PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Devoogdt, Nele; De Vrieze, Tessa; Heroes, An-Kathleen; Bechter-Hugl, Beate; Fieuws, Steffen; Godderis, Lode; Segers, Katarina; Maleux, Geert; Deltombe, Thierry; Frippiat, Jacqueline; Servaes, Maxime; Berners, Aline; Fosseprez, Philippe; Krug, Bruno; Kayser, Francoise; Falticeanu, Ana; Randon, Caren; Monten, Chris; Van Landuyt, Koen; De Pypere, Bernard; Degraeve, Liesl; Decorte, Tina; De Schryver, Mieke; Van Besien, Vickie; Devos, Daniel; Suominen, Sinikka; Ayala, Jaume Masia; Pons, Gemma; Fourneau, Inge; thomis, sarah

VERSION 1 – REVIEW

REVIEWER	Brorson, Håkan Lunds Universitet
REVIEW RETURNED	04-Sep-2023

GENERAL COMMENTS	Page 10 , line 25 ”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 stabilizing the results obtained in the previous phase.” Comment How is ”sufficient reduction of the pitting” defined? How is the pitting test standardized? Page 10, line 46 ”The transferred nodes induce lymphangiogenesis and if they are placed in the site of lymphadenectomy, scar tissue and adhesions are removed to improve vascularization.” Comment Removing scar tissue around veins alone can decrease edema. Can you differ any effect of removing scar tissue to the microsurgical reconstruction? This would be a separate randomized study per se. Jeong HH, Yoon IA, Al-Shomer FM, Suh HP, Pak CJ, Neligan P, Hong JP. Decompression of Axillary vein - An essential adjunct for advanced lymphedema. Plast Reconstr Surg. 2023 Aug 29. doi: 10.1097/PRS.0000000000011032. Epub ahead of print. PMID: 37647513. Page 10, line 52

	”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.” Comment If you initially see a patient who had had optimal conservative treatment elsewhere showing no or minimal pitting, would this patient be included in the study? Page 11, line 3 ”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.” Comment How do you define lymphedema volume, it is limb volume or excess volume? Page 11, line 29 ”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).” Comment Why do you choose ”lymphoedema-specific QoL” as primary outcome? Often patients with lymphedema, regardless of treatment, will get better values after intervention even if the reduction of the excess volume is small. Would not ”limb volume”, that is excess volume, be better as primary outcome because a reduction in excess volume is what the patient asks for. Any HRQoL questionnaire will positively parallel the reduction in excess volume. Page 13, line 5 ”Limb volume (key secondary outcome)” Comment I recommend that you use the expression ”excess volume” = the edematous arm volume – (minus) the normal arm volume (in mL), and add the increased volume in percent of the normal arm. This will give an optimal view of the swelling. The normal and affected arms/legs will differ in volume depending if measurements are performed in the morning or in the afternoon. Also, extremity volumes are affected if patients gain or lose weight. Using excess volume is therefore necessary to get accurate data especially during a three-year study. Page 13, line 17 ”Body weight” Comment Use BMI Page 14, line 24 ”This patient preferred arm volume (which is a key secondary outcome) as outcome measure.” Comment See previous comment. Arm volume or excess volume?

	Page 14, line 60 ”Lymphoedema stage 1 to 2b (according to staging 1-3 of International Society of Lymphology)” Comment ISL stage 2 is defined: ”Stage II involves more changes in solid structures, limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Later in Stage II, the limb may not pit as excess subcutaneous fat and fibrosis develop.” Sefine and describe stage 2b? Page 15, line 2 ”4) Objective diagnosis of lymphoedema: ≥ 5% volume difference OR ≥ 2 minor/ 1 major criteria on lymphoscintigraphy OR presence of ICG dermal backflow;” Comment Dominance may influence extremity volume up to 5%. Why do you choose 5% volume difference? Ten percent would be better. Page 15, line 55 ”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” Comment What costs are involved? Do patient pay for visits, decongestive treatment, ICG, lymphoscintigraphy and visits or is this covered by the study or health care insurance in Belgium. If not needed to pay anything, would this have a positive outcome of HRQoL? Page 16, line 56 ”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.” Comment Will outcomes during the study be analyzed? For example, in pharmacological studies outcomes are continuously analyzed to see if one treatment is much better or worse than no treatment at all so that the study is stopped due to ethical issues. Have you discussed this in this trial? Page 17, line 33 ”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” Comment Will outcomes be presented separately for any combination? This may lead to small groups. Have you made a power analysis in order to evaluate the minimum of patients in each group to be able to calculate statistical difference? Page 18, Table 2 “Choice of the type of compression garment is made pragmatically, as performed in the real clinical situation.” Comment Explain more what you mean with “pragmatically”.

	There is a big difference between round-knitted and flat-knitted garments regarding pitting and longevity. How do you address this? I miss estimation of pitting in mm, which is important in order to evaluate the amount of fluid. This can be standardized for example by press with the thumb during 3 minutes on the mid-ulnar aspect of the forearm or mid lower leg where the skin is directly above facies anterior tibiae. Page 20, line 11 ”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);” Comment Outcomes of ICG lymphofluoroscopy and lymph MRI can be affected if the patient has had optimal treatment before the investigation, thus showing less dermal backflow. Comment How do you interpret the outcomes in these cases when deciding what kind of surgery will be performed? Page 21, line 31 “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)). Comment Numerous papers have shown that MLD has no effect on volume reduction. Why is MLD included? To release oxytocin and increase well-being? Page 21, line 52 “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.” Comment Both extremities need to be measured (bilateral leg lymphedema excluded), see previous comment why this is important. Page 21, line 57 “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.” Comment Use the terminology ”excess volume”, that is if the ”excess volume” ”increases ≥5% compared to baseline ”excess volume”, the patient is planned for an intermediate checkup in the study center.”, see previous comment regarding daily change of extremity volume due to measurements in the morning or in the afternoon as well as weight change. For bilateral leg lymphedema, any reference why 5% is chosen?

	Page 27, line 24 Limb volume (key secondary outcome) ”Circumference measurements every 4 cm with perimeter; 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 AFFECTED ARM – volume UNAFFECTED ARM/ volume 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 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)” Comment Here you describe, for arms, the ”excess volume”. I recommend that you use ”excess volume” in the previous parts of the paper where you refer to limb volume only. For legs, where lymphoscintigraphy and ICG have shown normal function in the non-affected leg, I recommend you also use ”excess volume”. For bilateral lymphedema you can follow the limb volume since ”excess volume” cannot be calculated. Page 31, line 14 “The continuous data will be summarised using mean and SD or median and range values.” Comment Using mean and SD assume normal distribution. How will normality be calculated? Page 31, line 39 “The choice of the covariance structure for the five measurements will be based on the Aikake criterion.” Comment Reference needed. Page 31, line 48 “More specifically, starting from the MAR model, a jump-to-reference (JR) and tipping-point (TP) analysis will be applied.32” Comment Recommend you add a reference in English. Page 31, line 58 ”For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be calculated.” Comment Regarding excess volume, I recommend using percent reduction (or increase) from baseline excess volume at follow-up as and in addition show mean (□SD)/median (IQR) absolute excess volumes at baseline and at each time point at follow-up. Final comments Lymphoscintigraphy

	For lymphoscintigraphy outcomes I recommend using the Transport Index as described by Kleinhans, that is quantitative lymphoscintography (99Tc-nanocolloid clearance rate) with calculation of the transport index performed at baseline and at follow-ups. Kleinhans E, Baumeister RG, Hahn D, Siuda S, Büll U, Moser E. Evaluation of transport kinetics in lymphoscintigraphy: follow-up study in patients with transplanted lymphatic vessels. Eur J Nucl Med. 1985;10(7-8):349-52. doi: 10.1007/BF00251310. PMID: 4006977. This will give an objective estimation of and change in lymph tramsport following surgery. Volumes Regarding volumes you may consider the suggestion below as a very easy method to evaluate the effect of surgery. Before surgery, for example 1 month before, the compression garment is removed and extremity volumes are measured and the excess volume is calculated. Then the patient is instructed to not wear the garment during one week and volumes and excess volume are measured again. This will show an increase in the volume of the affected extremity and excess volume. The garment is then applied again. After surgery, for example at 3 and/or at 6 months or more, the same measurements are made as described above during 1 week. Postoperative measurements are then compared with preoperative and the efficacy of surgery can be evaluated.

REVIEWER	Keeley, Vaughn University Hospitals of Derby and Burton NHS Foundation Trust
REVIEW RETURNED	14-Sep-2023

GENERAL COMMENTS	This is an important and ambitious study which should shed light on the role of reconstructive lymphatic surgery in the management of lymphoedema. I have a number of small queries: There is a start date included in the protocol but is there a date for completion of the study? Page 10: I suggest that “failure to reduce hours a day of wearing compression stocking” should read “hours a day of wearing compression stocking” as this is what is assessed and the failure to reduce hours per day is an outcome based on the assessments. Page 10: I cannot see that you have cited the reference for the SPIRIT guidelines in the reference list for the paper. Page 18: line 52: I think this should read 16 hours per day to 0 hours per day rather than 16 hours per week to 0 hours per week. Page 25 line 36 and Page 26 line 8: are the injections intradermal or subcutaneous? Page 34 reference 19 I think this was published in Lymphatic Research and Biology in 2021

REVIEWER	Chang, David University of Chicago SSA
REVIEW RETURNED	16-Sep-2023

GENERAL COMMENTS	Primary & secondary? These are very different in terms of the cause, outcomes? Why include both? How about just limit to secondary only? 30 authors? Many NOT from these 3 centers? Pragmatic? What does that mean? Authors state that “Currently, scientific evidence for reconstructive lymphatic surgery is not of high quality” I would disagree with statement. There are now ample scientific evidence to support reconstructive lymphatic surgery. Applaud the effort for prospective, randomized trial. This is an on-going study? So why publish now? would resubmit once the study is completed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Prof. Håkan Brorson, Lunds Universitet, Lund University Cancer Centre

Comments to the Author: We are very grateful that the reviewer has spent so much time at reviewing the paper. We have answered the questions/ comments as good as possible. We hope that the answers meet the reviewer's expectations.

Introduction

1. Page 10 , line 25

”Once that sufficient reduction of the pitting is obtained and the patients received education to improve their self-management skills, the maintenance phase starts, which aims at stabilizing the results obtained in the previous phase.”

Comment
How is ”sufficient reduction of the pitting” defined?
Answer ND: sufficient reduction of the pitting = no pitting or minimal pitting
Changed in text as follow: Once that sufficient reduction of the pitting is obtained *(i.e. no or minimal pitting)* …

How is the pitting test standardized?
Answer ND: pitting test is a well-known test in the lymphoedema clinics; during the pitting test, a pressure with the thumb is performed during 5-10 seconds; if an indentation is felt/ seen, this is called pitting

2. Page 10, line 46

”The transferred nodes induce lymphangiogenesis and if they are placed in the site of lymphadenectomy, scar tissue and adhesions are removed to improve vascularization.”

Comment
Removing scar tissue around veins alone can decrease edema. Can you differ any effect of removing scar tissue to the microsurgical reconstruction? This would be a separate randomized study per

se. Jeong HH, Yoon IA, Al-Shomer FM, Suh HP, Pak CJ, Neligan P, Hong JP. Decompression of Axillary vein - An essential adjunct for advanced lymphedema. Plast Reconstr Surg. 2023 Aug 29. doi: 10.1097/PRS.0000000000011032. Epub ahead of print. PMID: 37647513.
Answer ND: this is correct, this cannot be differentiated. The enhancement of vascularization can be due to the transferred lymphatic tissue, or due to the removal of scar tissue and adhesions lowering the pressure on the vein.
Changed in text as follow: 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

3. Page 10, line 52

”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.”
Comment
If you initially see a patient who had had optimal conservative treatment elsewhere showing no or minimal pitting, would this patient be included in the study?
Answer ND: Yes, this patient will be included.

4. Page 11, line 3

”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.”
Comment
How do you define lymphedema volume, it is limb volume or excess volume?
Answer ND: depending of the location of the lymphedema (lower or upper limb) this is different. As the major part of the subjects with breast cancer related arm lymphoedema develop the lymphoedema on one side (i.e. unilateral lymphoedema), we are able to determine and follow the excess volume in patients with upper limb lymphoedema. As many patients with lower limb lymphoedema develop the lymphoedema on both legs, we are not able to determine and follow the excess volume for the whole group and as a consequence we decided to determine and follow the leg absolute volume over time.

Objectives

5. Page 11, line 29

”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).”
Comment
Why do you choose ”lymphoedema-specific QoL” as primary outcome? Often patients with lymphedema, regardless of treatment, will get better values after intervention even if the reduction of the excess volume is small. Would not ”limb volume”, that is excess volume, be better as primary outcome because a reduction in excess volume is what the patient asks for.
Any HRQoL questionnaire will positively parallel the reduction in excess volume.
Answer ND: We deliberately have chosen a patient-reported outcome. 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. Inadvertent unblinding should not be considered a meaningful source of

bias, and patient-reported outcomes should be included in trials regardless of blinding status. See paper Atkinson 2017.
We have discussed the primary outcome thoroughly with the whole Trial Steering Committee, which consists of surgeons providing reconstructive surgery (believers) and care providers offering conservative management (non-believers or neutral believe), with the patient board and with the statistician.
Following text is added in the paper: *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.*[15]

Moreover, we have included two key secondary outcomes that are objective outcomes, i.e. lymphoedema volume and ability to reduce the hours a day of wearing the compression garment; our sample size is large enough to make strong conclusion based on these outcomes as well.
We have adapted the text as follow (in the section 'outcomes'): 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 17-19 *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.
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.

6. Page 13, line 5

"Limb volume (key secondary outcome)"
Comment
I recommend that you use the expression "excess volume" = the edematous arm volume – (minus) the normal arm volume (in mL), and add the increased volume in percent of the normal arm. This will give an optimal view of the swelling. The normal and affected arms/legs will differ in volume depending if measurements are performed in the morning or in the afternoon. Also, extremity volumes are affected if patients gain or lose weight. Using excess volume is therefore necessary to get accurate data especially during a three-year study.
Answer ND: We agree with this; however, this is only possible for patients with upper limb lymphoedema (arm lymphoedema), as these patients often only have unilateral lymphoedema. So, for patients with upper limb lymphoedema, the outcome 'limb volume ' = the excessive volume, determined as the relative difference between affected and nun-affected arm. However, for patients with lower limb lymphoedema (leg lymphoedema), it is not possible to define limb volume as excessive volume. The reason is that more than 2/3rd of the patients with leg lymphoedema have it on both sides (or have bilateral lymphoedema) (based on own data set of 350 patients with lower limb lymphoedema, treated in our clinic between 2018-2022; Heroes 2023, in publication). So, for patients with lower limb lymphoedema, the outcome 'limb volume' = the volume of the leg. See explanation of determining the outcome 'limb volume' in table 3.
Since we will perform separate analyses for patients with arm lymphoedema (n=90) and patients with leg lymphoedema (n=90), we may use different ways to define 'limb volume'.

7. Page 13, line 17

”Body weight”

Comment

Use BMI

Answer ND: We of course will calculate BMI as well and will present it as a patient characteristic. It is also used to determine whether the patients may be included or not (subjects with BMI >35 are excluded) (see in paper ‘eligibility criteria’). We also will use BMI to perform subgroup analyses: whether patients with BMI ≤ 25 have another result than patients with BMI >25) (see in paper ‘exploratory analyses’). However, as outcome, we prefer to use body weight (see in paper ‘table 3’). From a clinical point of view, the change in body weight (5 kg) says more than the change of BMI (1 kg/m²). Moreover, only body weight changes over time and not body length.

Patient and public involvement in the trial design

8. Page 14, line 24

”This patient preferred arm volume (which is a key secondary outcome) as outcome measure.”

Comment

See previous comment. Arm volume or excess volume?

Answer ND: see comment 6. In patients with upper limb lymphoedema, limb volume = excessive arm volume; in patients with lower limb lymphoedema, limb volume = leg volume.

Eligibility criteria

9. Page 14, line 60

”Lymphoedema stage 1 to 2b (according to staging 1-3 of International Society of Lymphology)”

Comment

ISL stage 2 is defined: ”Stage II involves more changes in solid structures, limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Later in Stage II, the limb may not pit as excess subcutaneous fat and fibrosis develop.” Define and describe stage 2b?

Answer ND: stage 2b = later in stage 2. So, it means that all patients of stage 1 and all patients of stage 2 may participate.

Changed in text as follow: Lymphoedema state 1 to *2* (according to staging 1-3 of International Society of Lymphology)

10. Page 15, line 2

”4) Objective diagnosis of lymphoedema: ≥ 5% volume difference OR ≥ 2 minor/ 1 major criteria on lymphoscintigraphy OR presence of ICG dermal backflow;”

Comment

Dominance may influence extremity volume up to 5%. Why do you choose 5% volume difference? Ten percent would be better.

Answer ND: We want to include patients in our trial that have mild to moderate lymphoedema. Therefore, a 10% volume difference criterion is too severe. The natural volume difference (based on hand dominance) between both arms is 3%. So a 5% volume difference, which falls slightly beyond the natural difference is correct. This has also been confirmed in the best practice guideline of Gebruers et al (2017).

Recruitment, participant screening and consent

11. Page 15, line 55

”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”
Comment
What costs are involved?
Do patient pay for visits, decongestive treatment, ICG, lymphoscintigraphy and visits or is this covered by the study or health care insurance in Belgium.
If not needed to pay anything, would this have a positive outcome of HRQoL?
Answer ND: As this is a pragmatic trial, the cost for the conservative treatment (physical therapy sessions/ compression garment) is born by the health insurance. The part that is not reimbursed is born by the patients (physical therapy sessions) and study budget (compression garment). As in all clinical trials, all the study-specific investigations and interventions are born by the study budget. This means: ICG lymphofluoroscopy, lymphoscintigraphy, lymph MRI, study visits and the reconstructive lymphatic surgery.
The fact that the study-specific interventions are offered for free will not influence the completion of the patient-reported outcome. See also the paper of Atkinson discussed in point 5.

Allocation and randomisation

12. Page 16, line 56

”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.”
Comment
Will outcomes during the study be analyzed? For example, in pharmacological studies outcomes are continuously analyzed to see if one treatment is much better or worse than no treatment at all so that the study is stopped due to ethical issues. Have you discussed this in this trial?
Answer ND: This has been discussed in the part about the ‘sample size’. So, after inclusion of 40 subjects per group the already available information will be used to verify if the assumptions regarding the variability of the lymphoedema-specific QoL and the correlation with the baseline measurement were correct. 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. However, adverse events and serious adverse events are collected meticulously. See outcome ‘adverse events (whole group) and complications of surgery (in intervention group)’ in table 3. Every 6 months a Trial Steering Committee is organized, where among others these problems are discussed.

Intervention

13. Page 17, line 33

”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”
Comment
Will outcomes be presented separately for any combination? This may lead to small groups. Have you made a power analysis in order to evaluate the minimum of patients in each group to be able to calculate statistical difference?
Answer ND: One of the exploratory analyses will be the comparison of the outcomes between the group with the combination of LVA/ LNT, the group with only LVA and the group with only LNT (see in

paper ‘exploratory analyses’). As this is one of our exploratory analyses, we have not performed a sample size calculation and also have not determined the minimum number of patients in every group. If we look to our clinical numbers, most of the patients receive an LVA, less patients receive the combination LVA/ LNT and least patients only receive LNT. But there will be a number of patients in every group.

14. Page 18, Table 2

“Choice of the type of compression garment is made pragmatically, as performed in the real clinical situation.”

Comment

Explain more what you mean with “pragmatically”. There is a big difference between round-knitted and flat-knitted garments regarding pitting and longevity. How do you address this? I miss estimation of pitting in mm, which is important in order to evaluate the amount of fluid. This can be standardized for example by press with the thumb during 3 minutes on the mid-ulnar aspect of the forearm or mid lower leg where the skin is directly above facies anterior tibiae.

Answer ND: ‘Pragmatically’ means that it is performed as in the real clinical situation. The study is performed in 3 recognised lymphoedema clinics in Belgium that already provides conservative treatment to patients with lymphoedema for many years. The type of compression garment (length, options, compression class, flat/round-knitted, standard/custom-made) is determined patient-specific. So, if a flat-knit garment is needed, a flat-knit garment is provided (in most of the cases). If only a round-knit garment is needed, this is also possible. All compression garments are fitted by persons with a large experience in fitting compression garments. These persons are specifically selected by the investigators of every study center. All information regarding type and amount of pieces of compression garments is collected during the trial and as a consequence can be verified at the end of the trial (see table 2).

15. Page 20, line 11

”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);”

Comment

Outcomes of ICG lymphofluoroscopy and lymph MRI can be affected if the patient has had optimal treatment before the investigation, thus showing less dermal backflow.

Comment

How do you interpret the outcomes in these cases when deciding what kind of surgery will be performed?

Answer ND: The study-procedure is that before inclusion of the patient, maximal decongestion must be obtained. Then we perform the different investigations and then we judge whether it is possible to perform surgery. LVA can be performed if there is presence of a functional lymphatic/ functional lymphatics. If before the investigation, decongestion is not obtained, we will not see the lymphatic and we will decide to not perform surgery. As a consequence, it is important that we first obtain decongestion of the limb.

16. Page 21, line 31

“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)).

Comment:
Numerous papers have shown that MLD has no effect on volume reduction. Why is MLD included? To release oxytocin and increase well-being?
Answer ND: We completely agree that MLD is not an evidence-based modality for treatment of lymphoedema. However, it has been demonstrated that by performing MLD the flow of lymph through the functional lymphatics is stimulated (see paper Tan 2011). Many surgeons specialized in performing reconstructive lymphatic surgery believe that performing MLD after LVA is important to keep the anastomosis open. We want to avoid that in case we cannot demonstrate an added value of reconstructive lymphatic surgery and have not performed MLD, that surgeons will say that this is because of not performing MLD. Therefore, we decided with the Trial Steering Committee to add MLD to the conservative treatment.

17. Page 21, line 52

"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."
Comment
Both extremities need to be measured (bilateral leg lymphedema excluded), see previous comment why this is important.
Answer ND: During the assessments in the study center, every time both arms/ both legs are measured. However, between month 6 and month 12, the weekly measurements are performed by the own physical therapist of the patient. These measurements are performed in the period that the patient is reducing the hours a day of wearing the compression garment. To avoid putting too much load on the physical therapist, we ask to measure only one limb. This measurement is not an outcome. It is only to verify whether it is safe to reduce the hours of wearing the compression garment further. If there is an increase, the patient is invited for an intermediate evaluation in the study center. Moreover, during this short period of 6M, we do not expect a change of the limb volume due to a change of fat tissue or muscle volume.

18. Page 21, line 57

"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."
Comment
Use the terminology "excess volume", that is if the "excess volume" "increases ≥5% compared to baseline "excess volume", the patient is planned for an intermediate checkup in the study center.", see previous comment regarding daily change of extremity volume due to measurements in the morning or in the afternoon as well as weight change.
For bilateral leg lymphedema, any reference why 5% is chosen?
Answer ND: 1) We use the term 'excessive volume' for the analyses of patients with arm lymphoedema. However, as previously discussed in point 6., this is not possible for patients with leg lymphoedema. 2) We have indeed chosen the 5% increase of limb volume as the criterion for a real increase. This is based on two studies that have investigated test-retest reliability of performing circumference measurements (and calculating the volume) in lymphoedema arms and legs. Smallest Real Difference of the calculated arm volume (based on circumferences with the perimeter) was 4.2% (Devoogdt 2010). Smallest Real Difference of the calculated leg volume was 3.6% (Jönsson 2023).

Outcomes

19. Page 27, line 24

Limb volume (key secondary outcome)

”Circumference measurements every 4 cm with perimeter; 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 AFFECTED ARM – volume UNAFFECTED ARM/ volume 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)

Answer ND: as previously discussed in point 6: 1) as the analyses of patients with arm lymphoedema and patients with leg lymphoedema are separately performed, we can define limb volume differently in the two studies, 2) too many patients with lower limb lymphoedema have bilateral lymphoedema; as a consequence we cannot exclude patients with bilateral lymphoedema (otherwise the study is not representative for all patients with lower limb lymphoedema), 3) as more than half of the participants have bilateral lymphoedema, we cannot use the outcome excessive volume.

Following text is added in the paper: *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.*

20. Hand/ foot volume

    Water displacement method of hand or foot 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)”

Comment

Here you describe, for arms, the ”excess volume”. I recommend that you use ”excess volume” in the previous parts of the paper where you refer to limb volume only.

For legs, where lymphoscintigraphy and ICG have shown normal function in the non-affected leg, I recommend you also use ”excess volume”. For bilateral lymphedema you can follow the limb volume since ”excess volume” cannot be calculated.

Answer ND: As previously discussed, the outcome for the study with arm lymphoedema patients is excessive arm volume. The outcome for the study with leg lymphoedema patients is leg volume. To be consistent, we have decided to evaluate the hand/ foot volume in the same way. It is a good suggestion to verify in patients with objective unilateral lymphoedema (based on lymphoscintigraphy; ICG lymphofluoroscopy is only performed on the limb followed in the trial) whether following the progression of the leg volume gives the same result as following the excessive leg volume.

21. Page 31, line 14

“The continuous data will be summarised using mean and SD or median and range values.”

Comment

Using mean and SD assume normal distribution. How will normality be calculated?

Answer ND (suggested by our statistician): Calculation of a mean does not assume a normal distribution. For every symmetrical distribution the median and mean value will be equal. Normality is not an issue when reporting descriptive statistics. Since we prefer to give as much information as possible on the distribution of a variable, we deemed it more appropriate to report mean (SD) and median (range/IQR).

The text is changed as follow: The continuous data will be summarised using mean *and* SD and median and range values.

22. Page 31, line 39

“The choice of the covariance structure for the five measurements will be based on the Aikake criterion.”

Comment

Reference needed.

Answer ND (advised by our statistician): following reference is added ‘Fitzmaurice, G. M. (2008). Longitudinal data analysis. Boca Raton (Fla.): Chapman & Hall/CRC.’

23. Page 31, line 48

“More specifically, starting from the MAR model, a jump-to-reference (JR) and tipping-point (TP) analysis will be applied.32”

Comment

Recommend you add a reference in English.

Answer ND (advised by our statistician): following reference is added ‘Molenberghs, G., Fitzmaurice, G. M, Kenward, M. G, Tsiatis, A. Athanasios, & Verbeke, G. (2015). Handbook of missing data methodology. Boca Raton (Fla.): CRC Press/Taylor and Francis.’

24. Page 31, line 58

”For the arm/ hand volume, ratios of the volume of the ipsilateral versus the contralateral side will be calculated.”

Comment

Regarding excess volume, I recommend using percent reduction (or increase) from baseline excess volume at follow-up as and in addition show mean (±SD)/median (IQR) absolute excess volumes at baseline and at each time point at follow-up.

Answer ND (advised by our statistician): First of all, percentage reduction/increase is an asymmetrical measure and should always be analyzed on a logarithmic scale (for a short explanation, see for example https://biostat.app.vumc.org/wiki/Main/MeasureChange). Further, The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient (see for example A. Vickers, BMC Medical Research Methodology (2001) 1:6). Therefore, we have opted for an ANCOVA type of approach which is expected to have higher power. Since there will be missing values, the comparison of the groups will be based on a cLDA model (which has an Ancova flavor).

Final comments

25. Lymphoscintigraphy

For lymphoscintigraphy outcomes I recommend using the Transport Index as described by Kleinhans, that is quantitative lymphoscintigraphy (99Tc-nanocolloid clearance rate) with calculation of the transport index performed at baseline and at follow-ups. Kleinhans E, Baumeister RG, Hahn D, Siuda S, Büll U, Moser E. Evaluation of transport kinetics in lymphoscintigraphy: follow-up study in patients with transplanted lymphatic vessels. Eur J Nucl Med. 1985;10(7-8):349-52. doi: 10.1007/BF00251310. PMID: 4006977. This will give an objective estimation of and change in lymph transport following surgery.

Answer ND: This is indeed a good suggestion. Besides the outcomes for lymphoscintigraphy mentioned in table 3, we will determine the transport index as well.

The Transport Index can be calculated using the following formula to categorize the lymphatic transport as normal or pathological. So: TI= K+ D + (0.04 × T)+ N+ V, where

K= transport kinetics (scored as 0—normal, 3—mild delay, 5—marked delay, 9— no transport);

D= distribution of the tracer (scored as 0—normal, 3—mild dermal diffusion, 5—marked dermal diffusion, 9—absent visualization);

T= time to visualize the lymph nodes (min);

N= visualization of lymph nodes (scored as 0— normal, 3—mild, 5—poor, 9—absent);
V= visualization of lymph vessels (scored as 0—normal, 3—mild, 5—poor, 9—absent).
The higher the score the worser is the lymphatic transport.

Changed in text as follow: Lymphoscintigraphy;[30] 55MBq ^{99m}Tc nanocolloids are injected 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*[31]
We have added a more recent reference: 31. Villa G, Campisi CC, Ryan M, et al. Procedural Recommendations for Lymphoscintigraphy in the Diagnosis of Peripheral Lymphedema: the Genoa Protocol. Nucl Med Mol Imaging 2019;53(1):47-56. doi: 10.1007/s13139-018-0565-2 [published Online First: 20190107]

26. Volumes

Regarding volumes you may consider the suggestion below as a very easy method to evaluate the effect of surgery.
Before surgery, for example 1 month before, the compression garment is removed and extremity volumes are measured and the excess volume is calculated. Then the patient is instructed to not wear the garment during one week and volumes and excess volume are measured again. This will show an increase in the volume of the affected extremity and excess volume. The garment is then applied again.
After surgery, for example at 3 and/or at 6 months or more, the same measurements are made as described above during 1 week. Postoperative measurements are then compared with preoperative and the efficacy of surgery can be evaluated.
Answer ND: Thank you for this suggestion. This is a pragmatic trial. So, in the clinical situation we will advise the patient to wear the compression garment less often. Some patients are careful and will gradually decrease the hours of wearing the garment. Other patients, will immediately stop the wearing. We have decided to standardize it by decreasing the hours a day of wearing the garment every month.

Reviewer: 2
Dr. Vaughn Keeley, University Hospitals of Derby and Burton NHS Foundation Trust
Comments to the Author:
This is an important and ambitious study which should shed light on the role of reconstructive lymphatic surgery in the management of lymphoedema.
Answer ND: Thank you so much for reviewing our paper and for your suggestions. We have answered the questions/ comments as good as possible. We hope that the answers meet the reviewer's expectations.

I have a number of small queries:

1) There is a start date included in the protocol but is there a date for completion of the study?
Answer ND: This is currently unknown. We included the first patient in March 2022 and included up to now 37 patients. The inclusion rate can be followed at: https://trials.kce.be/dashboard/index.html; the study short title is SurLym. We have to include at least 180 patients and have to follow them first up to

18M (primary end point) and thereafter up to 36M (end of trial). Different papers will be written for the short-term outcome (18M) and for the long term as well (36M). So, a long way to go. The inclusion rate is much slower than expected. We expected to include 180 patients during 24 months in the 3 study centers. Currently we have included 37 patients during 18 months. The reason of the slow recruitment rate is the design of the trial. A patient either prefers to receive surgery or do not want to receive surgery, but something in between is rare.

2) Page 10: I suggest that “failure to reduce hours a day of wearing compression stocking” should read “hours a day of wearing compression stocking” as this is what is assessed and the failure to reduce hours per day is an outcome based on the assessments.
Answer ND: I have changed it in table 1.

3) Page 10: I cannot see that you have cited the reference for the SPIRIT guidelines in the reference list for the paper.
Answer ND: I have added the reference.

4) Page 18: line 52: I think this should read 16 hours per day to 0 hours per day rather than 16 hours per week to 0 hours per week.
Answer ND: Thank you. This is indeed a mistake. I corrected it in the text.

5) Page 25 line 36 and Page 26 line 8: are the injections intradermal or subcutaneous?
Answer ND: Intradermally. I have added it in the text.

6) Page 34 reference 19 I think this was published in Lymphatic Research and Biology in 2021
Answer ND: Thank you. I have adapted the reference.

Reviewer: 3
Dr. David Chang, University of Chicago SSA
Answer ND: Thank you so much for reviewing our paper and for your suggestions. We have answered the questions/ comments as good as possible. We hope that the answers meet the reviewer's expectations.

Comments to the Author:

1) Primary & secondary? These are very different in terms of the cause, outcomes? Why include both? How about just limit to secondary only?
Answer ND: The study group are patients with arm lymphoedema on the one hand and patients with leg lymphoedema on the other hand. We aim to perform a study which is representative for all lymphoedema patients. Of course, we only perform surgery in patients in which we judge that reconstructive lymphatic surgery can have an effect. A patient with absence of lymphatic transport or with tortuous and dilated lymph vessels (as in some cases with primary lymphoedema) will certainly not be included.

2) 30 authors? Many NOT from these 3 centers?
Answer ND: Indeed many investigators cooperate in this trial. There are 3 study centers. In every center there is a group of surgeons, a study coordinator and assessor and a group of experts in imaging. There is also expertise needed of a statistician, persons who can help us with the economic analyses, of the clinical trial centre and of some independent experts. The whole study is coordinated by the chief investigator and project manager.
An overview hereunder in more detail:
- Sponsor UZ Leuven:

- Chief investigator: Nele Devoogdt
- Project manager: Tessa De Vrieze
- Head of dpt of vascular surgery: Inge Fourneau
- Head of center for lymphoedema: Sarah Thomis
- Statistician: Steffen Fieuws
- Economic analysis: Lode Godderis

- Study center UZ Leuven:
  - Principle investigator: Nele Devoogdt
  - Surgeons:
    - Sarah Thomis
    - Katarina Segers
    - Beate Bechter
  - Study coordinator, recruitment and assessor:
    - An-Kathleen Heroes:
  - Imaging:
    - Geer Maleux (Lymph MRI)
    - Sarah Thomis (ICG lymphofluoroscopy)
- Study center UZ Gent:
  - Principle investigator: Caren Randon
  - Surgeons:
    - Liesl Degraeve
    - Bernard De Pypere
  - Study coördinator, recruitment and assessor
    - Tina Decorte
    - Chris Monten
    - Mieke De Schryver
    - Vickie Van Besien
  - Imaging
    - Daniel Devos (Lymph MRI)
- Study center CHU UCL Namur
  - Principle investigator: Thierry Deltombe
  - Surgeons:
    - Philippe Fosseprez
    - Aline Berners
    - Maxime Servaes
  - Study coordinator, recruitment and assessor
    - Jacqueline Frippiat
  - Imaging:
    - Bruno Krug (lymphoscintigraphy)
    - Francoise Kayser (lymph MRI)
    - Ana Falticeanu (lymph MRI)
- Independent experts:
  - Sinikka Suominen (Finland)
  - Jaume Masia (Spain)
  - Gemma Pons (Spain)

3) Pragmatic? What does that mean?

Answer ND: Pragmatically' means that it is performed as in the real clinical situation. It involves dealing with things in a way that is based on practical considerations and actual circumstances rather than theoretical or idealized concepts. So the intervention (reconstructive lymphatic surgery) and also the usual care is performed as in the real clinical situation.

4) Authors state that “Currently, scientific evidence for reconstructive lymphatic surgery is not of high quality” I would disagree with statement. There are now ample scientific evidence to support reconstructive lymphatic surgery. Applaud the effort for prospective, randomized trial.
Answer ND: We mean with this statement that we miss randomized controlled trials. In literature, we find many (prospective or retrospective) observational studies following patients who had reconstructive lymphatic surgery ánd conservative treatment. So, it is unknown whether the result is attributed to the surgery or the conservative treatment or both. As a consequence, a randomized controlled trial is needed.
Changed in text as follow: 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 for lymphoedema has so far not been procured.* Therefore, the objective of this trial is to investigate the added value of reconstructive lymphatic surgery to the conservative treatment in patients with lymphoedema.

5) This is an on-going study? So why publish now? Would resubmit once the study is completed.
Answer ND: We want to publish the protocol of the trial because of different reasons: 1) To be transparent about the study design, primary and secondary outcomes, intervention, planned statistical analyses, etc.; 2) A publication about the results and further discussion of a clinical trial always has a word limit. If the protocol of the trial is already published, the author needs less words to explain the methodology of the trial and so saves words to show and discuss the results; and 3) To improve the visibility of the trial among potential participants.