PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Methotrexate and Prednisolone study in Erythema Nodosum Leprosum (MaPs in ENL) Protocol- A double-blind randomised clinical trial
AUTHORS	de Barros, Barbara; Lambert, Saba; Shah, Mahesh; Pai, Vivek; Darlong, Joydeepa; Rozario, Benjamin; Alinda, Medhi; Sales, Anna; Doni, Shimelis; Hagge, Deanna; Shrestha, Dilip; Listiawan, M. Yulianto; Yitaye, Abeba; Nery, Jose; Neupane, Kapil; Dias, Vivianne; Butlin, C. Ruth; Nicholls, Peter; Lockwood, Diana; Walker, Stephen

VERSION 1 – REVIEW

REVIEWER	Todd Schwartz University of North Carolina at Chapel Hill USA
REVIEW RETURNED	05-Mar-2020

GENERAL COMMENTS	This review is primarily statistical in nature. Page 10, Line 9: Will randomization also be stratified on site/country or any other key factor? Page 11, Line 1: Please indicate whether any blocking is being implemented. Page 11, Line 20: Please justify the expected 20% loss to follow-up. Also, please modify the sample size to be n=143 which would allow for 20% loss to follow-up. Page 11, Line 32: Likewise, please justify the expected 20% loss to follow-up in this stratum. Please harmonize the final sample size with that reported in the protocol. If this number is n=400, please discuss the expected power after the 20% loss to follow-up, as this number is substantially larger, and please justify this increase. Page 13, Line 33: Please harmonize the specification of the primary outcome variables here and in the sample size justification, as the latter specification for each stratum was unclear to me. Page 16, Line 19: Please consider imputation methods other than LOCF, or at least dicuss the merits on the LOCF approach. Could a sensitivity analysis be considered that considers best and worst case scenarios for missing values to permit comparison to the LOCF imputation? Also, please address imputation for outcomes other than the primary outcomes.

	Please note that lacking a draft of the Statistical Analysis Plan, I am unable to assess appropriateness with regard to the planned approach with respect to statistical methods, control of Type I error for multiplicity, etc.

REVIEWER	Dr PUGAZHENTHAN T MD,DNB,MNAMS ALL INDIA INSTITUTE OF MEDICAL SCIENCES (AIIMS) RAIPUR INDIA
REVIEW RETURNED	03-Apr-2020

GENERAL COMMENTS	This is an important RCT in the field of ENL. Available drugs with toxicity profile is better than the newly developed molecule working differently in different genomics. I wish the team to positively execute the research, as the practical aspects of recruitment in ENL is very difficult. THE ENLIST severity scale is being utilized in the RCT that will also a good strategy.

REVIEWER	Nimer Ortuño-Gutiérrez Damien Foundation, Belgium
REVIEW RETURNED	09-Jun-2020

GENERAL COMMENTS	This research is very important for the search a better treatment for the ENL, the study will be conducted in leprosy-endemic countries. Therefore, the results will be very relevant and may change the policy of clinical care of ENL. Also, it is in line of the current Global Leprosy Strategy aiming zero disabilities.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Page 10, Line 9: Will randomization also be stratified on site/country or any other key factor?

Answer to all these is No.

Page 11, Line 1: Please indicate whether any blocking is being implemented.

Thank you for this input. Yes, the randomisation is blocked. Each drug pack is identified with a serial number and there are equal numbers of active and placebo treatment packs in each block. Drug packs are to be distributed to centres in a way that maintains the serial numbering, so there will be only minor differences in the number of active and placebo drug packs available in each centre. In each centre the drug packs are to be distributed in order by serial number.

This answer was added to the article.

Page 11, Line 20: Please justify the expected 20% loss to follow-up. Also, please modify the sample size to be n=143 which would allow for 20% loss to follow-up.

Thank you, we corrected the sample size reported in the earlier version. The estimated loss to follow-up is based on experience in earlier trials in the same or similar centres. The centres vary widely, some working with people resident in rural communities which are not so mobile (Indonesia, DBLM, Ethiopia, Anandaban). Others work among communities living in shanti or bustee areas whose residents are more likely to move to places where they can find work. This can also include returning to home villages many hundreds of miles away to take temporary seasonal work (BLP, Delhi). In all locations, it is a particular problem as participants recognise improvement in their health status and seek new or additional work opportunities rather than take time out to attend clinic visits.

Page 11, Line 32: Likewise, please justify the expected 20% loss to follow-up in this stratum. Please harmonize the final sample size with that reported in the protocol. If this number is n=400, please discuss the expected power after the 20% loss to follow-up, as this number is substantially larger, and please justify this increase.

In the protocol, by recruiting up to 400 participants we ensure we have a sufficient number to protect ourselves from a higher loss of follow up than predicted.

Page 13, Line 33: Please harmonize the specification of the primary outcome variables here and in the sample size justification, as the latter specification for each stratum was unclear to me.

I have changed the order in the manuscript sections, so outcomes are before the sample size calculation, which clarifies the latter.

The primary outcomes variables are harmonised.

Page 16, Line 19: Please consider imputation methods other than LOCF, or at least discuss the merits on the LOCF approach.

Thank you. We have discussed the merits of LOCF approach on page 13 of the manuscript.

Could a sensitivity analysis be considered that considers best and worst case scenarios for missing values to permit comparison to the LOCF imputation?

The reasons for loss to follow-up and their impact on outcomes will be explored using appropriate forms of regression analysis.

Also, please address imputation for outcomes other than the primary outcomes – the secondary outcomes:

Analyses of secondary outcomes will parallel those for the primary outcomes and will also be assessed in relation to patient-reported outcomes.

Please note that lacking a draft of the Statistical Analysis Plan, I am unable to assess appropriateness with regard to the planned approach with respect to statistical methods,

Analysis Plan attached to the submission.

Control of Type I error for multiplicity, etc.

Given the large number of additional statistical tests to be conducted to avoid Type 1 errors a more demanding level of probability will be applied to define statistical significance (e.g. 1%).

I hope this answers all the questions.

I am available to answer further comments.

VERSION 2 – REVIEW

REVIEWER	Todd Schwartz University of North Carolina at Chapel Hill United States of America
REVIEW RETURNED	28-Jul-2020

GENERAL COMMENTS	I appreciate the additional details that have been included in this revision. I was unable to view the SAP, so I could not assess detailed analytic plans for the trial data. My only remaining comments regarding the authors' response are 1) my preference for imputation methodology other than LOCF alone, and 2) for consideration of harmonization of the significance levels for both statistical inference (i.e., 1%) and the power/sample size calculations (i.e., 5%).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Todd Schwartz

Institution and Country

University of North Carolina at Chapel Hill

United States of America

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below

I appreciate the additional details that have been included in this revision. I was unable to view the SAP, so I could not assess detailed analytic plans for the trial data. My only remaining comments regarding the authors' response are 1) my preference for imputation methodology other than LOCF alone, and 2) for consideration of harmonization of the significance levels for both statistical inference (i.e., 1%) and the power/sample size calculations (i.e., 5%).

Response: Thank you for your input. We have considered using alternative methods. We will harmonize the significance levels for both statistical inference and power calculation.

I hope this addresses all the comments.

I am available to answer further comments.

VERSION 3 – REVIEW

REVIEWER	Todd A Schwartz University of North Carolina at Chapel Hill USA
REVIEW RETURNED	21-Oct-2020

GENERAL COMMENTS	Thank you for your response; I have no further comments.