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

TITLE (PROVISIONAL)	The effects of adding adjunctive hyperbaric oxygen therapy to standard wound care for diabetic foot ulcers: a protocol for a systematic review with meta-analysis and Trial Sequential Analysis.
AUTHORS	Vinkel, Julie; Holm, Niels; Jakobsen, Janus; Hyldegaard, Ole

VERSION 1 – REVIEW

REVIEWER	Game, Frances National Health Service, Department of Diabetes Recently completed similar systematic review but no meta analysis of the data performed
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	Thank you for asking me to review this proposed protocol manuscript. This is a welcome review, as this is a controversial and costly treatment strategy. I general I am supportive of the work planned, but am concerned that the authors apparent lack of understanding od the usual care and pathogenesis of people with Diabetes and foot ulcers may lead to flaws in the authors critical analyses. They may be advised to read Jeffcoate et al ; International Working Group on the Diabetic Foot and the European Wound Management Association Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol. 2016; 4(9):781-8, for what the IWGDF would consider important aspects of trial design and clinical measures. The comments above relate particularly to the following statements in the manuscript: Page 33 Line 3: Painful neuropathy is not a consequence of worsening neuropathy but a consequence of the different types of nerve fibres affected. Painful neuropathy is not always seen in people with DFUs . Last paragraph lines 38 onwards. The majority of patients with neuropathic pain do not require walking aids. The authors need to distinguish symptoms from signs. They describe signs of infection around the wound, not symptoms of ulceration. The majority of DFUs are symptomless. I don't understand where the figure of 25% of patients with DFUs undergoing "bone removal" comes from the papers quoted, in the UK the rate of minor amputations (NDA data 20/10000 population with diabetes) – which do not necessarily cause lifelong disability, and major amputations (8/10000 population years, approx. 3% of

	patients presenting with DFUs). Please be more specific, population data is readily available, and probably more recent than the papers quoted. Page 8. Line 19 I disagree that HBOT has been shown to be cost effective, when clinical effectiveness if not proven, and the data were analysed post hoc. Outcome measures and assessment of bias. The authors say that there are a number of classification systems in use (they say more than 10 but I think it is almost double that) but then plan to use outcome by Wagner scale in their outcome measures. The IWGDF have repeatedly suggested that this classification is outdated and gives little detail about the pathogenesis of patients included in studies. It has been suggested it should not be used as a way of defining baseline characteristics for patients in trials as a result. I would suggest that this analysis should be abandoned. The assessment of PAD is similarly difficult if the protocol does not define this. Repeated reviews have suggested that although HBOT may improve wound healing in some patients, but it is unclear which, if PAD is not defined, this review will not advance our knowledge. This is particularly important if amputation is an outcome. The assessment of ulcer area, considered one of the most important predictors of healing surprisingly not included. In general please avoid using the term “diabetic” to describe people with diabetes.

REVIEWER	Jacek Kot National Center for Hyperbaric Medicine Institute of Maritime and Tropical Medicine, Gdynia Medical University of Gdansk Poland
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	This is an excellent proposal for the systematic review with meta-analysis and trial sequential analysis. I am looking forward to the result of your study.

REVIEWER	Juan Carlos Ascencio-Lane Department of Emergency Medicine Department of Diving and Hyperbaric Medicine Royal Hobart Hospital Tasmania Australia
REVIEW RETURNED	06-Aug-2019

GENERAL COMMENTS	Nice journal. good introduction with sufficient explanation of what they want to achieve and an explanation of Hyperbaric medicine and their methods. There were a few grammatical and spelling errors that can be cleaned up when they review the paper again.

	I was happy overall with this paper and feel it does not require any major changes

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Reviewer Name: Frances Game
Institution and Country: UHDB, UK
Please state any competing interests or state 'None declared': Recently completed similar systematic review but no meta analysis of the data performed]
Comment 1.1: Thank you for asking me to review this proposed protocol manuscript.
This is a welcome review, as this is a controversial and costly treatment strategy.
Response: Dear Frances Game. We sincerely thank you for taking your time to do this thoroughly and in-dept review of our manuscript. We have used your constructive criticism and valuable comments to revise our manuscript. Each of your comments have been discussed in the author group, prompted another review of the literature in the field, and given rise to changes and additions to the original manuscript, as you will see below.

Comment 1.2: I general I am supportive of the work planned, but am concerned that the authors apparent lack of understanding od the usual care and pathogenesis of people with Diabetes and foot ulcers may lead to flaws in the authors critical analyses. They may be advised to read Jeffcoate et al ; International Working Group on the Diabetic Foot and the European Wound Management Association Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol. 2016; 4(9):781-8, for what the IWGDF would consider important aspects of trial design and clinical measures.
Response: We are in close cooperation on with Copenhagen Wound Heling Center, University of Copenhagen, Bispebjerg Hospital, from where most of our patients are referred and receive their standard wound care. We most certainly agree that International Working Group on the Diabetic Foot (IWGDF) and the European Wound Management Association provides a great and valuable work to consider when planning a study assessing the effects of treatment and management of diabetic foot ulcers. We also refer to the work of the IWGDF when describing the diagnostic procedure (please see page 4, section 2), the classification of foot ulcers (please see page 4, section 3), the standard wound care (please see page 5, section 2) and the therapeutic protocol for treating diabetic foot ulcers with hyperbaric oxygen (please see page 5, section 3). The paper by Jeffcoate et al. 2016 summarises the core details required in the planning and reporting of intervention studies regarding diabetic foot ulcers and is not concerned with the use of adjunctive hyperbaric oxygen. However, the current manuscript is a protocol for a systematic review. We hope to find the support and fundraising to perform an intervention study on the effect of hyperbaric oxygen in the treatment of diabetic foot ulcer, and we have included the report by jeffcoate et al. 2016 when planning the trial design of this intervention study. Nevertheless, the clinical outcomes in the present protocol for a systematic review match those prioritised in the report by Jeffcoate et al. 2016., with the exception of wound infection. Besides the already included outcomes, IWGDF has specifically mentioned persistence of infection as an outcome of interest in future trials concerning the effect of hyperbaric oxygen therapy on Diabetic foot ulcers (please see page 231 in Huang ET, Mansouri J, Murad MH, et al. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med 2015;42(3):205-47.). Therefore, we decided to include this outcome as a secondary outcome.

The comments above relate particularly to the following statements in the manuscript:
We a responded to your comments (1.3 to 1.10) in the following.

Comment 1.3: Page 33 Line 3: Painful neuropathy is not a consequence of worsening neuropathy but a consequence of the different types of nerve fibres affected. Painful neuropathy is not always seen in people with DFUs.
Response: As also stated in the very beginning of the section, we agree that diabetic foot ulcers can be asymptomatic, even in the presence of severe tissue loss. We have changed the wording of this phrase in order to avoid further misunderstandings (Please see page 3, line 22)

Comment 1.4: Last paragraph lines 38 onwards. The majority of patients with neuropathic pain do not require walking aids. The authors need to distinguish symptoms from signs. They describe signs of infection around the wound, not symptoms of ulceration. The majority of DFUs are symptomless.
Response: We agree that Diabetic foot ulcers can be asymptomatic, even in the presence of severe tissue loss as also stated in the very beginning of the section. We have changed the wording in order to avoid further misunderstandings. Please see page 3, line 25-26.

Comment 1.5: I don't understand where the figure of 25% of patients with DFUs undergoing "bone removal" comes from the papers quoted, in the UK the rate of minor amputations (NDA data 20/10000 population with diabetes) – which do not necessarily cause lifelong disability, and major amputations (8/10000 population years, approx. 3% of patients presenting with DFUs). Please be more specific, population data is readily available, and probably more recent than the papers quoted.
Response: The two papers quoted refer the following figures:
Armstrong DG, Diabetes Care 1998; "Of all patients presenting for care, 28.6% received some form of lower extremity amputation" (please see first line, page 857 in the article). Where patients presenting for care refer to 360 diabetic patients presenting for care of a complicated foot wound to a multidisciplinary tertiary care diabetic foot clinic.
Jeffcoate WJ, Lancet 2003; "15–27% of all ulcers result in surgical removal of bone" (please see page 1, last section in the third paragraph in the article).
Therefore, we summarized these figures into one quarter of persons with diabetic foot ulcers. We acknowledge that the prevalence of amputation among people with diabetic foot ulcers varies in different publications. This is partly due to disagreement of the definition of amputation. Therefore, we chose the wording "bone removal" as it is more precise than amputation. However, based on your comment, we see that this simplification may confuse the reader, therefore we have chosen to elaborate on the subject (please see page 3, last section).

Comment 1.6: Page 8. Line 19 I disagree that HBOT has been shown to be cost effective, when clinical effectiveness if not proven, and the data were analysed post hoc.
Response: We agree that the cost effectiveness of adjunctive hyperbaric oxygen therapy is poorly investigated. Based on your comment, we have changed the wording (please see page 7, line 13).

Outcome measures and assessment of bias.

Comment 1.7: The authors say that there are a number of classification systems in use (they say more than 10 but I think it is almost double that) but then plan to use outcome by Wagner scale in their outcome measures. The IWGDF have repeatedly suggested that this classification is outdated and gives little detail about the pathogenesis of patients included in studies. It has been suggested it should not be used as a way of defining baseline characteristics for patients in trials as a result. I would suggest that this analysis should be abandoned.
Response: We most certainly agree that the Wagner classification system is outdated and of limited use in scientific research. We would recommend the classification system PEDIS developed by the International Working Group on the Diabetic Foot (IWGDF) for this purpose, as we also state in our description of classification systems (Please see page 4, section 3). The Wagner classification system is not included in our outcome measures. Our outcomes are All-cause mortality, Serious adverse events, Quality of life and our secondary outcomes include major amputation, healing and wound

infection. However, we chose to include the Wagner classification in our subgroup analysis to support our investigation of this heterogenous dataset, knowing that sub-group analysis also has its limitations. This has now been clarified in our revised protocol (please see page 20, 2nd section in the discussion). Our preliminary search on the trials included in this review showed that they did not provided enough details to describe the wound by any other classification system.

Comment 1.8: The assessment of PAD is similarly difficult if the protocol does not define this. Repeated reviews have suggested that although HBOT may improve wound healing in some patients, but it is unclear which, if PAD is not defined, this review will not advance our knowledge. This is particularly important if amputation is an outcome.
Response: We agree. In order to investigate if the presence of PAD influences our outcomes measures in the two groups, we have included PAD in our subgroup analysis. As with our other outcome measures PAD will be included as defined by the trialist. If PAD is defined in various ways in the included trials, then it will be described throughout fully when interpreting the review results. Based on your comment we have added the phrase '(as defined by the trialist)' to several of subgroup analyses (please see page 18, last section, sub-group analysis numbered 5-10).

Comment 1.9: The assessment of ulcer area, considered one of the most important predictors of healing surprisingly not included.
Response: Based on your comment we have included 'change in ulcer area' in our sub-group analysis (please see page 18, last section, sub-group analysis numbered 10)

Comment 1.10: In general please avoid using the term "diabetic" to describe people with diabetes.
Response: In general, we have used the words; 'persons with diabetes' and 'diabetic foot ulcer patients'. However, based on your comment, we have changed the wording 2 places in the manuscript. Please see page 4, line 1 and page 7, line 11.

Reviewer: 2
Reviewer Name: Jacek Kot
Institution and Country:
National Center for Hyperbaric Medicine
Institute of Maritime and Tropical Medicine, Gdynia
Medical University of Gdansk, Poland
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below.
Comment 2.1: This is an excellent proposal for the systematic review with meta-analysis and trial sequential analysis. I am looking forward to the result of your study.
Response: Dear Jacek Kot. We sincerely thank you for taking your time to review our manuscript entitled; "The effects of adding adjunctive hyperbaric oxygen therapy to standard wound care for diabetic foot ulcers: a protocol for a systematic review with meta-analysis and Trial Sequential Analysis.".

Reviewer: 3
Reviewer Name: Juan Carlos Ascencio-Lane
Institution and Country:
Department of Emergency Medicine
Department of Diving and Hyperbaric Medicine
Royal Hobart Hospital
Tasmania
Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment 3.1: Nice journal. good introduction with sufficient explanation of what they want to achieve and an explanation of Hyperbaric medicine and their methods.
Response: Dear Juan Carlos Ascencio-Lane. We sincerely thank you for taking your time to review our manuscript entitled; "The effects of adding adjunctive hyperbaric oxygen therapy to standard wound care for diabetic foot ulcers: a protocol for a systematic review with meta-analysis and Trial Sequential Analysis." We are please to know that a researcher within the field has approved our description of hyperbaric medicine.

Comment 3.2: There were a few grammatical and spelling errors that can be cleaned up when they review the paper again.
Response: We have revised our manuscript and corrected grammatical and spelling errors to the best of our ability.

Comment 3.3: I was happy overall with this paper and feel it does not require any major changes.
Response: Thank you again for your encouraging comments. In response to reviewer Frances games valuable comments we have made some changes to the manuscript as described above.

Missing affiliation: We became aware that one author had a missing affiliation in version 1.0. of the manuscript. This has been added in the current version.

VERSION 2 – REVIEW

REVIEWER	Game, Frances University Hospitals of Derby and Burton NHS Foundation Trust
REVIEW RETURNED	24-Dec-2019

GENERAL COMMENTS	Thank you for revising this manuscript which is considerably improved.