Reviewer’s report

Title: Prospective Randomized, Double-blind, and Placebo-controlled Clinical Trial with Hydroxychloroquine (HCQ) in Patients with Inflammatory and Erosive Osteoarthritis (OA) of the Hands (Acronym: OA TREAT)

Version: 2
Date: 14 July 2014
Reviewer: Marissa Lassere

Reviewer’s report:

1. Will study design adequately test the hypothesis?
   Yes. This is a generally well-conceived and well written protocol article that addresses an important question in an important subset of OA patients. Given the centrality of the AUSCAN as the primary outcome I think it deserves more discussion – list of its 15 components, scales used, are scores summed, etc. Also see 3 below.

2. Sufficient detail to allow replication?
   Yes, generally, except as noted below.

3. Statistical analysis appropriate?
   Can the sample size paragraph include more information? It is difficult to put an effect size in a clinical context for this trial and its outcome measures. Please provide a mean and a standard deviation for both the pain and function components of the AUSCAN that drives the sample size as described.

   For the clinical co-primary endpoint, AUSCAN pain and function, there needs to be a proviso in the analysis and discussion in the paper of how the authors will defend a positive result against the argument that the positive outcome was due not to the treatment but to imbalanced co-use of NSAID and/or analgesics. For example, co-use could be included as a covariate in the model. I note co-use is a secondary outcome measures in the trial.

   I am unclear about the use of the procedure (Ref 31) proposed to deal with multiple outcome measures in its first co-primary analysis of 52 week AUSCAN pain and 52 week AUSCAN function.

   Could your statistician provided further information to clarify exactly how this decreases type 1 error without increasing type 2 error. What are the assumptions of this method and will they be met in the context of this trial's data? What if the assumptions are not met?

4. Writing acceptable?
   The manuscript reads more as a protocol that as a manuscript. Therefore there should be introduction, specify all hypotheses explicitly, methods and discussion, as one would have in a manuscript. Furthermore, the discussion could include
any potential biases and discuss how they the authors intend to resolve the bias. For example, in 3 above, imbalance in NSAIDS and analgesia is a potential bias. How likely is this bias (why or why not), how will it be resolved, if present in the analysis.

Proof the references please. For example, ref 9 has no pages; ref 31 has no volume number (it is vol 52 issue 3).

The writing is otherwise acceptable.