Dear Editor,

Re: BRHM-D-18-00040

Thank you for the useful comments regarding our manuscript. We wish to submit a revised version that takes into account the Reviewer’s comments. Changes are highlighted using track changes. All authors have read the manuscript and approve its submission to the journal. They declare no conflict of interest. Our responses to the points raised are as follows:

Reviewer 2
Q1: Introduction - "Though elective TNF-alpha inhibitor discontinuation is justified in several RA patients, there is lack of sufficient data to guide the decision. Further, the course of action post-withdrawal also remains to be understood, although a decision based on sustained remission has been proposed [5]. Nonetheless, a consensus about patient selection and the timing of withdrawal remains to be reached. The objective of the study is to address this issue by investigating the pooled relapse rates after elective withdrawal of TNF-alpha inhibitor therapy in RA patients through meta-analysis of eligible studies." There appears to be a mismatch between the study questions proposed in the introduction and in the main objective. In the last part of the introduction, three questions are proposed that are of clinical interest, i.e:

1. Which patients can be selected to withdraw TNF-alpha inhibitor therapy
2. At what moment should the therapy be withdrawn and
3. How should RA be managed after withdrawal of therapy.

Although relevant, the main objective of the study does not directly answer any of these questions. I would suggest to add something like: "As a first step to answering these questions, we investigated whether TNF-alpha therapy can be withdrawn in general. To this end, we performed a meta-analysis..." In order to make the introduction connect well with the main aim.

A1: As suggested, we have rephrased the paragraph as follows (page 5, lines 8-10): “As an initial step to address these issues, we investigated whether TNF-α inhibitors can be withdrawn in general. To this end, we performed a meta-analysis...”

Q2: Methods - Bullet 3 inclusion criteria: "considering that biologic disease-modifying antirheumatic drugs (DMARDs) are the major class of drugs that interfere with the entire RA process [8]". The reasoning is not clear to me. Other outcomes of interest than relapse rate could have been of interest (i.e. radiographic progression, time to flare). Also, other DMARDs could have been of interest, as all DMARDs by definition, have an impact on disease activity. To do a meta-analysis one should make a focus, which is fine. Argumentation for this should be made in the introduction. I think the quoted part here is redundant and can best be removed.

A2: As requested, Bullet 3 has been removed. Furthermore, we have modified Bullet 2 as follows: “Studies that investigated the relapse rate following elective withdrawal of TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) as a first line or non first line biologic in patients with RA.”

Q3: Data extraction and methodological quality assessment: "If most [ do we have a cut-off point or % of positives (...) is considered of limited quality] (...)" The quoted part between square brackets [] should be removed. Based on the "majority of items on CASP positive" criterion all studies are high quality now. What would be the impact if another definition were chosen, i.e.
high quality if number of items positive > median number of positive CASP items of included non-randomized studies?

A3: We apologize for the confusion. The section in bracket has been removed. We selected a priori a value of $\geq 5$ positive items. This is now clarified as follows: “The quality of non-randomized trials was evaluated by CASP (The Critical Appraisal Skills Programme) checklist for Cohort study [10]. If $\geq 5$ of the questions in CASP provided positive results about a non-randomized trial, then the study was considered high quality.”

Q4: Results - A short and general discussion of highlighted aspects of included studies is currently missing. This should be added, with reference to table 2.

A4: As requested, a general overview of the studies identified is now provided (page 8, lines 6-12).

Q5: "Four RCTs were of high quality, whereas Moghadam et al., 2016 scored a 2 and was considered a low-quality study (Table 3)." This is true according to the definition authors used to define low- and high-quality studies. Being the only low-quality study among 16 studies, this makes the study look rather bad when presented in this way. However, looking at Table 3, all "good-quality" studies only scored 3 points out of 5 as well. Hence, the difference in quality may not be as large as is (implicitly) suggested. Perhaps it would be fair to also mention the number of points of the other studies, so that it is clear that it is not a large difference. Also, it may be of interest to the reader to explicitly mention the criterion that Moghadam failed to fulfill compared to the other studies, so that the reader can make his or her own judgement on the quality and potential impact on the results.

A5: We have rephrased as follows: “The JADAD score was 3 in four out of the five identified RCTs, and 2 in the remaining RCT by Moghadam et al (Table 3). The different score in the study by Moghadam et al was due to its open label randomized study design.

Q6: "The shape of the funnel plot reveals visual evidence of asymmetry. Publication bias was detected in the included set of studies as more studies were plotted on the left side of the graph (Figure 5)" Looking at figure 5, I count 9 points on the left side and 7 points on the right side. I wonder if this is sufficient to make the claim that the plot indicates publication bias. Although subjective, the plot looks quite symmetric to me and in agreement with what one would expect to find under the null-hypothesis of no publication bias.

A6: We have revised as follows: “The shape of the funnel plot did not reveal a clear evidence of asymmetry, suggesting no publication bias (Figure 5). Furthermore, imputation plotted no missing studies on the right side.”

Q7: "A meta-analysis of six trials reported that TNF-alpha inhibitor treatment continuation, in RA patients in sustained remission or low disease activity, increased the probability of low
disease activity (relative risk [RR] = 0.66, 95% CI 0.51-0.84) and remission (0.57, 95% CI 0.44-0.74), and reduced radiographic progression (RR = 0.91, 95% CI 0.85-0.98) though these results were not statistically significant [21].” None of the 95% CIs of reported relative risks include the null-hypothesis of RR=1, yet the authors claim that none of the results were statistically significant. This appears to be a discrepancy.

A7: We apologize for the confusion. The following has been removed: “though these results were not statistically significant.”

Q8: "The observed pooled relapse rate (...) and follow-up in individual studies". Several old studies from the eighties and nineties, in which conventional synthetic DMARDs were withdrawn, are mentioned here. As treatment of RA was very different then compared to nowadays, patients from these different times, in my opinion, cannot be compared as they might respond very differently to DMARD withdrawal. In this light, I think that this part is of limited importance and interest.

A8: We wish to retain this section as it provides opportunities for comparison with previous studies. However, we agree with the Reviewer that such studies do not reflect current management strategies. Therefore, we have added the following sentence: “Furthermore, the RA treatment strategies in these relatively old studies are quite different from those recommended by current professional guidelines.”

Q9: Several other systematic reviews and meta-analyses on withdrawal of TNF-alpha inhibitors have been published, which are not discussed, for example:


Please mention relevant systematic reviews / meta-analyses on discontinuation of TNF-alpha inhibitors in your discussion section and whether your findings are in agreement or not.

A9: The systematic review and meta-analysis by O'Mahony et al (2010) investigated the relapse rate with conventional DMARDs, not TNF-α inhibitors. Comparisons with the study by Kuijper et al (2015) are now discussed (page 11, lines 4-8).

Q10: "All the studies included in this analysis, employing rigid criteria for measuring disease activity and monitoring remissions, used improvement in DAS28 scoring system. (...) Such patients even after declare to have remitted will be more likely to relapse." The authors mention an important caveat of using the DAS28 remission criterion alone to define remission and initiate treatment de-escalation. It is well known that active disease may occur even when the DAS28 remission criterion is fulfilled. This has led to the development of other remission criteria (e.g. Boolean), but these are not frequently used in clinical practice and may be too conservative. The discussion on active disease being present despite a DAS28 indicating remission is certainly
relevant in this context and should be part of the discussion. However I do not understand the
claim the authors make: "Such patients even after declare to have remitted will be more likely to
relapse". If these patients have low DAS28 despite active disease, this by itself will not lead to
higher relapse rates measured if relapse itself is also defined by DAS28. What is of greater
concern is that the relapse rate measured by DAS28 in the meta-analysis of 47% may in reality
be even higher because of under-estimation by DAS28. I suggest to emphasize this in the
discussion.

A10: We agree with the Reviewer that the sentence is rather unclear. It has now been removed.
We have also added the following sentence in regards to the interpretation of the study results:
“As a result, it is possible that the relapse rate in ‘real-life’ is even higher than that (47%)
reported in our meta-analysis.

Q11: Figure 1 - Some rectangles contain numbers of included/retained studies (first and last),
while others contain numbers of excluded studies (middle two rectangles). Although the text
explains what is meant, it still makes the figure difficult to read. Please show in the bottom line
of each rectangle the number of included/retained studies, e.g.

Records excluded (n=351): abstracts,
reviews and unpublished trials without
results
(n=39)

A11: Figure 1 has been revised as requested.

Q12: Table 2 - It is unclear to me what is meant by the column "category" with values <1 and
>1. Please clarify this.

A12: We agree that this parameter is not useful. Therefore, it has been removed.

Q13: Table 2 - For the first study by Quinn et al., the event% is 70. But based on the number of
events (3) and total number (10) I would expect an event% of 30 here. Please look into this and
correct if necessary.

A13: We apologize for the confusion. Rates for this study have now been corrected.

Q14: Table 2 - For study number 5 by van den Broek et al., DAS44 rather than DAS28 was used.
This should be changed.

A14: We apologize for the confusion. The correct DAS has been added.
Q15: General - The included studies are not incorporated in the reference list. References to the studies included in the meta-analysis should be added to the main reference list and being referred to from the tables and figures and main text.

A15: As requested, barring the three studies referring to NCT identifying numbers, references of the identified studies have been added in table 2.

Q16: Introduction page 4: "(...) e.g. 5-6% in some Native American groups vs % in caribbean region) [1]." The percentage should be added and "carribean" should be written with a capital letter.

A16: Changes done.

Q17: Introduction page 4: "The pharmacologic therapies for RA comprise of nonsteroidan (...)"

"of" should be removed.

A17: Changes done.

Q18: Introduction page 4: "(...) increased risk of cancer and heart failure, demyelinating disorders (...)" "and" should be replace by ","

A18: Changes done.

Q19: Introduction page 4: "(...) sustained response, whether remission or even low disease activity and retarded radiographic progression in a number of published metaanyses." This should be changed to: "(...) sustained response (whether remission or low disease activity) and retarded radiographic progression in a number of published metaanyses." And references to the metaanalyses should be added.

A19: Changes done. Relevant references have also been added.

Q20: Introduction page 5: "favoring continuation and those with elective discontinuation after remission with almost half of the patients withdrawing biologicals maintaining low disease activity. [5,6]" Reference 6 refers to the 1987 classification criteria for RA and seems not to be of relevance here.

A20: We apologize for the confusion. The reference has been removed.

Q21: Results page 8: "(...) were finally eligible for inclusion criteria." "criteria" should be removed

A21: Changes done.

Q22: Results page 8: "(...) and I2=68.92%) random-effects model was used." should be changed to "(...) and I2=68.92%), hence a random-effects model was used"
A22: We have amended the sentence as follows: “As significant heterogeneity was observed (Cochrane’s Q-statistics = 48.27; p-value: 0.00 and I²= 68.92 %), a random-effects-model was used.”

Yours sincerely,

Arduino A Mangoni, on behalf of:
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