

4) Objective diagnosis of lymphoedema: ≥ 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: ≥ 25/ 100 (= moderate level of problems in functioning related to the development of lymphoedema)(14);

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 (summary)' document. In addition, the patient receives an appointment for the screening (A0). Some patients are informed about the trial through another way, e.g. by their oncologist. In that case, the patient contacts the study coordinator by phone, who performs the fast eligibility check and discusses the study during the phone call. If the patient is interested to participate, the Informed Consent Form and the 'study at a glance' document is sent. In addition, the patient receives an appointment for the screening (A0).

During the *screening appointment* (A0), patients receive all information and explanation they request or need before signing the Informed Consent Form. Thereafter, the complete screening procedure is executed to verify whether the participant fulfils all eligibility criteria.

In order to optimally recruit patients with lymphoedema, the study is presented inside (at other departments) as well as outside the hospitals of the study centers by lectures, posters and mailing. Potential candidates with lymphoedema as well as their treating physicians, physical therapists and other health care providers are informed about the trial (through social media, publication in local journals and on websites).

Allocation and randomisation

Given the nature of the trial, *blinding* of participants and care providers (surgeon/ physical therapist/ compression specialist) is not feasible. Because the participants fill out different questionnaires to determine the primary outcome and some of the secondary outcomes, detection bias may be a potential risk. However, bias of the participants will be limited as much as possible because the study

will be explained by a neutral person (physical therapists ND, AKH, VVB, MDS, JF or physical medicine & rehabilitation physician TD (hospital of Ghent), TD (hospital of CHU UCL)).

The *randomisation* is computer generated. To obtain concealment of allocation, the randomisation list is prepared by the trial's statistician (SF) and is incorporated in the data management tool 'REDCap'. Randomisation is performed by using varying block sizes. A 1:1 allocation ratio is applied. A stratification is applied for study centre (UZ Leuven vs UZ gent vs CHU-UCL Namur) and for region of lymphoedema (upper limb vs lower limb, with a ratio 1:1). At each participating site, only the chief investigator (ND) and trial manager (TDV), investigators and study coordinators have access to the randomisation tool in REDCap. After randomisation, the study coordinator of the specific study centre plans the intervention if applicable (surgery), as well as the usual care and the follow-up assessments.

After all patients have finished the trial and the database is locked to analyse the data, the randomisation code will be broken.

Intervention

All participants are randomised to the intervention or control group. The intervention group is treated with reconstructive lymphatic surgery in addition to conservative DLT (decongestive lymphatic therapy; usual care). In the control group patients only receive conservative DLT (usual care) without surgery (see figure 1).

The researchers will follow the protocol as strictly as possible. However, since the pragmatic nature of the trial, a deviation of the protocol is allowed if necessary. This protocol deviation has to be registered in the protocol deviation log.

Reconstructive lymphatic surgery

The intervention treatment is reconstructive lymphatic surgery and is performed by the team of vascular and/ or plastic surgeons from each study center (ST and KT of UZ Leuven; BDP and LD of Ghent University Hospital; and MS, AB and PF of CHU UCL Namur). As reconstructive technique, a lymphovenous anastomosis (LVA), lymph node transfer (LNT) or a combination of both is applied. The choice of the technique is determined by the surgeons of the study centre. See table 2 for the overview of the preparation and for the technical description of the reconstructive procedure (which is based on Chang et al).(7) In table 3 the aftercare is discussed.

To obtain standardisation and to ascertain the quality of the reconstructive lymphatic surgery, all surgeons received training in the Reconstructive Microsurgery European School (by JM and GP) in May 2021. Moreover, to improve standardisation of the patient selection and the reconstructive lymphatic procedure between the surgeons and between the centres, every patient that is planned for surgery in the trial is discussed during a monthly meeting with at least one surgeon per centre attending. A final quality control measure is that the first 10 surgical procedures are discussed with the whole surgical team including the independent experts JM, GP, SS and KVL.

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 1st 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	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.	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	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	

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 ≥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.

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

Outcomes

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

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

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

The primary outcome is lymphoedema-specific QoL (= problems in functioning related to development of lymphoedema) at 18 months, evaluated with the Dutch or French version of the Lymph-ICF questionnaire for upper or lower limb lymphoedema.(13-15, 32) Besides this patient-

reported outcome, the trial contains also two key secondary outcomes at 18 months that are objective outcomes. These are limb volume and failure to reduce the hours a day of wearing the compression garment. In addition, these outcomes will be investigated at other time points in the short term (1, 3, 6, 12 months) and longer term (24 and 36 months) as a secondary outcome parameter. The outcome limb volume is determined differently in participants with upper and lower limb lymphoedema. Since most of the patients with upper limb lymphoedema have unilateral lymphoedema, limb volume is determined as the relative excessive arm volume. As too many patients with lower limb lymphoedema have bilateral lymphoedema, limb volume is determined as the leg volume.

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

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

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.(34) 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 clinical important difference,(14, 15) 36 subjects are required per group (2x2x36=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, the assumed dropout rates will also be verified. No interim analyses are planned to stop the study earlier for efficacy or futility, this to avoid loss of information on the secondary endpoints.

Data analyses

Statistical analysis will comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarised using mean and SD and median and range values. Different analysis sets will be defined. The intent-to-treat analysis set (ITT) contains all randomised patients, grouped according to the allocated treatment. The modified intent-to-treat analysis set (mITT) contains all randomised patients grouped

according to the allocated treatment, but excluding patients who have withdrawn their consent to the randomised procedure. The as-treated analysis set also contains all randomised patients but grouping the patients according to their received treatment. The per-protocol analysis set contains all randomised patients who received the allocated treatment. The main analyses will be performed on the ITT analysis set. Results on the other analysis sets will be reported additionally.

Primary outcome

- Lymphoedema specific QoL

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

Key secondary outcomes

- Change of limb volume:

For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be calculated. A multivariate model for the longitudinal measured ratios (7 timepoints) will be used to compare (changes in) log-transformed ratios between both groups. A log transformation for the ratios is used since intervals between units are not equidistant. For the leg/ foot volume, the same model will be used but on the original measurements of the (most) affected limb instead of on the (log-transformed) ratios versus the contralateral side (since also patients with bilateral leg volume 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 ≤ 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.(37) 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. Furthermore, the study is approved by the Federal Agency for Medicines and Health Products (EudraCT: 2021-000397-29).

Dissemination of results

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

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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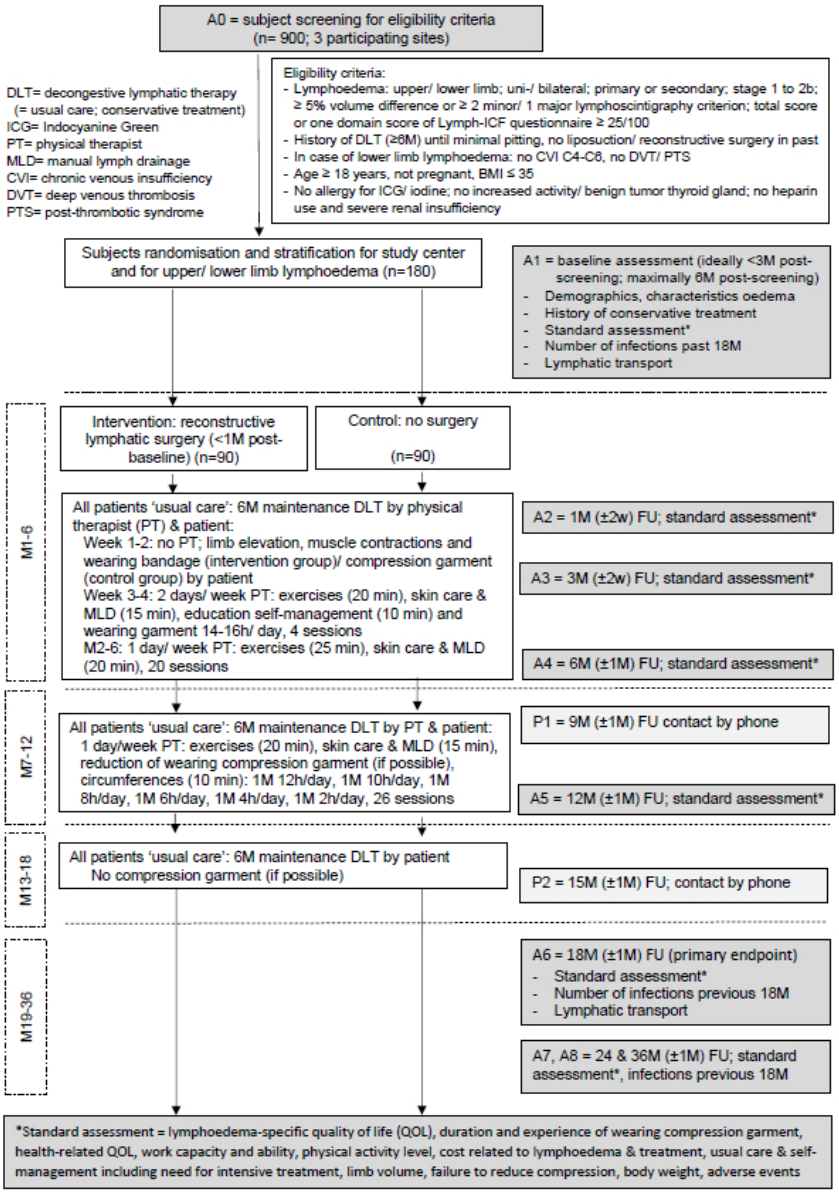

Figure 1. Flow diagram of SurLym trial

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

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 (%)

	QuickScan 18 – short version;(19) Chance for successful socio-professional reintegration (score between 0 certainly not and 5 certainly yes)
Physical activity level (MET-hours a week)	International Physical Activity Questionnaire;(20) 7 questions about hours a week of vigorous (8 MET), moderate (4 MET) and walking activities (3.3 MET), and sitting time
Costs related to lymphoedema and its treatment (in euro)	Study-specific questionnaire completed monthly by the patient; collection of patient and health care costs for material (such as compression or exercise material), medication, diagnostics or care giver (similar questionnaire as for Effort-BCRL trial)
Usual care & self-management §, including need for intensive treatment	Study-specific usual care & self-management questionnaire completed monthly by the patient; information regarding 1) physical therapy: number of sessions, duration and content; 2) intensive treatment: where, number of sessions, content; 3) other care giver; 4) self-management: number of days of each modality
Assessment (60 min)	
Limb volume (key secondary outcome)	Circumference measurements every 4 cm with perimeter;(21-24) limb volume is calculated with formula of truncated cone, in participants with upper limb lymphoedema: assessment of affected and non-affected arm; outcome is excessive arm volume (%) = (volume $_{\text{AFFECTED ARM}}$ – volume $_{\text{UNAFFECTED ARM}}$/ volume $_{\text{UNAFFECTED ARM}}$) x 100, in participants with lower limb lymphoedema: assessment of affected leg (= leg that is followed in trial); outcome is whole leg volume (in ml)
Hand/ foot volume	Water displacement method of hand or foot;(22, 25) volume is the mass of the displaced water, in participants with upper limb lymphoedema: assessment of affected and non-affected hand, outcome is excessive hand volume (%); in participants with lower limb lymphoedema: assessment of affected foot, outcome is foot volume (in ml)

Failure to reduce hours a day of wearing compression stocking (yes, not able vs no, able)	Assessor determines whether participant is able to reduce the hours a day of wearing the compression garment as stated by the protocol (see figure 1, M7-12); Not able = excessive arm volume/ leg volume increased more than the smallest real difference, i.e. 5% or more compared to baseline(14)
Body weight (in kg)	Scale
Infection previous 18 months (number)	Interview
Recurrence of cancer (yes/ no)	Interview and medical file; only collected in the group with history of cancer
Adverse events (whole group) and complications of surgery (in intervention group) (yes/ no)	Interview and medical file; registration of adverse events related to pre-surgical or study-specific investigations: ICG fluoroscopy, lymphoscintigraphy, lymph MRI, CT angiography, of complications of reconstructive lymphatic surgery: 1) in general blue spot, wound healing problem, infection of wound, decrease of sensibility around wound, erysipelas of limb, deep venous thrombosis, 2) LNT-specific seroma, lymphocele, donor site lymphoedema, loss of flap
Costs related to lymphoedema and its treatment (in euro)	Study-specific questionnaire completed by the compression specialist after delivery of compression material; registration of company, compression product, region of compression, type, compression class, cost for health insurance/ patient Inter Mutuality Agency (IMA) database (= agency collecting data from different mutual health insurance companies), based on national number of the study participant
Lymphatic transport	

ICG fluoroscopy (60 min)	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 SPIRITreporting 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

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Paper p3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Paper p3
Protocol version	#3	Date and version identifier	Paper p3
Funding	#4	Sources and types of financial, material, and other support	Paper p3, study agreement KCE-UZ Leuven
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Paper p30
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Paper p3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Protocol v3.0 p9

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol v3.0 p10
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Paper p7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Paper p6
Objectives	#7	Specific objectives or hypotheses	Paper p7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Paper p9
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Paper p9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Paper p10-11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Paper p13-18
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Paper p13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Paper p19, Protocol v3.0 p44
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Paper p18

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Paper p19-25
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Paper figure1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Paper p26
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Paper p11-12
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Paper p12
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
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Paper p12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Paper p12
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

Methods: Data collection, management, and analysis			
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
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
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
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

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Paper p27-28
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Paper p27
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Paper p29
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Paper p26
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Protocol v3.0 p46-47; manual adverse events

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
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Protocol v3.0 p57
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
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
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Paper p30
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data Management Plan p3-4
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not specified
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Paper p30, Protocol v3.0 p61
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol v3.0 p61, study agreement sponsor-study site
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol v3.0 p61

Appendices

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
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

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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Complete List of Authors:	Devoogdt, Nele; KU Leuven, Rehabilitation Sciences; KU Leuven University Hospitals Leuven, Center for lymphedema De Vrieze, Tessa; KU Leuven, Department of Rehabilitation Sciences Heroes, An-Kathleen; KU Leuven, Department of rehabilitation sciences; KU Leuven University Hospitals Leuven, Center for lymphedema Bechter-Hugl, Beate; KU Leuven University Hospitals Leuven, Vascular Surgery Fieuws, Steffen; Katholieke Universiteit Leuven, Biostats Godderis, Lode; KU Leuven, Centre for Environment and Health of KU Leuven Segers, Katarina; KU Leuven University Hospitals Leuven, Department of plastic and reconstructive surgery Maleux, Geert; KU Leuven University Hospitals Leuven, Department of radiology Deltombe, Thierry; CHU UCL Namur, Centre de Reference du Lymphoedème, Frippiat, Jacqueline; CHU UCL Namur, Centre de Reference du Lymphoedème, Servaes, Maxime; CHU UCL Namur Berners, Aline; CHU UCL Namur Fosseprez, Philippe; CHU UCL Namur Krug, Bruno; CHU UCL Namur Kayser, Francoise; CHU UCL Namur Falticeanu, Ana; CHU UCL Namur Randon, Caren; UZ Gent, Department of Thoracic and Vascular Surgery Monten, Chris; UZ Gent, Department of Radiotherapy Van Landuyt, Koen; UZ Gent De Pypere, Bernard; UZ Gent, Department of plastic and reconstructive surgery Degraeve, Liesl; UZ Gent, Department of plastic and reconstructive surgery Decorte, Tina; UZ Gent, Department of Physical Medicine and Rehabilitation De Schryver, Mieke; UZ Gent Van Besien, Vickie; UZ Gent Devos, Daniel; UZ Gent Suominen, Sinikka; Helsinki University Central Hospital Ayala, Jaume Masia; Universitat Internacional de Catalunya,

	Pons, Gemma; Hospital de la Santa Creu i Sant Pau, Department of plastic surgery Fourneau, Inge; KU Leuven University Hospitals Leuven, Vascular Surgery thomis, sarah; KU Leuven University Hospitals Leuven, Vascular Surgery
Primary Subject Heading:	Cardiovascular medicine
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Keywords:	Vascular medicine < INTERNAL MEDICINE, Plastic & reconstructive surgery < SURGERY, VASCULAR SURGERY

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

Nele Devoogdt[1,2], Tessa De Vrieze[2], An-Kathleen Heroes[1,2], Beate Bechter-Hugl[1], Steffen Fieuws[3], Lode Godderis[4], Katarina Segers[5], Geert Maleux[6], Thierry Deltombe[7], Jacqueline Frippiat[7], Maxime Servaes[8], Aline Berners[8], Philippe Fosseprez[8], Bruno Krug[9], Francoise Kayser[9], Ana Falticeanu[10], Caren Randon[11], Chris Monten[12], Koen Van Landuyt[13], Bernard De Pypere[13], Liesl Degraeve[13], Tina Decorte[14], Mieke De Schryver[14], Vickie Van Besien[14], Daniel Devos[15], Sinikka Suominen[16], Jaume Masia[17], Gemma Pons[17], Inge Fourneau[1, ¥], Sarah Thomis[1, ¥]

[¥] Contributed equally as last author to the SurLym trial

[1]University Hospitals Leuven, Department of Vascular Surgery, Centre for Lymphedema, Leuven, Belgium

[2]KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

[3]KU Leuven – University of Leuven, Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat), Leuven, Belgium

[4]KU Leuven – University of Leuven, Centre for Environment and Health, Leuven, Flanders, Belgium

[5]University Hospitals Leuven, Department of Plastic and Reconstructive Surgery, Leuven, Belgium

[6]University Hospitals Leuven, Department of Radiology, Leuven, Belgium

[7]CHU UCL Namur – Site Godinne, Department of Physical Medicine and Rehabilitation, Centre de Reference du Lymphoedème, Yvoir, Belgium

[8]CHU UCL Namur – Site St-Elisabeth, Department of Plastic and Reconstructive Surgery, Namur, Belgium

[9]CHU UCL Namur – Site Godinne, Nuclear Medicine Department, Université catholique de Louvain, Yvoir, Belgium

[10]CHU UCL Namur – Site Godinne, Department of Radiology, Yvoir, Belgium

[11]Ghent University Hospital, Department of Thoracic and Vascular Surgery, Lymphedema Clinic, Ghent, Belgium

[12]Ghent University Hospital, Department of Radiotherapy, Lymphedema Clinic, Ghent, Belgium

[13]Ghent University Hospital, Department of Plastic and Reconstructive Surgery, Lymphedema Clinic, Ghent, Belgium

[14]Ghent University Hospital, Department of Physical Medicine and Rehabilitation, Lymphedema Clinic, Ghent, Belgium

[15]Ghent University Hospital, Department of Radiology, Ghent, Belgium

[16]Helsinki University and Helsinki University Hospital, Department of Plastic Surgery, Helsinki, Finland

[17]Hospital de la Santa Creu i Sant Pau and the Hospital del Mar of Barcelona, Department of Plastic Surgery, Barcelona, Spain

Correspondence to:

Prof. Nele Devoogdt

UZ Leuven, centre for lymphedema, Weligerveld 1, 3212 Pellenberg, Belgium

00 32 16 34 25 15

nele.devoogdt@kuleuven.be

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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 **sur**gery versus no surgery, additional to decongestive lymphatic therapy (usual care), for the treatment of **lym**phoedema, 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; ≥ 5% volume difference or ≥ 2 minor/ 1 major lymphoscintigraphy criterion; total score or one domain score of Lymph-ICF questionnaire ≥ 25/100 -History of DLT (≥6M) until minimal pitting, no liposuction/ reconstructive surgery in past

	-In case of lower limb lymphoedema: no CVI C4-C6, no DVT/ PTS -Age ≥ 18 years, not pregnant, BMI ≤ 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 a 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)

Our hypothesis is that reconstructive lymphatic surgery partially restores the lymphatic transport which leads to a decrease of the lymphoedema volume and as a result lowers the need for a compression garment. This will probably improve lymphoedema-specific quality of life.

Robust evidence on the effectiveness of reconstructive lymphatic surgery for lymphoedema has so far not been procured. In 2019, a Cochrane systematic review of Markkula et al revealed that there is not enough high-quality research investigating the effect of reconstructive lymphatic surgery on lymphoedema.(10) Only one RCT so far evaluated the effect of LNT. Dionyssiou et al randomised 36 patients with breast cancer related arm lymphoedema.(11) After surgery/no surgery, all patients first received for 6 months DLT and DLT was discontinued for the next 12 months. At 18 months follow-up, mean limb volume reduction was superior in the group with LNT compared to no LNT (57% vs 18%, $p<0.01$). In the group with LNT infections were less frequent and subjective symptoms improved. An RCT evaluating the effect of LVA has not been performed yet.

Objectives

The main objective of this study is to investigate the added value of reconstructive lymphatic surgery to decongestive lymphatic therapy (usual care) in patients with lymphoedema of the upper limb or lower limb in terms of lymphoedema-specific QoL (primary outcome), limb volume and duration of wearing the compression garment (key secondary outcomes) at 18 months and of other outcomes at 1, 3, 6, 12, 18, 24 and 36 months post-baseline (secondary outcomes; see table 1 for the outcomes).

A secondary objective is to verify whether the rate of complications in participants receiving reconstructive lymphatic surgery is acceptable and if so, whether these complications are reversible. We also verify in patients with lymphoedema due to cancer treatment, if reconstructive lymphatic surgery causes higher cancer recurrence rates.

A first exploratory objective is to compare the added value of the reconstructive surgery between different subgroups (stage 1 vs stage 2; normal weight vs overweight; combination of LVA and LNT vs one method). A second exploratory objective is to investigate predictive variables for lymphoedema-specific QoL at 36 months.

Table 1 Overview of the primary and secondary outcomes and the assessment method at each time interval

Outcome	Method	A1 Baseline	A2, 3, 4 1, 3, 6M	A5 12M	A6 18M	A7 24M	A8 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

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

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

Eligibility criteria

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

1) Unilateral or bilateral, primary or secondary lymphoedema of the upper or lower limb;

2) If cancer-related lymphoedema, approval for participation from the multidisciplinary oncological board; participation only if estimated cancer-related survival is ≥3 years and no concerns on oncological safety are raised;

3) Lymphoedema stage 1 to 2 (according to staging 1-3 of International Society of Lymphology)(5);

4) Objective diagnosis of lymphoedema: ≥ 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: ≥ 25/ 100 (= moderate level of problems in functioning related to the development of lymphoedema)(14);

6) History of at least 6 months of DLT until minimal pitting (sustained thumb pressure on the skin is performed during 5 seconds; after removing the thumb, indentation of tissue is evaluated and is scored as 0 = no clinical pitting, 1 = slight/doubtful pitting and 2 = noticeably pitting; a patient with score 2 may not participate)(30);

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 (summary)' document. In addition, the patient receives an appointment for the screening (A0). Some patients are informed about the trial through another way, e.g. by their oncologist. In that case, the patient contacts the study coordinator by phone, who performs the fast eligibility check and discusses the study during the phone call. If the patient is interested to participate, the Informed Consent Form and the 'study at a glance' document is sent. In addition, the patient receives an appointment for the screening (A0).

During the *screening appointment* (A0), patients receive all information and explanation they request or need before signing the Informed Consent Form. Thereafter, the complete screening procedure is executed to verify whether the participant fulfils all eligibility criteria.

In order to optimally recruit patients with lymphoedema, the study is presented inside (at other departments) as well as outside the hospitals of the study centers by lectures, posters and mailing. Potential candidates with lymphoedema as well as their treating physicians, physical therapists and other health care providers are informed about the trial (through social media, publication in local journals and on websites).

Allocation and randomisation

Given the nature of the trial, *blinding* of participants and care providers (surgeon/ physical therapist/ compression specialist) is not feasible. Because the participants fill out different questionnaires to

determine the primary outcome and some of the secondary outcomes, detection bias may be a potential risk. However, bias of the participants will be limited as much as possible because the study will be explained by a neutral person (physical therapists ND, AKH, VVB, MDS, JF or physical medicine & rehabilitation physician TD (hospital of Ghent), TD (hospital of CHU UCL)).

The *randomisation* is computer generated. To obtain concealment of allocation, the randomisation list is prepared by the trial's statistician (SF) and is incorporated in the data management tool 'REDCap'. Randomisation is performed by using varying block sizes. A 1:1 allocation ratio is applied. A stratification is applied for study centre (UZ Leuven vs UZ gent vs CHU-UCL Namur) and for region of lymphoedema (upper limb vs lower limb, with a ratio 1:1). At each participating site, only the chief investigator (ND) and trial manager (TDV), investigators and study coordinators have access to the randomisation tool in REDCap. After randomisation, the study coordinator of the specific study centre plans the intervention if applicable (surgery), as well as the usual care and the follow-up assessments.

After all patients have finished the trial and the database is locked to analyse the data, the randomisation code will be broken.

Intervention

All participants are randomised to the intervention or control group. The intervention group is treated with reconstructive lymphatic surgery in addition to conservative DLT (decongestive lymphatic therapy; usual care). In the control group patients only receive conservative DLT (usual care) without surgery (see figure 1).

The researchers will follow the protocol as strictly as possible. However, since the pragmatic nature of the trial, a deviation of the protocol is allowed if necessary. This protocol deviation has to be registered in the protocol deviation log.

Reconstructive lymphatic surgery

The intervention treatment is reconstructive lymphatic surgery and is performed by the team of vascular and/ or plastic surgeons from each study center (ST and KT of UZ Leuven; BDP and LD of Ghent University Hospital; and MS, AB and PF of CHU UCL Namur). As reconstructive technique, a lymphovenous anastomosis (LVA), lymph node transfer (LNT) or a combination of both is applied. The choice of the technique is determined by the surgeons of the study centre. See table 2 for the

overview of the preparation and for the technical description of the reconstructive procedure (which is based on Chang et al).(7) In table 3 the aftercare is discussed.

To obtain standardisation and to ascertain the quality of the reconstructive lymphatic surgery, all surgeons received training in the Reconstructive Microsurgery European School (by JM and GP) in May 2021. Moreover, to improve standardisation of the patient selection and the reconstructive lymphatic procedure between the surgeons and between the centres, every patient that is planned for surgery in the trial is discussed during a monthly meeting with at least one surgeon per centre attending. A final quality control measure is that the first 10 surgical procedures are discussed with the whole surgical team including the independent experts JM, GP, SS and KVL.

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 1st 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	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.	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	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	

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 ≥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.

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

Outcomes

The outcome measures were chosen based on input from patients with lymphoedema (see section 'patient and public involvement') and on input from the investigators of this trial who have experience in evaluating and treating patients with lymphoedema. Patient-reported outcomes provide essential information about the patient experience with the intervention that cannot be reliably captured in another way, and are necessary for the complete evaluations of risks and benefits and the value of the intervention. As a consequence, the trial's primary outcome is a patient-reported outcome.(32) Moreover, recently, Chang et al stated in their systematic review and meta-analysis about the surgical treatment of lymphoedema that better designed studies are necessary: with objective reporting of outcomes using quantitative methods for measuring fluid and both physiologic and immunologic function during longer follow-up.(33)

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

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

The primary outcome is lymphoedema-specific QoL (= problems in functioning related to development of lymphoedema) at 18 months, evaluated with the Dutch or French version of the Lymph-ICF questionnaire for upper or lower limb lymphoedema.(13-15, 34) Besides this patient-reported outcome, the trial contains also two key secondary outcomes at 18 months that are objective outcomes. These are limb volume and failure to reduce the hours a day of wearing the compression garment. In addition, these outcomes will be investigated at other time points in the short term (1, 3, 6, 12 months) and longer term (24 and 36 months) as a secondary outcome parameter. The outcome limb volume is determined differently in participants with upper and lower limb lymphoedema. Since most of the patients with upper limb lymphoedema have unilateral lymphoedema, limb volume is determined as the relative excessive arm volume. As too many patients with lower limb lymphoedema have bilateral lymphoedema, limb volume is determined as the leg volume.

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

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),(35) 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.(36) 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 clinical important difference,(14, 15) 36 subjects are required per group (2x2x36=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, the assumed dropout rates will also be verified. No interim analyses are planned to stop the study earlier for efficacy or futility, this to avoid loss of information on the secondary endpoints.

Data analyses

Statistical analysis will comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarised

using mean and SD and median and range values. Different analysis sets will be defined. The intent-to-treat analysis set (ITT) contains all randomised patients, grouped according to the allocated treatment. The modified intent-to-treat analysis set (mITT) contains all randomised patients grouped according to the allocated treatment, but excluding patients who have withdrawn their consent to the randomised procedure. The as-treated analysis set also contains all randomised patients but grouping the patients according to their received treatment. The per-protocol analysis set contains all randomised patients who received the allocated treatment. The main analyses will be performed on the ITT analysis set. Results on the other analysis sets will be reported additionally.

Primary outcome

- Lymphoedema specific QoL

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

Key secondary outcomes

- Change of limb volume:

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

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. Furthermore, the study is approved by the Federal Agency for Medicines and Health Products (EudraCT: 2021-000397-29).

Dissemination of results

The results of the study owned by the sponsor shall be disseminated as soon as possible after the end of the trial, by disclosing them to the public by appropriate means, including publications in

peer-reviewed scientific journals and presentations at congresses and events. Open access will be 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

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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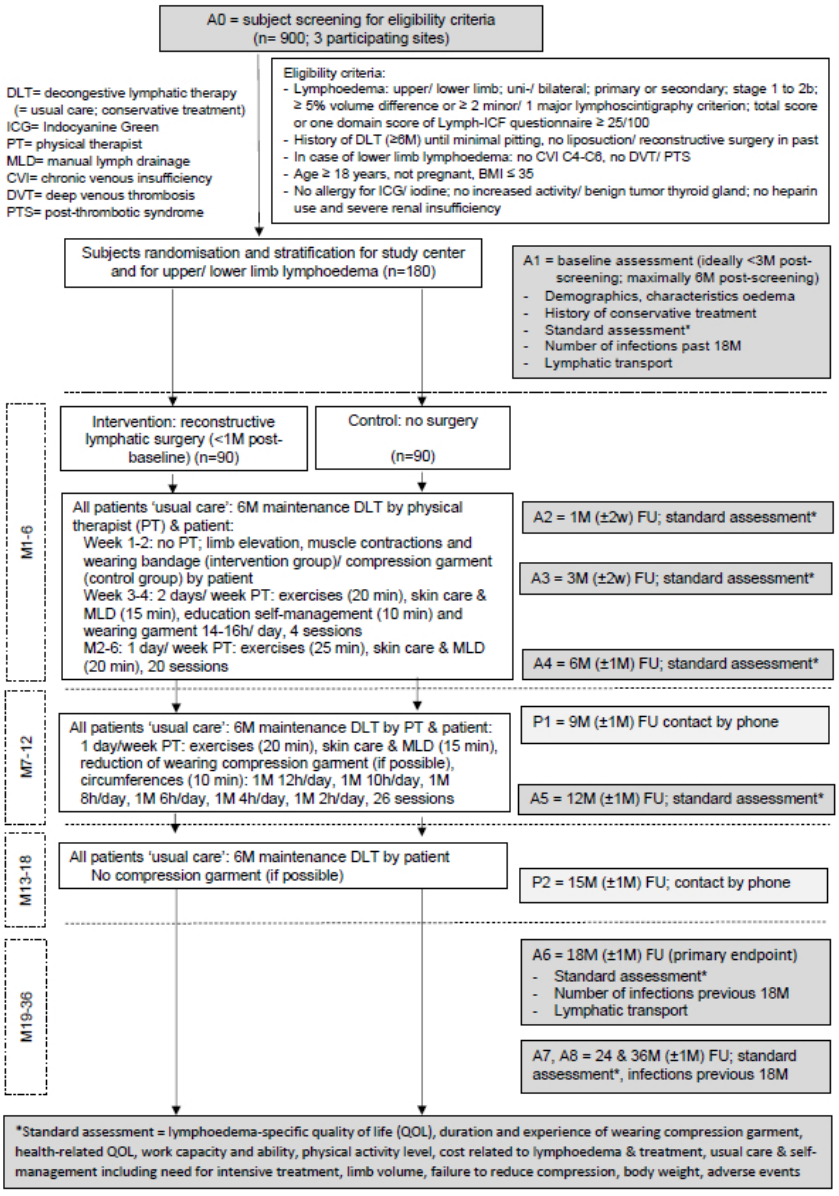

Figure 1. Flow diagram of SurLym trial

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

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 (%)

	QuickScan 18 – short version;(19) Chance for successful socio-professional reintegration (score between 0 certainly not and 5 certainly yes)
Physical activity level (MET-hours a week)	International Physical Activity Questionnaire;(20) 7 questions about hours a week of vigorous (8 MET), moderate (4 MET) and walking activities (3.3 MET), and sitting time
Costs related to lymphoedema and its treatment (in euro)	Study-specific questionnaire completed monthly by the patient; collection of patient and health care costs for material (such as compression or exercise material), medication, diagnostics or care giver (similar questionnaire as for Effort-BCRL trial)
Usual care & self-management §, including need for intensive treatment	Study-specific usual care & self-management questionnaire completed monthly by the patient; information regarding 1) physical therapy: number of sessions, duration and content; 2) intensive treatment: where, number of sessions, content; 3) other care giver; 4) self-management: number of days of each modality
Assessment (60 min)	
Limb volume (key secondary outcome)	Circumference measurements every 4 cm with perimeter;(21-24) limb volume is calculated with formula of truncated cone, in participants with upper limb lymphoedema: assessment of affected and non-affected arm; outcome is excessive arm volume (%) = (volume $_{\text{AFFECTED ARM}}$ – volume $_{\text{UNAFFECTED ARM}}$/ volume $_{\text{UNAFFECTED ARM}}$) x 100, in participants with lower limb lymphoedema: assessment of affected leg (= leg that is followed in trial); outcome is whole leg volume (in ml)
Hand/ foot volume	Water displacement method of hand or foot;(22, 25) volume is the mass of the displaced water, in participants with upper limb lymphoedema: assessment of affected and non-affected hand, outcome is excessive hand volume (%); in participants with lower limb lymphoedema: assessment of affected foot, outcome is foot volume (in ml)

Failure to reduce hours a day of wearing compression stocking (yes, not able vs no, able)	Assessor determines whether participant is able to reduce the hours a day of wearing the compression garment as stated by the protocol (see figure 1, M7-12); Not able = excessive arm volume/ leg volume increased more than the smallest real difference, i.e. 5% or more compared to baseline(14)
Body weight (in kg)	Scale
Infection previous 18 months (number)	Interview
Recurrence of cancer (yes/ no)	Interview and medical file; only collected in the group with history of cancer
Adverse events (whole group) and complications of surgery (in intervention group) (yes/ no)	Interview and medical file; registration of adverse events related to pre-surgical or study-specific investigations: ICG fluoroscopy, lymphoscintigraphy, lymph MRI, CT angiography, of complications of reconstructive lymphatic surgery: 1) in general blue spot, wound healing problem, infection of wound, decrease of sensibility around wound, erysipelas of limb, deep venous thrombosis, 2) LNT-specific seroma, lymphocele, donor site lymphoedema, loss of flap
Costs related to lymphoedema and its treatment (in euro)	Study-specific questionnaire completed by the compression specialist after delivery of compression material; registration of company, compression product, region of compression, type, compression class, cost for health insurance/ patient Inter Mutuality Agency (IMA) database (= agency collecting data from different mutual health insurance companies), based on national number of the study participant
Lymphatic transport	

ICG fluoroscopy (60 min)	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.

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In your methods section, say that you used the SPIRITreporting 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

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Paper p3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Paper p3
Protocol version	#3	Date and version identifier	Paper p3
Funding	#4	Sources and types of financial, material, and other support	Paper p3, study agreement KCE-UZ Leuven
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Paper p30
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Paper p3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Protocol v3.0 p9

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol v3.0 p10
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Paper p7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Paper p6
Objectives	#7	Specific objectives or hypotheses	Paper p7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Paper p9
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Paper p9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Paper p10-11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Paper p13-18
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Paper p13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Paper p19, Protocol v3.0 p44
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Paper p18

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Paper p19-25
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Paper figure1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Paper p26
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Paper p11-12
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Paper p12
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
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Paper p12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Paper p12
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

Methods: Data collection, management, and analysis			
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
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
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
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

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Paper p27-28
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Paper p27
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Paper p29
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Paper p26
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Protocol v3.0 p46-47; manual adverse events

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
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Protocol v3.0 p57
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
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
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Paper p30
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data Management Plan p3-4
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not specified
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Paper p30, Protocol v3.0 p61
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol v3.0 p61, study agreement sponsor-study site
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol v3.0 p61

Appendices

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
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