Author’s response to reviews

Title: The challenges of gout flare reporting: Mapping flares during a randomized controlled trial

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Author’s response to reviews:

Dear Dr Mockridge,

Thank you for the helpful comments of the reviewers and giving us an opportunity to submit a revised version of our manuscript. We believe that the study addresses an important methodological issue in gout clinical trials, and that the findings are novel. We have made substantial revisions to the manuscript in response to the reviewer comments. This includes additional analysis to address the comments of reviewer 1, and removal of sections that were concerning to reviewer 2. The changes are described in detail below. Page and paragraph numbers refer to the clean version of the revised manuscript.

Tristan Pascart (Reviewer 1):

1. I read with interest this study assessing the various methods of flare reporting and determine if these methods are able to capture the heterogeneity of flares. The main finding is the temporal variation of pain in gout that is not well captured so far in flare reporting. I would be very interested to know whether these discrepancies are seen late in the evolution of the disease, or also in early in the course of the disease. This would be of importance depending on the type of patients included in future trials (early in the course, gout arthopathy…)}
We have undertaken additional analysis to address Dr Pascart’s comments, which are now shown in table 3 and supplementary table 3. The results and discussion have also been substantially amended throughout the manuscript to address these comments (page 9, paragraph 2 and 3, page 11, paragraph 3). This work has included additional analysis about the impact of the baseline features, including tophus, disease duration, flare frequency and anti-inflammatory drug use at baseline. These findings have shown the properties of the flare measures do differ according to these baseline variables, particularly disease duration and anti-inflammatory medications at baseline.

2. Was there an attempt to adjust the assessment of the flare on on-going anti-inflammatory therapy? I find it difficult to compare flare definitions which include pain intensity assessment to self reports given that anti-inflammatory therapy will have an impact on pain intensity at least to some extent (and expectedly on the duration of the flare as well).

Response: we have not been able to capture anti-inflammatory therapy for every study visit, but now present data for patients according to their anti-inflammatory drug status at baseline (table 3, supplementary table 3, results text and discussion text, page 9, paragraph 2 and 3, page 11, paragraph 3).

3. Over the course of gout, flares to be prolonged with varied intensity. Did you study whether the discrepancies between flare assessment are related to disease duration? (e.g. reports of flares may be more homogenous in early diseases, where flares are probably more typical)

Response: we now present data for patients according to their disease duration at baseline (table 3, supplementary table 3, results text and discussion text, page 9, paragraph 2 and 3, page 11, paragraph 3). In addition, we now report the percentage of participants with ‘typical’ and not ‘typical’ flares, according to the 2015 ACR gout classification criteria. We have added further information about the typical flare analysis in the abstract, methods (page 6, paragraph 2), results (page 8, paragraph 1) and discussion (page 10, paragraph 2). These findings further support the variability of flares in this analysis.

Our analysis of the number of ‘typical’ and ‘atypical’ flares show that both are increased in people with prolonged disease duration. However, we have not presented this analysis in this paper, as we were not convinced about the reproducibility of analysis that includes the counting of typical and atypical flares (different values can be derived depending on rules about the definitions of when a flare stops and starts).
4. Page 8 line 27: ‘median (range) percentage of days with Gaffo CART-defined flare was 4% (12-54%)’. The numbers don't seem to add up, I guess the median percentage is missing the second figure?

Response: This has been corrected

5. Table 2: I am very surprised by the poor correlation between CRP levels and all assessments of flares, do you have an explanation? I understand that CRP levels were examined monthly, but did you try to correlate CRP levels with reported flares contemporary of the biological assessment?

Response: This analysis was not possible from our dataset, as we did not record whether patient had a flare at the time of their study visit. However, the additional analysis, now shown in Table 3 and covered in the results and discussion section, has demonstrated significant correlations between CRP for the time-dependent methods of reporting, particularly in those with tophi, longer disease duration, more frequent flares and anti-inflammatory medications at baseline (page 9, paragraph 3, page 11, paragraph 3).

Unnamed Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

PEER REVIEWER COMMENTS:

1. GENERAL COMMENTS: Overall impression: This is a secondary analysis of a RCT investigating flare reporting in patients with gout. Unfortunately the paper could be reported far clearer with study objectives not linked throughout to the Methods and Results. There is overlap with the trial results which precludes the clear reporting of the original study assumptions on validity of reporting methods. What the authors did well: They have selected an interesting question which I had anticipated would be answered with a systematic literature review.

Response: We wish to be clear that it is not our intention to report the results of the clinical trial again (these have been reported in full, consistent with the registered trial protocol), but rather to use the trial data to address an important methodological issue in gout clinical trial development. To avoid any confusion about this, we have removed the between-group analysis, which was presented only to address the question of whether any method of reporting had greater sensitivity to change.
We agree that the study question is an important and interesting methodological question. Unfortunately, the study question cannot be answered by a systematic literature review (or IPD meta-analysis), as individual participant level data from other trials or observational studies with this detail (daily flare dairy data) are not available in the public domain. We are currently undertaking a systematic literature review to further describe the methods of flare reporting in gout studies, but this method of analysis does not allow detailed mapping of flare diaries that is needed for this analysis. To provide further clarity to the reader, we have made adjustments to the title to ensure that it is clear that we are analysing data from a prior clinical trial.

REQUESTED REVISIONS:

2. Thank you for providing the opportunity to review this paper. Unfortunately there are some major issues with this work. This is largely on the overlapping report of the principal study findings in the methods used to answer this question. I think there is confusion in reporting the trial (between-group) findings here. I do not think that group allocation is as important as the authors suggest and I would have analysed the data irrespective of this. I think flare patterns are an important area for study and data on these patients have been presented in previous trials. I would therefore recommend that this question be answered with a meta-analysis or Individual Participant Data meta-analysis approach. This will provided more than 114 flare patients and would provide greater assurances over the conclusions.

Response: Please see our detailed response above. We have removed the between-group analysis, which was presented only to address the question of whether any method of reporting had greater sensitivity to change. The study question cannot be answered by a systematic literature review, as individual participant level data from other trials or observational studies with this detail (daily flare dairy data) are not available in the public domain.

3. I think the authors have got an interesting question but I don't think answering it with this data is particularly useful. There is also confusion in the title and abstract as I was initially expecting this to be a systematic review of flare reporting in patients with gout, and it turned out to be somewhat different.

Response: Please see our detailed response above. The title and abstract has been amended for clarity

4. From a reporting perspective, I think the authors may have used subheadings to greater effect in the results section. By structuring by subheading of the study objectives, there could
have been far clearly linkage throughout the paper to reporting what was intended, and this may have clarified the message of the paper.

Response: Subheadings have been added throughout the results section.

5. There is overlap in reporting the main study findings. Please consider whether there is a need to acknowledge results by group allocation. To answer this question, I don't think the intervention is important. The answer may have been more appropriately answered with an Individual Participant Data meta-analysis.

Response: We have removed the group allocation analysis, as outlined above. As described above, we are unable to complete an IPD meta-analysis, as there are no clinical trial data available in the public domain that includes such detailed flare information.

We hope these responses are satisfactory to you. Thank you for your consideration of our revised manuscript.

Yours sincerely,

Nicola Dalbeth