PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Leg Ischaemia Management collaboration (LIMb): study protocol for a prospective cohort study at a single UK centre
AUTHORS	Houghton, John; Nduwayo, Sarah; Nickinson, Andrew; Payne, Tanya; Sterland, Sue; Nath, Mintu; Gray, Laura; McMahon, Greg; Rayt, Harjeet; Singh, Sally; Robinson, Thompson; Conroy, Simon; Haunton, Victoria; McCann, Gerry; Bown, Matthew; Davies, Robert; Sayers, Rob

VERSION 1 – REVIEW

REVIEWER	Lars Norgren MD PhD Emeritus Professor of Surgery Dept of Surgery, Faculty of Medicine and Health, Örebro University, Sweden
REVIEW RETURNED	18-May-2019

GENERAL COMMENTS	The study intention is to reduce the major amputation rate in severe limb ischemia based on the Rapid Access Limb Salvage Clinic and modern revascularisation procedures. As historical control will the results from treatment of a corresponding cohort of patients treated during 2013-2015 serve. -Based on the fact that studies have shown a gradual decrease of major amputations during the recent decade, it seems difficult to find out whether an amputation rate decrease in the study population depends on a re-organised department and modern procedures -Has the access to and use of revascularisation procedures changed considerably at the study department from 2013-15 until present time ? -Could a comparison between the time period be done based on propensity score matching ? -Primary aim/outcome is major amputation, while mortality is depicted the last secondary outcome. Why is amputation-free survival not used ? (Most important outcome). Could AFS be calculated from the historical material (and population registries ?) -The Protocol does not inform about medical treatment and secondary prevention, issues with great impact on outcome -Patients are included if 18-110 years of age. Why are these not realistic limits used ? Very young individuals will -if anything- suffer inflammatory vascular disease, extremely old ones will most likely not appear. -The frailty, cognitive assessment part seems of great interest -The MRI study seems a substudy,more or less standing alone. ---it is stated the duration of the MRI is short, but several additional parts seem to be included (Cardiac MRI additional assessments), provided continuing consent. How will this be handled ? Patient

	consenting while in the tube ? The duration of each part might be added to the protocol (including for the extra muscle image). As member of the Ethical Board for many years, I react on the Discontinuation/withdrawal text: ..... "has the right to withdraw" is a weak statement as participation is completely voluntary, and the reason for withdrawal can never be asked for. (Your ethical committee might have accepted your text) -Apparently you will not report adverse events and not even serious adverse events, provided they can be expected in the study population. Has this been accepted by the sponsor and/or ethical board ? --- MRI data will remain blinded according to the protocol. Any pathology of interest to the anaesthesiologist, provided open surgery, should most reasonably be reported. -Blood will be saved in a Biobank for future biomarker assessment. Will patients consent for any biomarker (none is reported in the protocol) ? -Statistical plan is not provided, only very general comments. A preliminary elaboration should be included. -Study registration data required by the publisher -The abstract needs an ending (Conclusion)

REVIEWER	Kyohei Yamaji Kokura Memorial Hospital
REVIEW RETURNED	12-Jun-2019

GENERAL COMMENTS	This is a design paper for a single center observational cohort study in which clinical outcomes of prospectively included severely limb ischemia patients will be compared with those of historical cohort. Since data will be retrospectively collected in the historical cohort, there would be an under-reporting bias at least to some extent. The authors should acknowledge this inherent limitation. On the other hand, in the primary cohort, frailty and cognitive impairment, cardiac MRI, and biomarkers will be prospectively assessed. As this reviewer assumes that those data are not available in majority of the historical cohort, the authors should state the rationale to collect those additional data.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments & responses:

Reviewer: 1

Reviewer Name: Lars Norgren MD PhD Emeritus Professor of Surgery

Institution and Country: Dept of Surgery, Faculty of Medicine and Health, Örebro University, Sweden

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The study intention is to reduce the major amputation rate in severe limb ischemia based on the Rapid Access Limb Salvage Clinic and modern revascularisation procedures. As historical control will the results from treatment of a corresponding cohort of patients treated during 2013-2015 serve.

-Based on the fact that studies have shown a gradual decrease of major amputations during the recent decade, it seems difficult to find out whether an amputation rate decrease in the study population depends on a re-organised department and modern procedures. We would agree with this statement and this is a limitation of the study. As this is an observational study any change in amputation rate may be influenced by other confounding factors outside of the changes to local practice. We have added a short discussion at the end of the manuscript where this is highlighted as a limitation.

-Has the access to and use of revascularisation procedures changed considerably at the study department from 2013-15 until present time ? There has not been significant change to the access to or use of revascularisation during the two timeframes other than introduction of CERAB. The times to vascular assessment and investigation have been reduced by implementing the rapid-access limb salvage clinic so any observed improvements are more likely to be due to earlier vascular assessment, investigation and decision making. The new Vascular Society of Great Britain & Ireland guidelines (referenced in the manuscript) set ambitious targets of 5 days from referral to treatment of severe critical limb ischaemia which we are aiming to adhere to. Also, a new diabetic foot pathway has been implemented whereby all patients admitted acutely with diabetic foot disease are initially admitted onto the vascular surgery ward regardless of pedal pulse status reducing the time to vascular assessment, investigation and intervention. It is hoped that these reductions in delays will improve major amputation rate. Further detail to these changes to management pathways at our unit have been included in the “Rationale” section of the manuscript.

-Could a comparison between the time period be done based on propensity score matching ? Yes (although propensity score adjustment may be more appropriate) and this has been included in the “Data & Analysis” section of the revised manuscript.

-Primary aim/outcome is major amputation, while mortality is depicted the last secondary outcome. Why is amputation-free survival not used ? (Most important outcome). Could AFS be calculated from the historical material (and population registries ?) Primarily the aims of changes to local management pathways were to reduce the amputation rate and, whilst this may improve AFS, we are unsure as to the impact these improved pathways will have on long-term mortality. It may be that AFS is unchanged long-term despite a reduced amputation rate (which would still be an interesting result). For these reasons amputation rate was chosen as the primary outcome measure and power calculations made for this outcome accordingly. However, it will be possible to calculate amputation free survival for both the prospective cohort and historical controls so comparison can be made and reported as a secondary outcome measure. AFS has been added to the listed secondary outcome measures for clarity.

-The Protocol does not inform about medical treatment and secondary prevention, issues with great impact on outcome. The manuscript does not address these points in detail but is mentioned in the “Rationale”. It is not within the scope of this study to investigate medical therapies for SLI. There has not been any significant change to the medical management or secondary preventative management of patients with SLI at our unit during the period of changes to management pathways and it is local policy to discharge all patients on clopidogrel and atorvastatin unless contraindicated. We will collect data regarding medications and smoking status on admission as well as smoking status at the 1 and 2 year follow-up time points. It is unlikely we will be able to collect reliable data on secondary preventative measures beyond these. Smoking status has been added to the list of data that will be collected in “Study procedures” in the revised manuscript.

-Patients are included if 18-110 years of age. Why are these not realistic limits used ? Very young individuals will -if anything- suffer inflammatory vascular disease, extremely old ones will most likely not appear. It is extremely rare that children are managed at our unit and as such will not be recruited. To our knowledge our unit has never managed a patient aged >110 years and the upper limit of age was stipulated by our study sponsor rather than the research team. We feel it very unlikely that any patients would not be able to participate in the research due to the age restrictions. However, these data will be captured during screening patients, and it will be possible to report the numbers of patients ineligible due to age at the end of the study. Additionally, we intend to submit a protocol amendment to the ethics board to remove this upper age limit. Severe Limb Ischaemia not caused by PAOD is listed as an exclusion criterion (Table 1).

-The frailty, cognitive assessment part seems of great interest Thank you. We hope this study will provide useful data in the management of frail vascular surgery patients.

-The MRI study seems a substudy, more or less standing alone. Patients undergoing MRI will provide useful additional data to that collected in the rest of the study. It is anticipated that a number of patients will consent to multiple additional assessments so it will be possible to compare data both in isolation and in combination with other assessments/factors. The sponsor requested we framed the MRI, frailty and cognitive assessments, and biomarkers assessments as “additional assessments” rather than as “sub-studies” so that all aspects to the study could be included in a single participant/personal consultee information sheet and consent form.

---it is stated the duration of the MRI is short, but several additional parts seem to be included (Cardiac MRI additional assessments), provided continuing consent. How will this be handled ? Patient consenting while in the tube ? The duration of each part might be added to the protocol (including for the extra muscle image). We do not believe that we describe the cardiac MRI duration as “short” in the manuscript. The reason for stating the ability to perform “highly accelerated sequences” is to highlight that modern techniques allow the investigation to be performed free-breathing (without breath-holds) which is important to enable frail and breathless patients to undergo the investigation. The cardiac MR sequence is detailed in Figure 2. Patients will provide consent to both an axial image at the level of L3 to assess for sarcopenia, and the cardiac MRI separately on the consent form. Patients will be fully counselled and consented as to the cardiac MRI procedures at the point of recruitment, prior to the cardiac MRI. Further pre-MRI checks and confirmation of ongoing consent to participate will be undertaken prior to the investigation. The entire sequence is anticipated to last around 45 minutes as described in Figure 2. MRI can be abandoned at any point at the patient’s request or if clinically indicated.

As member of the Ethical Board for many years, I react on the Discontinuation/withdrawal text: ..... "has the right to withdraw" is a weak statement as participation is completely voluntary, and the reason for withdrawal can never be asked for. (Your ethical committee might have accepted your text) The ethics committee reviewed all the relevant study documentation including the study protocol, consent form, personal consultee declaration form, and both the personal consultee and patient information sheets. The text from the consent form reads “I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected”. The text from the patient information sheet reads “If you agree to take part, but later change your mind, you may withdraw at any time, without giving a reason by contacting the research team. This will not affect your care in any way.” The text of the manuscript has been revised to reflect the wording of the ethically-approved statements in the consent form and patient information leaflets.

-Apparently you will not report adverse events and not even serious adverse events, provided they can be expected in the study population. Has this been accepted by the sponsor and/or ethical board ? Apologies as the wording of this section was not clear. Thank you for highlighting this. To be clear, non-serious adverse events/reaction (AEs/ARs) will not be reported to the sponsor as this is a non-

interventional study. Expected serious adverse events (SAEs) unrelated to the study (listed in supplementary file 1) will not be reported. All serious adverse reactions (SAEs related to the study) and unexpected SAEs will be reported to the sponsor, and number of SAEs reported to the regional ethics committee. This safety reporting plan is written in more detail, with definitions, in the full protocol and has been approved by sponsor and the ethics committee, but has needed to be edited to a much more concise form for this manuscript. We have revised this section of the manuscript to make the safety reporting plan clearer.

--- MRI data will remain blinded according to the protocol. Any pathology of interest to the anaesthesiologist, provided open surgery, should most reasonably be reported. The cardiac MRI scan is only being undertaken as a part of the research study and it is not standard practice for patients with SLI to undergo cardiac stress testing pre-operatively at our unit. Additionally, patients will only become eligible for cardiac MRI if a decision has been made for them to undergo an intervention for SLI which, in the case of open surgery, often involves an anaesthetic review prior to this decision being made. The analysis of the cardiac MR data will be extremely detailed, the majority of which will be not be relevant to the clinical team regarding decision making. There is a risk that injudicious release of clinical MR data will bias the treatments received by patients who undergo cardiac MR as part of this study.

The protocol submitted to the ethics board did not contain information regarding blinding of the results to clinicians or patients. We are currently in the process of submitting a protocol amendment to the ethics board to discuss and clarify the indications for releasing a clinical MR report to the clinical team. In the meantime, a clinical report including details of LV function, ischaemia and scar tissue will be available to the clinical team upon request and patients are informed of this current arrangement as part of the consent process. We have removed the mention of blinding from the revised manuscript, detailing only how the MRI will be reported for the purposes of research.

-Blood will be saved in a Biobank for future biomarker assessment. Will patients consent for any biomarker (none is reported in the protocol) ? This is correct. The wording of the consent form states “I understand and agree to additional blood samples being taken and stored for analysis and agree that they may be used in future ethically approved studies”.

-Statistical plan is not provided, only very general comments. A preliminary elaboration should be included. A more detailed statistical analysis plan has been included in the revised manuscript including detail regarding propensity score adjustment.

-Study registration data required by the publisher. We have submitted this study for registration with ClinicalTrials.gov and is currently under review and as such hasn’t been assigned an NCT ID yet. We will update the manuscript once the NCT ID has been assigned.

-The abstract needs an ending (Conclusion). The manuscript and abstract have been prepared in accordance with BMJ Open instructions to authors which state the abstract “should be structured with the following sections. Introduction; Methods and analysis; Ethics and dissemination.” We would be happy to revise the abstract to include a conclusion at the discretion of the editor. A conclusion has been added after a short discussion section in the revised manuscript.

Reviewer: 2

Reviewer Name: Kyohei Yamaji

Institution and Country: Kokura Memorial Hospital

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

This is a design paper for a single center observational cohort study in which clinical outcomes of prospectively included severely limb ischemia patients will be compared with those of historical cohort.

Since data will be retrospectively collected in the historical cohort, there would be an under-reporting bias at least to some extent. The authors should acknowledge this inherent limitation. The retrospective collection of historical data is a significant limitation of the study and is listed in the “Strengths & limitation” section of the manuscript. A short discussion has been included at the end of the revised manuscript further detailing the ways in which this may limit and bias the results of the study.

On the other hand, in the primary cohort, frailty and cognitive impairment, cardiac MRI, and biomarkers will be prospectively assessed. As this reviewer assumes that those data are not available in majority of the historical cohort, the authors should state the rationale to collect those additional data. A sentence has been added at the end of the “rationale” section of the revised manuscript detailing the rationale for undertaking these additional assessments. All are discussed in depth in the introduction as well as their listing in the secondary aims of the study.

VERSION 2 – REVIEW

REVIEWER	Lars Norgren Dept of Surgery, Faculty of Medicine and Health, Örebro University, Sweden
REVIEW RETURNED	18-Jul-2019

GENERAL COMMENTS	Revision is clear and well balanced. The Introduction includes one "new" issue regarding infection "Drainage of sepsis". Please rephrase.

REVIEWER	Kyohei Yamaji Kokura Memorial Hospital
REVIEW RETURNED	23-Jul-2019

GENERAL COMMENTS	No additional comments from this reviewer.