PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Improving the quality of life of patients with breast cancer-related lymphedema by lymphaticovenous anastomosis (LVA): Study protocol of a multicenter randomized controlled trial.
AUTHORS	Wolfs, Joost; Beugels, Jop; Kimman, Merel; Piatkowski de Grzymala, Andrzej; Heuts, Esther; Keuter, Xavier; Tielemans, Hanneke; Ulrich, Dietmar; van der Hulst, R; Qiu, Shan Shan

VERSION 1 – REVIEW

REVIEWER	Margaret McNeely University of Alberta, Canada
REVIEW RETURNED	20-Nov-2019

GENERAL COMMENTS	The authors are proposing the first multicentre RCT comparing lympaticovenous anastomosis surgery to conservative treatment for women with breast cancer related lymphedema. The manuscript is a protocol paper of a study that is currently underway (started November 2018) . This research is greatly needed, and will help us to better understand the safety, benefits, appropriateness of this type of surgery for women with chronic lymphedema due to breast cancer. Strengths: Multicentre design, proposed cost effectiveness analyses, length of follow-up (24 months). Limitations: Unclear allocation concealment and lack of blinding of assessors for objective outcomes. The limitations (allocation concealment and blinding) should be included in the section on "Strengths and Limitations of this study" . As well, the limitations of the study should be included in the main paper. No planned stratification is described that may control for imbalances between the groups; although the authors state that any imbalances will be controlled statistically. i.e. related to duration or severity (amount of swelling involved in the women with early Stage 1-2a) of the lymphedema or body weight/ body mass index. This could be discussed further in relation to the eligibility criteria. The use of conservative treatment in the post-operative phase is a strength of the study; however, more information is needed on the use of the conservative treatment and use of MLD in the maintenance phase - how will ongoing conservative treatment (either group) be controlled? More information is needed specific to the post-operative conservative therapy (3 months) for the surgical group? How will you know if the findings are due to the

	surgery or a result of the women receiving more conservative treatment? Minor revisions: References supporting introduction and rationale could be updated. There are a number of grammatical errors and poor wording choices: i.e. Term "stockings" refers to garments used for lower limb. With the upper limb the terms more commonly used are: "compression sleeve" or "compression garment" or "compression hosiery".

REVIEWER	Didem KARADIBAK Dokuz Eylul Univ, school of physical therapy and rehabilitation
REVIEW RETURNED	21-Nov-2019

GENERAL COMMENTS	1.How long will take to treat(CDT) the group A? 2. References should be updated? 3. Reference 24 should be removed. Reference is too old. 4. The current number of references(2017-2019) is not enough. 5. The authors said that after surgery, patients will be treated with conservative therapy for 3 months.. Therefore, subjects who continue to CDT regularly should be added in inclusion criteria.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Reports:

Reviewer: 1
Reviewer Name: Margaret McNeely
Institution and Country: University of Alberta, Canada
Please state any competing interests or state ‘None declared’: None declared

The authors are proposing the first multicentre RCT comparing lympaticovenous anastomosis surgery to conservative treatment for women with breast cancer related lymphedema. The manuscript is a protocol paper of a study that is currently underway (started November 2018) .

This research is greatly needed, and will help us to better understand the safety, benefits, appropriateness of this type of surgery for women with chronic lymphedema due to breast cancer. Strengths: Multicentre design, proposed cost effectiveness analyses, length of follow-up (24 months).

Limitations:
Unclear allocation concealment and lack of blinding of assessors for objective outcomes. The limitations (allocation concealment and blinding) should be included in the section on "Strengths and Limitations of this study". As well, the limitations of the study should be included in the main paper.

Thank you for your kind comments. We agree that allocation concealment and blinding is not well referenced in the SPIRIT checklist as well as in the manuscript. After inclusion and informed consent, participants will be randomly assigned to either the operation (LVA) or conservative treatment (CDT) group with a 1:1 allocation as per a computer generated randomization schedule, stratified by site using block randomization. This allocation is done within the eCRF in CASTOR EDC. The SPIRIT checklist is updated and the allocation procedure is explained more in detail in the manuscript.

Blinding is not possible in this study, since the patients know if they underwent the operation or not. For the researcher, the operation scars are easily detectable during the measurements of the arm. However, health related quality of life is the primary outcome, which is examined by a digital standardized questionnaire. The researcher has no influence on this data.

The following changes are made in the manuscript:

Page 3, paragraph 2;

> Blinding of patients or researcher is not possible in this study due to visible scars postoperatively.

Page 6, paragraph 3;

This computer generated randomization is done within the electronic Case Report Form (eCRF) in CASTOR EDC ©.

Page 6, paragraph 4;

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

No planned stratification is described that may control for imbalances between the groups; although the authors state that any imbalances will be controlled statistically. i.e. related to duration or severity (amount of swelling involved in the women with early Stage 1-2a) of the lymphedema or body weight/ body mass index. This could be discussed further in relation to the eligibility criteria. Stratification between groups in every participating center is done.

We agree that stratification could be explained more in the manuscript. As stated above, stratification is explained on page 6 of the manuscript. Patients with only early stage lymphedema (ISL stage 1-2a) are included in the study (see Ref. #43 page 19). Therefore, no stratification is needed for severity and duration of lymphedema, since the differences in severity are quite small and duration of lymphedema might not be considered as a predictor for severity of lymphedema (see Ref. #26, 28, 29 page 18). Regarding BMI, in standard care, patients with a high BMI are not eligible for an operation, except in life-threatening cases. This is also applicable for this study, narrowing the differences in BMI (usually <30). Furthermore, the Upper Extremity Lymphedema-index (UEL-index) will be calculated from the circumference measurements and corrected by the BMI. Therefore, no stratification for BMI is mandatory. In the statistical analysis, any imbalance at baseline will be computed using linear regression.

The following changes are made in the manuscript:

Page 6, paragraph 3;

Since only early stage lymphedema patients are included and no large imbalances are expected, no stratification for other demographic data is applied.

The use of conservative treatment in the post-operative phase is a strength of the study; however, more information is needed on the use of the conservative treatment and use of MLD in the maintenance phase - how will ongoing conservative treatment (either group) be controlled?

We agree that the postoperative conservative treatment is not clearly explained in the manuscript. In this study we have a network of qualified skin therapists in the Netherlands who are treating the patients in this study. They are all connected to the Dutch Society of Skin therapists (NVH) and can be found via this link https://www.huidtherapie.nl/vind-een-huidtherapeut/. The communication between our department and the skin therapists is good and fluently. It is up to the skin therapists to decide the frequency suitable to each patient. The ongoing conservative treatment is evaluated during every follow-up moment by anamnesis and the digital patient diary.

The following changes are made in the manuscript:

Page 8, paragraph 3;

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

Page 9, paragraph 2 and 3;

From 2 weeks after surgery, when the stitches are removed, patients will be treated with conservative therapy the same way and in the same frequency as preoperatively. (45). After 3 months, the plastic surgeon will determine whether conservative therapy can be reduced or stopped, depending on the decrease of subjective complaints and swelling of the arm. The frequency of manual lymphatic drainage will be controlled by the skin therapist and noted in the patient diary.

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

More information is needed specific to the post-operative conservative therapy (3 months) for the surgical group?

Patients undergoing the LVA operation are advised not to restart with the conservative therapy until the stitches are removed, 2 weeks after the surgery. Thereafter, patients will continue conservative treatment as they were treated before the operation, with the same frequency. After 3 months, which is the first follow-up moment, it will be evaluated if conservative treatment (i.e. compression garment and/or manual lymphatic drainage) can be decreased or stopped. The plastic surgeon and researcher will examine the arm and evaluate differences in subjective complaints. The skin therapist would lead the frequency and type of manual lymphatic drainage for each patient. Patients are allowed to discontinue the use of compression garment in this first three months. All this information is noted in the patient diary.

The following changes are made in the manuscript:

Page 8, paragraph 3;

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

Page 9, paragraph 2 and 3;

From 2 weeks after surgery, when the stitches are removed, patients will be treated with conservative therapy the same way and in the same frequency as preoperatively. (45). After 3 months, the plastic surgeon will determine whether conservative therapy can be reduced or stopped, depending on the decrease of subjective complaints and swelling of the arm. The frequency of manual lymphatic drainage will be controlled by the skin therapist and noted in the patient diary.

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

How will you know if the findings are due to the surgery or a result of the women receiving more conservative treatment?

We understand the statement. To date, in our clinical experience, the benefits could be due to the combination of the LVA operation and manual lymphatic drainage. Most of the patients will continue with their regular conservative treatment from 2 weeks after surgery, with the same frequency as they received preoperatively. Differences in conservative treatment will be evaluated during every follow-up moment, the 3 month follow-up moment being the first. During this first 3 months, the frequency of the lymphatic drainage will not be changed.

The main objective in this study is the Health Related Quality of Life which increases after subjective complaints decrease or patients may discontinue the use of compression garment. We hypothesize that the manual lymphatic drainage does not have to be intensified after surgery and can be reduced in a large group. After performing the power analysis a total of 120 patients must be included in order

to get some statistical significant results. With this large study group, we hope to show high level evidence results regarding this question.

Minor revisions:
References supporting introduction and rationale could be updated.

We agree that some references are a little outdated. The reference list is updated (See ref #1,20,21,37,38,39,40,41,42 page 16-18).

There are a number of grammatical errors and poor wording choices:
i.e. Term "stockings" refers to garments used for lower limb. With the upper limb the terms more commonly used are: "compression sleeve" or "compression garment" or "compression hosiery".

We agree that the term “compression garment” is more commonly used. Therefore, the term “compression stocking” is changed to “compression garment”. Furthermore, the whole manuscript is checked again on grammar and spelling.

Reviewer: 2
Reviewer Name: Didem KARADIBAK
Institution and Country: Dokuz Eylul University, School of Physiotherapy and Rehabilitation, Izmir/Turkey
Please state any competing interests or state ‘None declared’: None

1.How long will take to treat(CDT) the group A?

Thank you for your kind comments. The follow-up period for both groups in this study is 2 years. CDT treatment in lymphedema patients is a lifelong treatment, since lymphedema is a progressive and chronic disease. CDT is initially aimed at alleviating symptoms without curative intent. Therefore, we follow the BCRL patients 2 years during their regular conservative treatment. It differs per patient for how long they already have conservative treatment depending on the onset of lymphedema, before participating in this study. However all of the participants must have at least 3 months of conservative treatment before being included in the study.

Patients in group B already have conservative treatment before participating in this study. After the 2 years follow-up they can choose to continue conservative treatment or plan another LVA operation if possible. More information regarding the CDT treatment is added in the manuscript.

The following changes are made in the manuscript:

Page 7-8, paragraph 1

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

2. References should be updated?

We agree that the references list must be updated. More recent published articles are added (See ref #1,20,21,37,38,39,40,41,42 page 16-18).

3. Reference 24 should be removed. Reference is too old.

We agree that this reference is too old and, therefore, is removed and replaced by more recent references (see ref #26 page 18).

4. The current number of references(2017-2019) is not enough.

We agree. As stated above, the references list is updated. More recent published articles are added (See ref #1,20,21,37,38,39,40,41,42 page 16-18).

5. The authors said that after surgery, patients will be treated with conservative therapy for 3 months. Therefore, subjects who continue to CDT regularly should be added in inclusion criteria..

It is true that patients will conceive conservative treatment after the LVA operation the same way they were treated before the operation. After 3 months, which is the first follow-up moment, it will be evaluated whether conservative treatment (i.e. compression garment and/or manual lymphatic drainage) can be decreased or stopped. Patients are allowed to discontinue the use of compression garment in this first three months. If subjective complaints or swelling does not decrease, conservative treatment will be continued. This will be evaluated every follow-up moment by the plastic surgeon and researcher. It is up to the skin therapists to decide the frequency suitable to each patient.

Conservative treatment (for at least 3 months) is one of the inclusion criteria (See manuscript page 7, Table 1 for the inclusion criteria). This applies for patients in both groups.

VERSION 2 – REVIEW

REVIEWER	Margaret McNeely University of Alberta, Canada
REVIEW RETURNED	09-Dec-2019

GENERAL COMMENTS	The authors have addressed all of my questions. Thank you for the clarifications. Suggestion: Add the 'lack of a standardized protocol for conservative interventions' among study participants as a limitation of the study.

VERSION 2 – AUTHOR RESPONSE

Thank you for reviewing the revision of the manuscript.

We agree that the standardized protocol is not well mentioned for all participants in both groups.

All participants are treated according to the same standardized lymphatic drainage method applied in the Netherlands (Verdonkmethod or Asdonkmethod), see manuscript page 8, paragraph 3.

For Group A: there is a protocol for the skin therapists how and in which frequency the participant must be treated during the study. This is mostly the way they are treated before participating in the study, since this is the standard treatment.

For Group B: the participants are treated by the same method, however, frequency is individualized depending on subjective complaints and swelling.

The following changes are made:

Page 8, paragraph 3;

See the Supplementary Data for the CDT protocol.

Page 9, paragraph 3;

The participants are treated by the same method as group A if needed, as described in phase 2 (maintenance phase) of the CDT protocol.

Supplementary Data: the CDT protocol was added.