

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Endovenous ablation and surgery in great saphenous vein reflux: A systematic review and network meta-analysis of randomised controlled trials protocol.
<b>AUTHORS</b>	Siribumrungwong, Boonying; Srikuea, Kanoklada; Orrapin, Saritphat; Benyakorn, Thoetphum; Rerkasem, Kittipan; Thakkinstian, Ammarin

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Alun Davies Imperial College London
<b>REVIEW RETURNED</b>	09-Jul-2018

<b>GENERAL COMMENTS</b>	Need to include new non thermal techniques for this to be meaningful. Need to be clear about difference of technique when doing network analysis ie laser is not just one uniform group. Also outcome measure, think re intervention needs to be discussed. . .? Use QoI rather than occlusion rate
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<b>REVIEWER</b>	Sari Vähäaho Vascular surgeon at Päijät-Häme Central Hospital, Finland Researcher at University of Helsinki, Finland
<b>REVIEW RETURNED</b>	06-Aug-2018

<b>GENERAL COMMENTS</b>	<ul style="list-style-type: none"> <li>- The study objective is quite interesting. We always need hard evidence to back up treatment solutions. Long-term results are still quite scarce on the subject, though thermal ablation methods are well established.</li> <li>- Abrasion is, to my knowledge, not quite the same as "ablation", which is the term that is consistently used in published papers about venous interventions. I would change "abrasion" to "ablation".</li> <li>- Endovenous steam ablation (SVS) is not mentioned with other endovenous techniques, is it going to be excluded from this study?</li> <li>- It hasn't been proven consistently, but open surgery (high ligation) can lead to neo-varicosities from the groin, the cause being surgical trauma; I would definitely say that endovenous techniques have an advantage over open surgery on this, and mention it as such (introduction).</li> <li>- The patency of the GSV is a good outcome, but in the study design it's not clearly defined. Also, after endovenous ablation and especially sclerotherapy, the GSV can be partially open i.e. have occluded segments and open segments. This can also be defined differently in different studies. Is a partially open GSV classified to</li> </ul>
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	"occluded" or "failed" in your study design? Or do you plan to address this problem in the final article?
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<b>REVIEWER</b>	Kathleen Gibson Lake Washington Vascular Surgeons Bellevue, WA, USA
<b>REVIEW RETURNED</b>	12-Aug-2018

<b>GENERAL COMMENTS</b>	<p>Endovenous ablation and surgery in great saphenous vein reflux. A systematic review and network meta-analysis of randomized controlled trials protocol. BMJopen-2018-024813</p> <p>I have the following questions/comments for the authors:</p> <ol style="list-style-type: none"> <li>1. The techniques to treat incompetence of the great saphenous vein have shifted in many regions of the world from open surgery to endovascular techniques. As briefly mentioned by the authors (beginning of page 4 and start of page 5), nonthermal/nontumescent techniques (included a proprietary foam sclerosant) are increasingly being used. There are some RCTs of these techniques, although the number of studies is not large. I encourage the authors to explain why they have chosen not to include these techniques in their study protocol. I suspect it is because of the limited number of studies, but the reader will be curious as to why. In the future, it will be important to review these new techniques in a similar fashion as at current time they are more expensive than existing technologies and may offer little to no added benefit to patients.</li> <li>2. I am concerned that all kinds of ultrasound guided foam sclerotherapy are lumped together. How do the authors plan to account for differences in technique, sclerosant used, and sclerosant concentrations? Are you including trials using proprietary endovenous microfoam (Varithena), or just trials of physician-compounded foam sclerotherapy?</li> <li>3. On page 9, Lines 50-54 the authors list possible sources of heterogeneity including concomitant phlebectomy. Concomitant UGFS (of branches conducted at the same time as endothermal ablation) is another potential source of heterogeneity.</li> <li>4. The authors use anatomical success as the outcome of interest. Anatomical success is a surrogate marker that may have little meaning to patients. The secondary outcomes of interest listed by the authors are much more important to patients, although they are much more difficult to compare in a meta-analysis due to the heterogeneity of instruments used. Nonetheless, I would encourage the authors to pay particular attention to the patient reported outcome measures in the analysis of their results.</li> <li>5. Edit for spelling and grammar. The word "abrasions" is used instead of "ablations" on page 3 line 28 and page 7 line 40.</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Alun Davies

Institution and Country: Imperial College London

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Need to include new non-thermal techniques for this to be meaningful.

*We have reconsidered to include non-thermal techniques (i.e., mechano-chemical ablation and cyanoacrylate injection) in our review as your suggestion, see Page 6, 7 and 8. Search terms and strategies have also been added accordingly, see Page 7.*

Need to be clear about difference of technique when doing network analysis i.e. laser is not just one uniform group.

*Our interventions of interest are comparisons among ablation types. Laser with different wavelengths (i.e., shorter (810, 940, 980 nm) and longer wavelength (1470, 1560 nm) and pull back type will also be considered if data are sufficient for pooling. More explanation about the methodology have been added in the Method section, see Page 8 and 10.*

Also outcome measure, think re intervention needs to be discussed.

..? Use QoI rather than occlusion rate

*We have added re-intervention rate as one of secondary outcomes as your suggestion, see page 6 and 9. Quality of life (QoI) had already been stated as one of our secondary outcomes.*

Reviewer: 2

Reviewer Name: Sari Vähäaho

Institution and Country: Vascular surgeon at Päijät-Häme Central Hospital, Finland, Researcher at University of Helsinki, Finland

Please state any competing interests or state 'None declared': I suspect my study will be included in the meta-analysis, though I think it has no effect on me reviewing this protocol.

Please leave your comments for the authors below

- The study objective is quite interesting. We always need hard evidence to back up treatment solutions. Long-term results are still quite scarce on the subject, though thermal ablation methods are well established.

- Abrasion is, to my knowledge, not quite the same as "ablation", which is the term that is consistently used in published papers about venous interventions. I would change "abrasion" to "ablation".

*We have corrected the terms for the whole proposal as suggested.*

- Endovenous steam ablation (SVS) is not mentioned with other endovenous techniques, is it going to be excluded from this study?

*We have included endovenous steam ablation as another endovenous techniques for comparison in the study as your suggestion, see Page 5, 6, and 8.*

*We also add more search terms that is relevant to endovenous steam ablation in the search strategy, see Page 7.*

- It hasn't been proven consistently, but open surgery (high ligation) can lead to neovaricosities from the groin, the cause being surgical trauma; I would definitely say that endovenous techniques have an advantage over open surgery on this, and mention it as such (introduction).

*We have mentioned more about advantage of endovenous techniques in neovascularization over open surgery in the Introduction section as your suggestion, see Page 5. We also added neovascularization and reflux in tributaries into secondary outcomes, see Page 6 and 9.*

- The patency of the GSV is a good outcome, but in the study design it's not clearly defined. Also, after endovenous ablation and especially sclerotherapy, the GSV can be partially open i.e. have occluded segments and open segments. This can also be defined differently in different studies. Is a partially open GSV classified to "occluded" or "failed" in your study design? Or do you plan to address this problem in the final article?

*As we knew that different studies defined anatomical successful differently. We are working on summary/aggregated meta-analysis, in which re-define definition is less likely and thus rely on definitions used according to the original studies. However, definition of anatomical success will be collected (i.e., non-occlusion, partially open without reflux, and reflux) and will be used to explore source of heterogeneity or subgroup analysis. We have added more explanation about this topic in Page 9, 10.*

Reviewer: 3

Reviewer Name: Kathleen Gibson

Institution and Country: Lake Washington Vascular Surgeons, Bellevue, WA, USA

Please state any competing interests or state 'None declared': Scientific Advisory Board/Research

Support: Medtronic; Consultant/research support: BTG, Vascular Insights; Research support:

Angiodynamics

Please leave your comments for the authors below

Endovenous ablation and surgery in great saphenous vein reflux. A systematic review and network meta-analysis of randomized controlled trials protocol. BMJopen-2018-024813

I have the following questions/comments for the authors:

1. The techniques to treat incompetence of the great saphenous vein have shifted in many

regions of the world from open surgery to endovascular techniques. As briefly mentioned by the authors (beginning of page 4 and start of page 5), nonthermal/nontumescent techniques (included a proprietary foam sclerosant) are increasingly being used. There are some RCTs of these techniques, although the number of studies is not large. I encourage the authors to explain why they have chosen not to include these techniques in their study protocol. I suspect it is because of the limited number of studies, but the reader will be curious as to why. In the future, it will be important to review these new techniques in a similar fashion as at current time they are more expensive than existing technologies and may offer little to no added benefit to patients.

*We have added these non-thermal non-tumescent techniques in the study protocol, see Page 6,7, and 8.*

2. I am concerned that all kinds of ultrasound guided foam sclerotherapy are lumped together. How do the authors plan to account for differences in technique, sclerosant used, and sclerosant concentrations? Are you including trials using proprietary endovenous microfoam (Varithena), or just trials of physician-compounded foam sclerotherapy?

*We have revised this to do not lump data for UGFS and also laser types as suggested if data are sufficient for pooling and there are also common comparators to link in the network. This has been revised in the method, see Page 10.*

3. On page 9, Lines 50-54 the authors list possible sources of heterogeneity including concomitant phlebectomy. Concomitant UGFS (of branches conducted at the same time as endothermal ablation) is another potential source of heterogeneity.

*We have added concomitant UGFS to varicosities as other sources of heterogeneity as your suggestion, see Page 10.*

4. The authors use anatomical success as the outcome of interest. Anatomical success is a surrogate marker that may have little meaning to patients. The secondary outcomes of interest listed by the authors are much more important to patients, although they are much more difficult to compare

in a meta-analysis due to the heterogeneity of instruments used. Nonetheless, I would encourage the authors to pay particular attention to the patient reported outcome measures in the analysis of their results.

*We agree that patient-reported outcome is very important, as statement in Page 5 paragraph 2, and have planned to pool self-reported quality of life as the secondary outcome, see Page 9.*

5. Edit for spelling and grammar. The word “abrasions” is used instead of “ablations” on page 3 line 28 and page 7 line 40.

*Done for the whole proposal.*

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Sari Vähäaho Paijat-Hameen keskussairaala
<b>REVIEW RETURNED</b>	01-Oct-2018

<b>GENERAL COMMENTS</b>	<ul style="list-style-type: none"> <li>- I see that steam, MOCA, and cyanoacrylate ablation have been added to this study protocol. This might make the meta-analysis quite complex especially since it aims to include so many outcomes, but like the other reviewers, I find NTNT's interesting and somewhat necessary.</li> <li>- The outcome of anatomical success has now been better defined; this outcome might still prove to be a problem, since different studies have different definitions.</li> <li>- In the paragraph "interventions", UGFS is not defined to be either thermal or NTNT ablation.</li> <li>- There are a number of grammar errors in the manuscript, such as in the paragraph "interventions" where some sentences are in the present tense and some in past tense. Some punctuation marks are missing and some sentences even miss the verb. I think the manuscript needs a proper language check before considering publishing.</li> <li>- In the end, this meta-analysis might prove difficult since UGFS can't be directly compared to UGFS done by another protocol; also, some studies have concomitant phlebectomies and some UGFS of tributaries etc. and this analysis aims to compare everything. But I am curious to see how this works out.</li> </ul>
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<b>REVIEWER</b>	Kathleen Gibson Lake Washington Vascular Surgeons
<b>REVIEW RETURNED</b>	30-Sep-2018

<b>GENERAL COMMENTS</b>	The authors have addressed the concerns of myself and the other reviewers. I recommend acceptance of the manuscript.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2<sup>[SEP]</sup> Reviewer Name: Sari Vähäaho<sup>[SEP]</sup> Institution and Country: Central Hospital of Päijät-Häme, Lahti, Finland and Department of Vascular Surgery, Helsinki University Hospital, Institute of Clinical Medicine, Faculty of Medicine, University of Helsinki, Helsinki, Finland<sup>[SEP]</sup> Please state any competing interests or state 'None declared': None declared<sup>[SEP]</sup> Please leave your comments for the authors below<sup>[SEP]</sup>

- I see that steam, MOCA, and cyanoacrylate ablation have been added to this study protocol. This might make the meta-analysis quite complex especially since it aims to include so many outcomes, but like the other reviewers, I find NTNT's interesting and somewhat necessary.

It is common for a systematic review and meta-analysis to consider as many relevant clinical outcomes as possible. If we can analyse, i.e., outcome data are mostly available and allow us to pool both benefit and risk outcomes, it will be very useful information for surgeons and physicians to decide which type of intervention is appropriate for their patients.

<sup>[SEP]</sup> The outcome of anatomical success has now been better defined; this outcome might still prove to be a problem, since different studies have different definitions.

Again, meta-analysis works based on summary data from original studies; different studies may have used different definitions in defining outcome. We were not able to re-classify or categorise it unless we could get individual patient data.

However, we still pooled data across studies, but their differences in definition may be a source of heterogeneity. We have rewritten the definition of anatomical success to make it clearer, see Page 8. In addition, outcome definition was explored as possible source of heterogeneity, see Page 10.

<sup>[SEP]</sup> In the paragraph "interventions", UGFS is not defined to be either thermal or NTNT ablation.

We have added UGFS as one type of NTNT, see Page 8.

<sup>[SEP]</sup> There are a number of grammar errors in the manuscript, such as in the paragraph "interventions" where some sentences are in the present tense and some in past tense. Some punctuation marks are missing and some sentences even miss the verb. I think the manuscript needs a proper language check before considering publishing.

This manuscript has been edited by Stephen Pinder, who is an British native speaker who specialised in manuscript editing.



<sup>11</sup><sub>SEP</sub> In the end, this meta-analysis might prove difficult since UGFS can't be directly compared to UGFS done by another protocol; also, some studies have concomitant phlebectomies and some UGFS of tributaries etc. and this analysis aims to compare everything. But I am curious to see how this works out.

Again, with the same definition of outcome, the same interventions may differ in term of dosage, frequency, or even technique like in our study. We can combine them together or separately combine depending on numbers of included studies. If there are many studies, that may allow us to separately pool, otherwise we will combine them all and consider difference as source of heterogeneity, see Page 10.