Author’s response to reviews

Title: PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2) – Protocol for a multicenter randomized clinical trial.

Authors:
Ayoola Ademola (ayoola.ademola@ucalgary.ca)
Kevin Hildebrand (hildebrk@ucalgary.ca)
Prism Schneider (prism.schneider@gmail.com)
Nicholas Mohtadi (mohtadi@ucalgary.ca)
Neil White (nwhite@ucalgary.ca)
Michael Bosse (mbosse@carolina.rr.com)
Alexandra Garven (Alexandra.Garven@albertahealthservices.ca)
Richard Walker (rewalker@ucalgary.ca)
Tolulope Sajobi (ttsajobi@ucalgary.ca)

Version: 1 Date: 07 Jan 2020

Author’s response to reviews:

Reviewer 1

1) Comments: Line 6, page 2: Background: Injuries and and resulting stiffness… (remove and)

   Our response: We had removed one of the “and”. The change is highlighted in yellow in the Background section of Abstract.

2) Comment: Line 55, page 2: Discussion: The results of this study will provide evidence for the use of KF in treating post-traumatic joint contractures and improving quality of life after joint injuries. Same as above: maybe preventing or reducing would be a more appropriate definition of the objective of intervention - use of medication

   Our response: We have changed “treating” to “reducing”. The change is highlighted in yellow in the conclusion section of Abstract.
3) Comment: Line 46, page 6 ..fracture healing, our interest is the number of participants with disappearance of radiographic fracture lines overtime - Maybe more specific criteria should be used to assess and classify bone healing, such as RUST or mRUST scores (J Bone Joint Surg Am. 2018;100:1871-8).

Our response: The subject of the article (RUST or mRUST scores RUST or mRUST scores - J Bone Joint Surg Am. 2018;100:1871-8) is cortical bone healing. Our fractures are largely metaphyseal fractures. We are currently studies on our PERK I radiograph database to standardized fracture healing evaluation in metaphyseal fractures. Therefore, no change was made.

4) Comment: Line 21, page 7 – same as above for fracture healing assessment.

Our response: The subject of the article (RUST or mRUST scores RUST or mRUST scores - J Bone Joint Surg Am. 2018;100:1871-8) is cortical bone healing. Our fractures are largely metaphyseal fractures. We are currently studies on our PERK I radiograph database to standardized fracture healing evaluation in metaphyseal fractures. Therefore, no change was made.

5) Comment: Line 28, page 9 – The TSC will will meet quarterly to review trial performance and adjust the RCT (remove will, duplicated)

Our response: We have removed one of the “will”. The change is highlighted in yellow in the Data Monitoring section.

6) Comment: Line 12, page 11: Contractures complicate other orthopaedic conditions or procedures, such as total knee arthroplasty (please review sentence or it needs a better explanation - knee?) and positive results in post-traumatic (post-traumatic) contractures could apply to these other orthopaedic conditions or procedures.

Our response: We have removed knee as suggested and revised the sentence to state when we can generalize the result to other studies.

The change is highlighted in yellow in the Discussion section of the main body of the manuscript.

7) Comment: Line 49, page 11: an extrernally funded...

Our response: We have changed extrernally to externally. The change is highlighted in yellow in the Funding section.
1) Comment: I suggest breaking down the exclusion criteria in Appendix 3 by subtopic (listed in lines 45-48 of page 4) to make this list clearer.

   Our response: As suggested, we have revised the exclusion criteria by using subtopic. The changes are highlighted in yellow in Methods/Design section and Appendix 3.

2) Comment: Is there any concern with not closely controlling the analgesic regimens across patients? A recent paper by Salib et al (J Ortho Res Dec 2019) showed that administration of an NSAID (celecoxib) led to increased ROM in a rabbit knee preclinical model. Could variation in analgesic types/doses among patients complicate the interpretation of results if one type of analgesic (e.g., NSAID) has a positive antifibrotic effect?

   Our response: Yes, it is a concern but NSAID is available without prescriptions. In designing the trial, we decided to document the use of NSAID instead of trying to control its use. No change was made.

3) Comment: It appears that there isn't much control over the use of the "standardized home therapy program". Meaning, it seems likely that some patients will be subjected to this type of therapy while others won't at all, or perhaps to only a limited extent. While it is well understood and appreciated that home-based physical therapy is very difficult to replicate across all patients, I wonder about the potential effect this might have on study results?

   Our response: Yes, we agree this is a concern. In the design of the study, we decided to use a therapy program where the participants are instructed on the exercises which they will perform in their own homes. Since this is a randomized controlled trial, we envisage that will be a balanced distribution of those who comply and those who do not comply with the program in the 3 groups. Nevertheless, we believe that compliance with home therapy cannot be controlled in the general population. No change was made.