PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The East Midlands Knee Pain Multiple Randomised Controlled Trial Cohort Study: Cohort Establishment and Feasibility study protocol
AUTHORS	Hall, Michelle; Fuller, Amy; Nomikos, Polykarpos; Millar, Bonnie; Ogollah, Reuben; Valdes, A; Greenhaff, Paul; dasNair, Roshan; Doherty, Michael; Walsh, David; Abhishek, A

VERSION 1 – REVIEW

REVIEWER	Aileen Ledingham PT, MS, PhD USA
REVIEW RETURNED	20-Apr-2020

GENERAL COMMENTS	The aim of this manuscript is to describe the protocol of a feasibility study designed to develop and assess a nurse-led intervention for people with knee pain, following NICE guidelines. Two phases are to be used: (1) develop a nurse training package, assess intervention fidelity, and explore nurse and patient acceptability of intervention; and (2) examine the feasibility of a nurse-led versus usual care randomized control trial assessing crossover outcome of pharmacological vs non-pharmacological interventions. I am impressed by the amount of work the authors have embarked upon for this feasibility study. I believe the purpose of this manuscript has good value and would accept this paper for publication with revisions for clarification. 1. I am not familiar with “cohort-randomization controlled trial” and believe readers would appreciate an explanation on how this design offsets bias associated with pragmatic RCTs in the introduction or methods vs in the discussion. 2. Under aims and objectives the phrase “provide core analgesia” is a new term. Please provide more background of this aspect of your study in the introduction in order to help the reader understand what you mean here and to support your crossover methodology later in the paper when describing phase 2 methods. 3. Phase 1 Methods: a) “Knee pain will be scored between 4-7” What happens if the participant has a rating of 8, are they excluded? b) How are the nurses recruited? Are there inclusion or exclusion criteria? Are you targeting a particular Band level? c) Are nurses considered participants that are consenting to the study? d) Please provide a description of your patient advisory group. e) “Fidelity scores will be presented as the percentage of specified components that were delivered as intended for the overall delivery of the intervention and for individual components” is unclear. Could you provide a hypothetical example?

	f) Qualitative methods: Who will conduct the interviews? What training or experience will he/she have? Because…"It is therefore essential that studies using the Framework Method for analysis are overseen by an experienced qualitative researcher…" (Gale et al, Using the framework method for the analysis of qualitative data in multi-disciplinary health. BMC Medical Research Methodology 2013;13:117. page 2) 4. Phase 2 methods: a) Will you be using the same nurses as in phase one? b) Table 1 I. Under assessment please clarify what gait and functional activity assessments you plan to use II. Under exercise please clarify strengthening exercises, at least provide references for evidence-based exercises you might choose to use. I understand your study is not intended to show effectiveness, however, the type of exercise used is very important to feasibility outcomes. c) Pharmacological component, please consider using a table. d) Qualitative methods and analysis need more details. Is the reader to assume that phase two will follow the same procedures as phase one? Please include the dates of the study. It was a pleasure to review this manuscript, thank you for your time and efforts sharing this important work.

VERSION 1 – AUTHOR RESPONSE

Reviewer's Comments to Author:

1. **I am not familiar with "cohort-randomization controlled trial" and believe readers would appreciate an explanation on how this design offsets bias associated with pragmatic RCTs in the introduction or methods vs in the discussion.**

We agree that explanation for the cohort-RCT is better placed in the introduction and this has been moved to the introduction Page 4/5
There is a short expansion in the section on strengths and limitations Page 3
The protocol for IMWH cohort (one of the recruitment routes) which has recently been published has been added to the recruitment routes Page 6. The Baseline PIS and Informed consent Form which explain the cohort phase of the cohort-RCT have been included in Additional file 5: Model Informed Consent Materials
We hope that this gives the readers an earlier understanding of the study design.

2. **Under aims and objectives the phrase "provide core analgesia" is a new term. Please provide more background of this aspect of your study in the introduction in order to help the reader understand what you mean here and to support your crossover methodology later in the paper when describing phase 2 methods.**

We agree that the term “core analgesia” is a misnomer as NICE guidelines do not refer to pharmacological interventions as core. Rather they should be consider additional pharmacological treatment delivered after the core treatments of education, exercise and weight loss have been used. We have removed the word “core” in relation to analgesia from the aims and objectives on page 5. We have also elaborated on why we have addressed this in the study in the Introduction on page 4.

3. Phase 1 Methods:
a) “Knee pain will be scored between 4-7” What happens if the participant has a rating of 8, are they excluded?

Yes, this has been added to the exclusion criteria. Page 6

b) How are the nurses recruited? Are there inclusion or exclusion criteria? Are you targeting a particular Band level?

We recruited nurses regardless of prior experience of musculoskeletal conditions or seniority. Page 7

c) Are nurses considered participants that are consenting to the study?

Yes, the nurses will be considered participants in the both qualitative component of the study and in the fidelity assessment.

d) **Please provide a description of your patient advisory group.**

This has been added to the section on PPI on page 7

e) **“Fidelity scores will be presented as the percentage of specified components that were delivered as intended for the overall delivery of the intervention and for individual components” is unclear. Could you provide a hypothetical example?**

We have attached a supplementary file 1 with the fidelity checklist and explained how scores will be calculated in the text. Page 8

f) **Qualitative methods: Who will conduct the interviews? What training or experience will he/she have? Because…“It is therefore essential that studies using the Framework Method for analysis are overseen by an experienced qualitative researcher…” (Gale et al, Using the framework method for the analysis of qualitative data in multi-disciplinary health. BMC Medical Research Methodology 2013;13:117. page 2)**

The interview will be carried by a doctoral student (PN) and overseen
by two experienced qualitative researchers AF & RN. This has been added to the qualitative methods section: Page 8

4. Phase 2 methods:
a) Will you be using the same nurses as in phase one?

Yes the same nurse will be used but additional nurses if recruited will receive the same training. This has been added under the intervention section on page 9

b) Table 1 Under assessment please clarify what gait and functional activity assessments you plan to use.

Assessment in this table refers to the nurse assessment of the patient and not research assessment. Assessment of gait refers to observation of gait pattern only looking for ease of movement, limping, Trendelenburg gait etc which may guide selection of exercises or advice on using a walking aid. Function refers to observation of simple activities of daily living including rising from sit to standing, lowering from standing to sitting, stepping up and down from a low step. Again to guide selection of exercise and discussion of physical goals.

“Observation of” has been added to table 1.

c) Under exercise please clarify strengthening exercises, at least provide references for evidence-based exercises you might choose to use. I understand your study is not intended to show effectiveness, however, the type of exercise used is very important to feasibility outcomes.

We agree this has been an oversight and we have added an additional file with a more detailed description of the non-pharmacological intervention including the exercise used (additional file 2)

d) Pharmacological component, please consider using a table.

We thank the reviewer for this comment. We feel that a flow chart of analgesic sequence contained in figure 2 provides the level of detail required for the pharmacological component of the intervention. We feel that this sequence of treatment might not be conveyed well enough in the table.

e) Qualitative methods and analysis need more details. Is the reader to assume that phase two will follow the same procedures as phase one?

The details of the qualitative component is somewhat fragmented and has been brought together to provide a more cohesive description under Qualitative study outcomes on page 14
The qualitative analysis will follow the Framework approach used in Phase 1, this has been added to the text on page 15

Please include the dates of the study.

Recruitment was commenced in Nov 2018 and is ongoing. This is stated under Ethics and dissemination on page 16.

VERSION 2 – REVIEW

REVIEWER	Aileen Ledingham USA
REVIEW RETURNED	08-Jul-2020

GENERAL COMMENTS	Great work on the revision. My apologies for the late submission, I lost track of time. Please consider 2 minor edits: Abstract line 32: change to baseline, 13 and 26-weeks after randomization Pg 5 line 48: To be consistent, change "aged over 40" to 40 years or older