PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol
AUTHORS	Webb, Elizabeth; Neeman, Teresa; Gaida, Jamie; Bowden, Francis; Mumford, Virginia; Bissett, Bernie

VERSION 1 - REVIEW

REVIEWER	G Cooper-Stanton University of Wolverhampton
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	Thank you for your submission. I can see that the research proposed is required within the realms of chronic oedema/lymphoedema. This would also add to the existing evidence surrounding cellulitis beyond the use of antibiotics, such as in the Patch 1 and 2 trials. I will look forward to the results of the study and how they can be fed into patient care.

REVIEWER	Danwang Celestin School of public health, Université Libre de Bruxelles, Brussels, Belgium.
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	lower limb chronic oedema is one of the major risk factors of lower limb cellulitis. It is recognized that prevention and treatment of this condition could delay recurrence of cellulite. However, studies supporting this theory are scare. The authors propose a RCT protocol in order to determine if compression therapy delays the recurrence of lower limb cellulitis in adults with lower limb chronic oedema and recurrent cellulitis. Some aspects to clarify: 1. Trial design: The authors are planning to conduct a RCT 1:1 cross over design. With an intervention and control group. participants in the control group, once an episode of cellulitis has occurred, will cross-over into the intervention group. For patients in the intervention group at the beginning of the study, are they in the intervention group until the end of the study? At which moment will there cross-over? Clarify please. 2. Eligibility criteria: line 22. "…presence of oedema confirmed by a

	lymphoedema therapist through interview and physical examination". Which criteria will be used by the therapist to make the diagnosis of oedema? Clarify please. 3. Interventions: Line 22. " Compression therapy will involve application of compression garments (compression stockings or wraps) and may or may not involve compression bandaging". Which criterion will be used to decide if a patient will receive compression stockings or wraps associated with compression or not? To standardized the intervention for all participants, it may be preferable to choose and specify exactly the type of compression stockings and bandage that will be used for all participants and whether or not compression will be associated for all participants at the beginning. 4. Interventions: Line 24. What will be the criteria used to build the follow-up schedule for each patient? authors should standardize the follow-up schedule for all the participants in order to eliminate subjectivity of the therapist who could decide to give more appointments to patients in the intervention group. 5. The sample size after computation is estimated to 162. But this sample size doesn't take into consideration participants that will be loss to follow up. Correct the sample size according to that please. 6. Participant Retention, line 53: at the end of the study you will probably end up with missing data, how are you planning to do your statistical analysis considering this missing data? 7. References: Please write your references according to BMJ Open editorial office recommendations.

REVIEWER	Peter Mortimer St Georges University of London SW17 0RE UK
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	The proposed randomised controlled trial entitled Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol is much needed. The authors are correct in stating that the evidence base for justifying compression therapy in the prevention of recurrent cellulitis in chronic oedema/lymphoedema is lacking. I have the following comments: 1.There is often confusion as to the difference between chronic oedema and lymphoedema and the authors should define each condition/diagnosis. Lymphoedema is strictly a diagnosis of oedema caused by lymph drainage failure whereas chronic oedema is a physical sign/clinical condition due to an excess of transcapillary plasma filtration overwhelming lymph drainage over a period of time (Levick JR. An Introduction to Cardiovascular Physiology, 5th edn. London: Arnold, 2010). In clinical practice they can be considered one of the same because both represent lymph drainage failure. Lymph drainage is responsible for all interstitial fluid drainage as there is no venous reabsorption in the steady state. There is substantial evidence that with important exceptions such as the renal cortex and medulla, down- stream microvessels are not in a state of sustained fluid absorption as traditionally depicted. Although

	doggedly persistent in textbooks and teaching, the traditional view of filtration–reabsorption balance has little justification in the microcirculation of most tissues. Tissue fluid balance thus depends critically on lymphatic function in most tissues (Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 2010;87(2):198–210). Therefore, to use chronic oedema as a surrogate for lymphoedema is acceptable and is more likely to be identified for recruitment than using the term lymphoedema. 2. Criteria for the diagnosis of cellulitis should be considered. Cellulitis with lymphoedema can present differently with sometimes no raised inflammatory markers nor fever. However, in order to ensure lipodermatosclerosis (red painful swollen legs usually bilateral without systemic toxicity or raised inflammatory markers) is not recruited in place of cellulitis, entry criteria should ensure that in addition to local signs there should be either systemic toxicity (fever or flu-like symptoms) or raised blood inflammatory markers (www.lymphoedema.org/cellulitis consensus). 3. In the NEJM trail of prophylactic penicillin for recurrent cellulitis (Thomas KS, et al.; UK Dermatology Clinical Trials Network's PATCH I Trial Team (2013). Penicillin to prevent recurrent leg cellulitis. N Engl J Med, 368, 1695–703) which for some reason the authors do not reference, risk factors for a poor response included obesity, multiple previous attacks, and chronic oedema, all suggesting poor lymph drainage. The authors need to consider these factors in their outcome measures. 4. In the trial design I am not sure about a crossover study as there may be considerable benefit, on lymph drainage efficiency including improved immune cell trafficking, from wearing compression garments for some time afterwards. I cannot prove or provide a reference for this statement, it is purely hypothetical, but if it is true it will confound the results. 5. I am not sure the time spent measuring limb volume is well spent. A reduction in limb volume may be interesting but is not necessary for an effect of compression in preventing cellulitis. The benefit of compression (if it works) will be through a mechanism of improving immune cell function. This is why lymph drainage failure creates an infection risk, not because of swelling per se. The lymphatic system facilitates tissue fluid transport but is also designed to support communication between cells of the innate and adaptive immune systems and the functions are not inter-dependent. During inflammation, changes within the lymphatics can result in an altered response to infection. Neutrophils are one key cell type that facilitate antigen capture and presentation within the lymphatic system, enabling an effective adaptive immune response. (Stephens M, Liao S. Neutrophil-lymphatic interactions during acute and chronic disease. Cell Tissue Res. 2018 Mar;371(3):599-606).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Thank you very much for taking the time to read our manuscript. We also look forward to seeing how these results may guide patient care in the future.

Reviewer 2:

1. Trial design: The authors are planning to conduct a RCT 1:1 cross over design. With an intervention and control group. participants in the control group, once an episode of cellulitis has occurred, will crossover into the intervention group. For patients in the intervention group at the beginning of the study, are they in the intervention group until the end of the study? At which moment will there cross-over? Clarify please

- Thank you for the opportunity to clarify this aspect of our trial design. We have outlined that only the control group will undertake cross-over in paragraph 1 under the 'trial design' subheading and in figure 1. We have clarified this further by amending a sentence within the mentioned paragraph to say:

Following an episode of cellulitis, participants in the control group will cross-over into the intervention group, whereas intervention group participants will remain in their original group and continue to receive compression therapy.

- We have amended the following paragraph to clarify when cross-over occurs

Cross-over of control group participants will be triggered upon clinician identification of cellulitis. Recurrence of cellulitis will be checked at scheduled appointments, however if a participant reports a recurrence between scheduled assessments, they will be reviewed at an additional appointment to record outcome measures (table 1), and to commence cross-over for control group participants. Date of cross-over will be defined as the day compression garments are initially fitted.

2. Eligibility criteria: line 22. "…presence of oedema confirmed by a lymphoedema therapist through interview and physical examination". Which criteria will be used by the therapist to make the diagnosis of oedema? Clarify please.

- Thank you for the opportunity to clarify our diagnoses of lymphoedema. In our trial chronic oedema is a clinical diagnosis made by experienced accredited level 1 or 2 lymphoedema practitioners who meet the registration requirements for category one of the Australian National Lymphoedema Practitioners Register (as per paragraph one under the interventions subheading). For clarity we have amended the eligibility criteria regarding chronic oedema to say:

Chronic oedema (oedema persisting ≥ 3 months) in the leg/s that have had recurrent cellulitis diagnosed (presence of oedema confirmed by an accredited lymphoedema therapist through interview and physical examination, including a thorough medical history combined with limb palpation and visual assessment)

3. Interventions: Line 22. " Compression therapy will involve application of compression garments (compression stockings or wraps) and may or may not involve compression bandaging". Which criterion will be used to decide if a patient will receive compression stockings or wraps associated with compression or not? To standardized the intervention for all participants, it may be preferable to choose and specify exactly the type of compression stockings and bandage that will be used for all participants and whether or not compression will be associated for all participants at the beginning.

• While we agree that in this trial design it would be ideal to standardize compression therapy across all participants, this study takes a pragmatic approach replicating the individualized therapy provided in clinical practice. Compression therapy must be customized depending on oedema severity, limb shape and ability of the patient and/or their carer to don and doff garments. Patient's functional status, oedema severity and limb shape vary significantly and as such it is impossible to standardize treatment across all participants. This study aims to replicate clinical practice, where compression garments and bandaging will vary between patients, being prescribed based on clinical presentation, patient preference and patient capacity to don and doff garments.

4. Interventions: Line 24. What will be the criteria used to build the follow-up schedule for each patient? authors should standardize the follow-up schedule for all the participants in order to eliminate subjectivity of the therapist who could decide to give more appointments to patients in the intervention group.

• We agree that follow up of participants needs to be standardized as much as possible. The follow up schedule is the same for all patients. However, we have noted that patients in the intervention group may attend more appointments than those in the control group in order to undergo compression bandaging and fitting of compression garments. This has been acknowledged as a design weakness under the internal validity subheading where we stated "Control and intervention group participants have the same appointment schedule throughout the duration of the trial, however participants in the intervention group may attend more appointments than the control group. This systematic difference in clinician contact could influence participant's perceived benefit, allowing potential bias in self-reported measures (LYMQOL, EQ-5D)."

5. The sample size after computation is estimated to 162. But this sample size doesn't take into consideration participants that will be loss to follow up. Correct the sample size according to that please.

• For our primary outcome measure we are using time-to-event analysis, with our study being powered (assuming an effect size = hazard ratio) based upon the total number of events one needs to see. The total sample size is then estimated given the overall expected event rate. If the event rate is less than expected, then more subjects would be required. Similarly, if there is loss to follow-up, then more subjects may also be needed. The 162 patients was our best current estimate on the number that would be needed to see 45 events. We can revisit the assumptions of our time-to-event calculations should loss to follow-up become an issue.

6. Participant Retention, line 53: at the end of the study you will probably end up with missing data, how are you planning to do your statistical analysis considering this missing data?

• For the primary (time-to-event) analysis, patients lost to follow-up will be censored at the time of last follow-up. Under the 'Proposed methods for data analysis' subheading, we have stated "Right censoring will be used for participants who are lost to follow up".

7. References: Please write your references according to BMJ Open editorial office recommendations.

• Thank you for alerting us to our deviation from the BMJ open referencing guidelines. We have removed the journal issue which was incorrectly added and modified how we referenced the 'date accessed' for websites.

Reviewer 3:

1.There is often confusion as to the difference between chronic oedema and lymphoedema and the authors should define each condition/diagnosis. Lymphoedema is strictly a diagnosis of oedema caused by lymph drainage failure whereas chronic oedema is a physical sign/clinical condition due to an excess of transcapillary plasma filtration overwhelming lymph drainage over a period of time (Levick JR. An Introduction to Cardiovascular Physiology, 5th edn. London: Arnold, 2010). In clinical practice they can be considered one of the same because both represent lymph drainage failure. Lymph drainage is responsible for all interstitial fluid drainage as there is no venous reabsorption in the steady state. There is substantial evidence that with important exceptions such as the renal cortex and medulla, down- stream microvessels are not in a state of sustained fluid absorption as traditionally depicted. Although doggedly persistent in textbooks and teaching, the traditional view of filtration–reabsorption balance has little justification in the microcirculation of most tissues. Tissue fluid balance thus depends critically on lymphatic function in most tissues (Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 2010;87(2):198–

210). Therefore, to use chronic oedema as a surrogate for lymphoedema is acceptable and is more likely to be identified for recruitment than using the term lymphoedema.

• Thank you for this advice. We agree that adding both lymphoedema and chronic oedema definitions will add clarity and improve the manuscript. We have added the following paragraph to our manuscript:

Oedema occurs when capillary filtration overwhelms the available lymphatic drainage10. Lymphoedema specifically refers to persistent oedema resulting from lymphatic drainage failure11. Chronic oedema is an umbrella term that refers to oedema resulting from insufficient lymphatic drainage, where the principle cause of the oedema may be increased capillary filtration and/or lymphatic drainage failure11. As such, the term chronic oedema encompasses oedema of various aetiologies, including lymphoedema. For the purpose of this trial, we will use the term chronic oedema.

2. Criteria for the diagnosis of cellulitis should be considered. Cellulitis with lymphoedema can present differently with sometimes no raised inflammatory markers nor fever. However, in order to ensure lipodermatosclerosis (red painful swollen legs usually bilateral without systemic toxicity or raised inflammatory markers) is not recruited in place of cellulitis, entry criteria should ensure that in addition to local signs there should be either systemic toxicity (fever or flu-like symptoms) or raised blood inflammatory markers

(www.lymphoedema.org/cellulitis consensus).

• We completely agree that in an ideal study design we would use specific criteria to ensure cellulitis has been correctly diagnosed. In this study design patients are referred from GP practices and hospitals into the trial with a history of 2 or more episodes of cellulitis. Diagnosis is conducted independently from the trial with no oversight from clinicians providing intervention. This pragmatic approach best replicates clinical practice in Australia, where lymphoedema therapists would accept medical referrals of cellulitis on face value. We have acknowledged this limitation by the addition of the following sentence, and plan for this to be a discussion point when we publish the RCT results.

Participants enrolled in the trial have a history of 2 or more episodes of cellulitis diagnosed by medical practitioners independent to the trial. As misdiagnosis of lower limb cellulitis is not uncommon34, the trial may include incorrectly diagnosed participants leading to non-differential misclassification.

3. In the NEJM trail of prophylactic penicillin for recurrent cellulitis (Thomas KS, et al.; UK Dermatology

Clinical Trials Network's PATCH I Trial Team (2013). Penicillin to prevent recurrent leg cellulitis. N Engl J Med, 368, 1695–703) which for some reason the authors do not reference, risk factors for a poor response included obesity, multiple previous attacks, and chronic oedema, all suggesting poor lymph drainage. The authors need to consider these factors in their outcome measures.

- Thank you for reminding us about the need to contextualize our study with respect to the Patch Trials, which we are agree are critical in this space. We have modified our introduction to ensure we refer to this important research:

The time-intensive nature of compression therapy, and the fact that measuring meaningful outcomes requires lengthy assessment periods, probably contribute to the lack of research in this field. Only one study has been conducted on the impact of oedema management on cellulitis recurrence17, with a second study incidentally observing a reduction in 'infection' among patients receiving oedema management, although this was not a research objective.18 While both studies support the hypothesis that oedema management decreases cellulitis recurrence, their conclusions are hampered by methodological limitations, including pre-post intervention methods, small sample sizes and change in infection rate not being specified a research objective.17 18 Whilst research regarding compression therapy to prevent cellulitis recurrence is scarce, there is high quality evidence to support the use of prophylactic antibiotics. A multi-centre, double-blind, randomised controlled trial found that use of prophylactic antibiotics in patients experiencing recurrent cellulitis is effective in preventing subsequent attacks, although the effect diminishes following prophylaxis cessation.19 A 2017 Cochrane systematic review of interventions to prevent cellulitis identified 6 studies investigating prophylactic antibiotics, but no other randomised trials investigating other prophylactic measures such as oedema management or skin care.20 Thus further research into the efficacy of prophylactic measures other than antibiotic, is warranted.20

- We agree that these risk factors for prophylaxis failure are important to capture in our patient sample. Obesity (BMI) and chronic oedema volume (measured using perometry) are captured at enrollment and scheduled follow-up appointments (see table 1). Duration of chronic oedema prior to the trial is also captured at enrollment. In terms of previous attacks, due to the limitations of our processes and record systems, we are limited to capturing attacks during the 2 years prior to trial enrollment. We have amended the below sentence for clarity.

Prior to randomisation, baseline measures including number of episodes of cellulitis in the 2 years prior to referral, duration of chronic oedema, referral source and demographics will be captured.

4. In the trial design I am not sure about a crossover study as there may be considerable benefit, on lymph drainage efficiency including improved immune cell trafficking, from wearing compression garments for some time afterwards. I cannot prove or provide a reference for this statement, it is purely hypothetical, but if it is true it will confound the results.

• This is an interesting hypothesis that would be fascinating to explore further. For the purpose of this study we would just like to clarify that only to control group will be crossing over while the intervention group will remain in compression, and will hopefully continue to benefit as you described.

5. I am not sure the time spent measuring limb volume is well spent. A reduction in limb volume may be interesting but is not necessary for an effect of compression in preventing cellulitis. The benefit of compression (if it works) will be through a mechanism of improving immune cell function. This is why lymph drainage failure creates an infection risk, not because of swelling per se. The lymphatic system facilitates tissue fluid transport but is also designed to support communication between cells of the innate and adaptive immune systems and the functions are not inter-dependent. During inflammation, changes within the lymphatics can result in an altered response to infection. Neutrophils are one key cell type that facilitate antigen capture and presentation within the lymphatic system, enabling an effective adaptive immune response. (Stephens M, Liao S. Neutrophil-lymphatic interactions during acute and chronic disease. Cell Tissue Res. 2018 Mar;371(3):599-606).

• This is a valid point. The role of immune cell function in cellulitis recurrence is certainly something worth exploring and we would love to discuss this more in another context. In the absence of access to sophisticated technology, we have used limb volume

(perometry) as our best estimate of changes in chronic oedema. In clinical settings within Australia, measurement of limb volume is standard practice to assess oedema fluctuation and to some degree compression efficacy. We realise this measurement tool is not specific and far from perfect, but we plan to use it as simply as a secondary measure with the knowledge it may also allow us to compare our intervention outcomes (volume reduction) to other published research.

VERSION 2 – REVIEW

REVIEWER	Danwang Celestin School of Public Health, Universitè Libre de Bruxelles, Brussels, Belgium.
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	Most of our comments were addressed by the authors.

REVIEWER	Professor Peter Mortimer St George's University of London UK
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	The authors have satisfactorily addressed my concerns except for criteria for the diagnosis of cellulitis by infection. I predict there will be a lot of misdiagnoses due to lipodermatosclerosis. The authors should include criteria for the diagnosis of cellulitis e.g acute bouts of erythema with increased local heat, pain and swelling. Systemic

	upset such as feeling unwell with or without fever should be an essential requirement. A raised CRP and/or white cell count is desirable but not essential.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2:

Thank you very much for taking the time to review our manuscript amendments.

Reviewer 3:

Comment: The authors have satisfactorily addressed my concerns except for criteria for the diagnosis of cellulitis by infection. I predict there will be a lot of misdiagnoses due to lipodermatosclerosis. The authors should include criteria for the diagnosis of cellulitis e.g acute bouts of erythema with increased local heat, pain and swelling. Systemic upset such as feeling unwell with or without fever should be an essential requirement. A raised CRP and/or white cell count is desirable but not essential.

- This is an important point you have raised, and it will be a limitation of the study. Because the study participants are recruited after a diagnosis of cellulitis has already been made (by their general practitioner, emergency physician, or during their hospital admission), the study protocol presumes the doctors involved have followed the best available diagnostic guidelines as you have outlined. We have added a statement regarding the diagnostic criteria for cellulitis, as seen below. We acknowledge that diagnosed cellulitis episodes could include misdiagnosed lipodermatosclerosis and other conditions. However, in our local context, we do not have the capacity to rigorously ensure all prior diagnoses comply strictly with the criteria specified. We intend to acknowledge this clearly when the results are published. Whilst the results may include some misdiagnoses, the results will still inform treatment practice for patients presenting with a similar pattern of symptoms.

≥ 2 episodes of cellulitis diagnosed in the same leg in the past 2 years (at the time of referral). Clinical diagnosis of cellulitis ideally will have been based on the presence of acute erythema, oedema, warmth and pain, with spreading involvement of the skin and subcutaneous tissues, malaise, and possibly fever.

- We have also acknowledged this trial limitation in the sentence below, and plan to discuss this within the RCT publication.

Participants enrolled in the trial have a history of 2 or more episodes of cellulitis diagnosed by medical practitioners independent to the trial. As misdiagnosis of lower limb cellulitis is not uncommon (34), the trial may include incorrectly diagnosed participants leading to non-differential misclassification.