To the Editors-in-Chief
Trials Journal
Re: MS: 518536241020649
Dear Sirs,
We are very grateful for the constructive and helpful comments by the editors and the reviewers. We have revised the manuscript based on these comments. We have also attempted to provide more detailed explanation below where we believed detailed explanation was required. Two versions of the manuscript are submitted. In one of the versions, the changes we made are shown in track changes and in the other version the track changes are accepted. We hope these explanations and changes are adequate. However, we will be happy to make more changes if required.

Yours sincerely,
Abebaw Fekadu, on behalf of the authors

DETAILS OF REVISIONS
A. Responses to Editorial Requests:
1) Please ensure the title conforms to journal style for study protocol articles. The
title should follow the format ?___________: study protocol for a randomized controlled trial.?  

#Response: changes made to the title as per recommendation

2) Please move the ethical approval statement to the Method section of your manuscript. 

#Response: Statement on ethical approval moved to the method section

3) Please include a formal statement in your Methods section explaining that you obtained informed consent from each participant. 

#Response: Yes, participation will only be considered after appropriate consent procedures are completed.

4) Please mention each author individually in your Authors? Contributions section. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.?

#Response: Changes made as per the recommendation

B. Responses to comments by reviewers

Comment 1. The authors indicate in the inclusion criteria that participants are required to meet DSM-IV criteria for schizophrenia, but are being screened using the Operational Criteria for Research (OPCRIT). Is this tool acceptable and validated? 

#Response: The OPCRIT is a poly-diagnostic tool that generates diagnoses according to multiple diagnostic systems, including the DSM-IV. The content of the OPCRIT may be considered similar to the SCID, but unlike the SCID that is operationalized to allow diagnosis only according to the DSM-IV criteria, the OPCRIT does provide outputs according to the DSM-IV, ICD-10 and other older generation systems such as the Bluelerian classification. Although OPCRIT has not been used previously in Ethiopia, its predecessor, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) has been successfully used. OPCRIT employs similar stem questions to the SCAN and uses similar rating conventions. The SCAN also provides poly-diagnostic outputs. The PI of the MINOS study has experience in using and training in the use of both the SCAN and the OPCRIT systems and has also been trained by the originators of both. We have proposed validating the OPCRIT against the SCAN. We will be using psychiatry residents or qualified psychiatrists to administer the OPCRIT. The use of adequately trained psychiatrists and residents is also an important factor in ensuring the validity of the OPCRIT assessments. We hope that this explanation reassures the reviewers about the acceptability of using the OPCRIT approach.
Comment 2. Why aren't cognitive measures being included if this is a key outcome? The PANSS cognitive items are not generally used as a measure of cognition alone. It may be best to list this as a tertiary outcome.

# Response: This is a very important issue brought up by the reviewers. We would like to note first of all that cognitive function is an important outcome in schizophrenia that may be linked to the overall outcome of the illness, especially functional outcome. We also think that minocycline may have impact on cognitive function given its neuroprotective/neuroregenerative properties. Unfortunately there are no validated tools for the evaluation of cognitive function in Ethiopia other than the cognitive domain of the PANSS. Cognitive function tools require a substantial adaptation work, which will not be feasible to do as part of the MINOS trial. However, we would like to note that the performance of the PANSS cognitive subscale compared with the Wisconsin Card Sorting Test has been demonstrated to be good and the cognitive subscale has been considered to be clinically useful for the assessment of cognitive function in patients with schizophrenia [1, 2]. Therefore, despite the lack of a separate validated tool, given the relevance of the outcome and the demonstrated usefulness of the PANSS in recent reports, it seems reasonable to us to keep cognitive function measured with the PANSS as secondary outcome.

3. The statistical section is unclear. Mixed model repeated measures analysis is listed, but should be employed to analyse the primary outcome at week 12. More detail regarding the scales and the specific analyses should be included.

# Response: We have made corrections to this (Under sections on outcome and data management; Pages 19-21)

4. The introduction is lacking information on the anti-inflammatory effects of minocycline and the link to schizophrenia. There is brief information on animal models and clinical results, but a little more background would benefit the publication (for a review see Dean et al, CNS Drugs; 26(5):391-401).

# We are very grateful for this suggestion. We have now provided more details on the mechanisms that may be relevant to the action of minocycline are included.

5. There is a typographical error in paragraph #2 under "study objectives and aims"

# Response: We have made corrections

6. The sample size should be listed earlier

# Response: We are not entirely clear why the detail on the sample size should be presented above where it is currently presented. It is often acceptable to put the sample size estimation after the inclusion/exclusion criteria are described, as we have done here. If the recommended style of the journal is different or if the reviewer or the editor kindly advises us exactly where the section on the sample size estimation should go, we can make the recommended changes.

7. Are the authors concerned that their sample may be biased by having both the exclusion of women of child-bearing age, and the inclusion of those within 5
years of diagnosis? This will preclude most women from participating?
# Response: We do concede that the inclusion criteria is restrictive and is likely to exclude many women. As presented in the paper, minocycline has teratogenic potential. Women with schizophrenia may not take contraceptives as prescribed. Even if the recruited women were to take oral contraceptives, the potential drug-drug interaction (of minocycline and oral contraceptives) will reduce the efficacy of the oral contraceptives, as discussed in the manuscript. This restriction is an important limitation and potential findings may not have generalisability to women. But we believe that sufficient evidence can be generated from the study regarding the general benefit of minocycline in schizophrenia, which may also have implication to our understanding of the aetiology of schizophrenia.

8. The section on the CGI-SCH could be removed
# Response: Statements making reference to CGI-SCH are now deleted.
