Reviewer’s report

Title: Knee Pain and Related Health in the Community Study (KPIC): a cohort study protocol

Version: 1 Date: 23 Jul 2017

Reviewer: Erik Lenguerrand

Reviewer's report:

This is an interesting research but this protocol could be modified prior to submission:

- This research is aiming to investigate the natural history of knee pain using annual assessment over a period of three years. While the assessments are diverse and thorough, there is a risk that patients with transient and/or slower pain/OA "mechanisms" are not likely to be considered by this study. This is a limitation worse discussing.

- It is unclear whether patients with previous history of OA or arthroplasty in another joint will be recruited as well as patients receiving (pharmaceutical or not) treatment for pain in another part of their body. Such treatments is likely to influence the detection of patients with "no KP", "early KP"?

- Similarly the role of other comorbidities and level of physical activities prior and after the study could confound the planned analyses.

- Long-term participation in a longitudinal study is likely to be differential from one group of participant to another. In this specific study the loss to follow-up rate could differ by age, number and severity of comorbidities, severity of pain and function symptoms which could trigger an arthroplasty, or on the contrary limited interest in the research question in participants with no or minor KP symptoms at baseline. The resulting differential bias is likely to affect the investigation. Is there any strategy in place to maximise the participant/response rate in the course of the follow-up? If the current study design is not accommodating such a challenge, the authors could consider to use an imputation and/or weighting strategy during the analyses to reduce this bias.

- Please provide more details on the GP register as the international audience might not be familiar with this data source.

- Lines 19-24 Baseline, questionnaire section the sentence "...40,000 adults..registers" could be better located in the participants, inclusion section on the previous page.

- It would be informative to add the list of occupations classified by level of risk for OA in an appendix. It is unclear how unemployed and retired participants are going to be classified.
- In the participants section, methods "The questionnaire will be accompanied..." The questionnaire to check patient eligibility?

- In clinical assessment "...will then identified..." "...will then be identified..."

- "Written informed consent will then obtained.." "Written informed consent will then be obtained.."

- "research metrologist" the term metrologist is an unusual terminology.

- "in a standard fashion". I would advise to remove this term or to cite a guideline as the standard may differ from one place to another.

- Ultra sound: " the same equipment...were used...was performed...only one value per joint was recorded..." would it be better to use the present or future tense?

- Three areas will be scanned with US. Will the same areas be systematically scanned for all patients?

- Gait analysis. Please add some references. The following sentence "An average of 6 gait cycles ...and averaged for final analysis" Is it standard practice? Would it be better to discard the first cycle(s) and final cycle? A reference would help to have confidence in the proposed modelling strategy.

- the QST tests seem to be conducted at baseline and year 1 in the text but baseline and year 3 in the table.

- Please provide a reference to justify the calculation of the TS and mechanical sensitivity.

- "body pain mannequin" It could be informative to add this graphical representation in an appendix.

- It seems that there is two groups of "early KP", those identified at baseline and in the course of the follow-up. Are the same clinical assessments going to be performed on these two groups? Are they going to be analysed simultaneously? In this case, the benefit of the early matching is unclear.

- Figure 1 should stand alone. Please explain the "+", "+", "++", "+++" symbols". In the "questionnaire part" of this figure it seems that patients with "Knee pain -" at Year 1, and then with "knee pain +" at year 2" are not followed at year 3 (to become Knee ++), as it is done with those in the left hand side harm of this graph? Similarly, in the "assessment part", participants in the Knee - and then Knee + are not followed at year 3 in the similar way as the group with knee pain <= 3 years. Could it be justified in the text? I am also wondering whether the fact that patients with KP>=3y have not received further assessments at y2 and y3 deserves some explanations in the text.
- The section on sample size could be reformatted. It is quite long and difficult to read. Studies have generally a primary research question, a series of secondary ones, and are powered to address the main research question. If this is the case here, all the emphasis could be put on addressing the main research question:

"A sample of XXX will allow to detect a difference of YY in the primary outcome at a power of 90% (alpha=0.05, two-sided). This sample will also allow to test a difference of X points (ref) in secondary outcome XXX and of T points(ref) in outcome NNN…"

If all research questions are deemed equally important for this study and the authors want to stick to their current presentation, one might argue that the resulting multiplicity of statistical hypothesis tests ought to be accounted for in the derivation of the required sample sizes.

The authors could also simply provide one calculation on an outcome derived from the questionnaire to justify n=10,000; and another calculation on an outcome derived from the clinical assessment to justify n=400.

However, the concepts of incidence and prevalence are used interchangeably throughout the manuscript. A logistic regression cannot be used to model incidence rate. If the authors are keen to keep their current presentation of the sample size section, point 4 on risk factors needs to be reconsidered. Point 3 also needs to be revisited as the underlying tool used for a sample size calculation is different if one wants to detect a difference in two rates or a difference in two rate changes. More importantly, the sample size based on “incidence of KP” (prevalence? of KP) is unclear (point 2). Are the authors aiming to determine the required sample size to assess a prevalence of 3% within a specific precision in the estimates of this prevalence? The current presentation is unclear and seems to be more relevant to the comparison of two prevalence rates but without the mention to what the 3% would be compared to.

Saying that a sample of 10,000+ questionnaires should be really more than enough for all the analyses based on the questionnaire outcomes!

With regards to the analyses based on clinical assessments, it is unclear why a sample of 600 participants is required to conduct the analyses on PPT but only 400 participants will be recruited to this part of the study. Is it a typo? This paragraph could be better phrased especially the last sentence: "this unbalanced design…".

The section on US could be shortened.

This study is based on a cohort study design and the etiological/causal strength of its results is likely to be limited by the biases associated with most observational design. The findings are therefore more "descriptive" than causal and the question of power calculation is less important than for a trial, i.e. the question of exposing a larger group of participants than necessary to a
new potentially inefficient/dangerous treatment is irrelevant to the current context and the merit of a power calculation of lesser interest in this context. I would therefore recommend to keep this section short.

- The statistical analysis section could be better presented. This section is rather unbalanced: The section on "reproducibility of assessments" is too long and the one on SEM is disproportionate compare to the details proposed for the methods used to address objectives 1 and 5.

While I believe the authors have a clear idea of what they want to do, the current format of the statistical analysis plan does not reflect a clear strategy and comes across as a "catch-all" section. It might be difficult at this stage to have an exhaustive view of all future analyses and better to only present a subset of representative analyses to explain the general strategy which will be used. When dealing with baseline measurements, a logistic, multinomial, or anova/linear regression will be fine. However, for analyses requiring to model the follow-up measurements, generalised linear mixed models or survival analyses will be required to account for the time participants will have been at risk, i.e "person-time" (a simple logistic regression would be inadequate). The analyses based on the clinical assessments seem more complex with some based on participants only assessed once, on participants assessed several times or on participants matched to "control" participants with no KP.

The analyses might differ from one research question to another and one outcome to another. On top of the issue associated with repeated measurements and longitudinal follow-up, the clustering within surgery will need to be explored and if necessary accounted for in any analysis.

I would therefore encourage the authors to structure the presentation of their "broad" analysis plan around the 5 research questions listed in the objective sections.

They could list the key outcomes which would be investigated in each research question with a description of the main statistical framework which could be used and potential adjustments. Ultimately, it will be easier to assess the relevance of the proposed statistical plan and more readable for the lay audience.

- With regards to the discussion section, some of the limitations mentioned above could be discussed. While I do agree with the risk of table 2 fallacy bias, there are other more or as important biases which could be mentioned in particular those inherent to an observational study design. Unless further explanations are provided to help the readership of the journal, I recommend to remove this comment and focus on other limitations more relevant to a clinical readership such as the selection bias associated to a potential differential loss to follow-up in the group with severe pain or frail participants.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

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