Reviewer’s report

Title: Risk factors for foot ulceration in adults with end-stage renal disease on dialysis: study protocol for a prospective observational cohort study

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Reviewer: Kirsten Leyland

Reviewer’s report:

This manuscript outlines a study protocol for a prospective cohort study examining the risk factors for foot ulcers and other lower extremity complications in a group of patients with end stage renal disease undergoing dialysis. There is a distinct lack of cohort studies examining foot-related issues in high risk patients, and the results of this research will fill an important gap in knowledge.

This protocol focuses on an important research question using detailed patient assessment and patient records collected at both a baseline and follow-up visits. The data being collected appears as though it will be high quality and rigidly assessed. However, several important aspects of study design, statistical analysis, and the need for a well-defined primary outcome measure need to be addressed. The inclusion of a statistician with experience in designing and analysing similar types of cohort studies may strengthen this research.

Comments have been divided into subject matter rather than manuscript subheadings as they may affect more than one section. Please address comments in all relevant sections.

Outcome Measures:

1. ‘Number of new ulcers’ is described as the primary outcome (both new and recurring) in several locations of the manuscript. This appears to be a count variable, which is not normally usable as a continuous variable for linear regression. Possibly Poisson regression might be more appropriate for this type of outcome. If not, have you considered thresholds to create a binary variable if linear regression is not feasible in order to use logistic regression?

2. While mortality and kidney failure are important to account for in this analysis in terms of bias, it does not appear that the study has been designed to look at these measures as an outcome, as risk factors were selected for foot-related outcomes. Please clarify.

3. The secondary outcome, ‘time to first ulcer’ will require a different type of analysis than is described in your statistical plan as it is time to event data. Please include in the stats methods section whether you will be using survival analysis for this outcome or an alternative method.

Study Design/Statistical Analysis:

1. Please clarify which specific variables will be assessed as risk factors and
which will be included as confounders in the multivariable models. For example, the biomechanical assessment and quality of life variables are not in the risk factor list as identified by the systematic review and listed in the abstract, and it is not clear if these will be treated as risk factors or confounders.

2. The abstract is misleading as it implies that the risk factors identified in the systematic review are the factors that will be included in this analysis – however there seems to be a large variation between these lists – please clarify in the abstract and body of the manuscript which specific variables are the risk factors of interest.

3. How will risk factors be assessed? With each risk factor individually in univariable model and then in a multivariable model which includes confounders? Or will you be doing predictive modelling which includes all risk factors of interest in the same model using stepwise regression? Please clarify.

4. Will results/models be stratified by diabetes? Is this likely to have an interaction with risk factors on the risk of having the outcome? If so, is your sample size large enough to have diabetes as an interaction term?

5. Please identify the confounders you expect to include in your multivariable analyses and add a section into the statistical methods.

6. Please identify whether interactions will be identified a priori and which variables these are.

7. In a cohort made up of such severely ill patients, mortality and loss of follow-up due to comorbidities would be expected to be high. In a brief search of the literature, I found a yearly mortality rate of 241 per 1000 patient hours at risk, which with the sample size for this study could be quite high. Please include the expected rate of loss due to mortality, and discuss how this may introduce bias into the study as a limitation. For the secondary outcome (time to ulcer) there are established methods to account for mortality as a competing risk using survival analysis if the mortality rate is found to be significant in this study.

8. Related to point 7, will sensitivity analyses be done to assess the bias due to loss to follow up?

9. Are there differences in the types of patients who are recruited from satellite dialysis units and home-therapy units? Does this variable need to be included in the analysis as a confounder?

Other:

1. Exclusion criteria – will you exclude subjects with bilateral lower-limb amputations?

2. Is the data collection sheet labelled ‘prospective’ the follow-up data sheet?

3. Which variable will be used to assess the presence of a baseline foot ulcer – the one from the baseline recording sheet (4.1.2) or from the follow-up data sheet (1.1)? Which will be used in case of disagreement?

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.