Author's response to reviews

Title: Safety and Efficacy of miltefosine alone and in combination with sodium stibogluconate and liposomal amphotericin B for the treatment of primary visceral leishmaniasis in East Africa: study protocol for a randomized controlled trial

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Author's response to reviews: see over
Response to reviewer’s comments:
Comments to authors:
Number the pages from 1 to 16.

Page numbers have been inserted.

1. P(age), authors, l(ine) 3 and Correspondence, l 1. Why is the name listed as [Ahmed Musa] on l 3 while [Ahmed Mudawi Musa] on l 1? Are they the same person, and if so, why not the same name?

   They are indeed the same person and the names have been harmonized to ‘Ahmed Mudawi Musa’.

   Please note that we have also deleted ‘on behalf of the Leishmaniasis East Africa Platform (LEAP) Study group’ from the author list since all the relevant people are already listed individually as authors.

2. P 2, p(aragraph) 2, l 8 and 9. Always insert a space between an inequality and a number, ie, [< 75] and [> 90].

   This has been done.

3. P 2, p 4. Insert the date of registration as well as the date of the first patient randomized and the date of the last patient entered if these have happened.

   The dates of registration and first randomization have been inserted. The trial is currently recruiting.

5. P 4, p 3, l 1. The word [proportion] is interchanged with reports in percentages. Do you think these two concepts should be kept distinct? Consider changing the word to [percentage]. Also P 5, p 5, l 5 and p 8, l 1.

   These have been harmonized to ‘percentage’.

6. P 4, p 4, l 3. What is being done to ensure that exactly one envelope is opened for each eligible patient? Do you also plan to report the integrity of the randomization as part of the study report?

   The envelopes are numbered sequentially externally. Inside each one there is a randomization sheet with the same sequential number as well as the treatment allocation. These randomization sheets are filed in the source documents which the monitor verifies at each site visit to confirm that only one envelope was opened for each patient. For integrity, yes, the clinical study report will also include the complete randomization list as generated by the Data Centre at the start of the trial, alongside the patient allocated during the trial.
7. P 4, p 6, b(ullet) 3. Add an [s] to [day] to read [days].

Added.

8. P 5, p 1, l 5. Rewrite as [haemoglobin < 5], [WBC < 1], and [platelets < 40,000]. See # 2 above.

Inserted space.

9. P 5, p 1, l 6,7. Did you consider making these standard across the two countries? If not, why not?

Methodology was standardised but it is not feasible to standardise routine clinical laboratory assessments as different machines and reagents may be used. However both internal and external QC will be carried out at both sites on a regular basis and training will be offered to site staff at the beginning and during the trial to ensure that the data collected is reliable and comparable.

10. P 5, p 3, l 4. Is there a plan to get assent from the children?

Yes, the investigator obtains assent of the child which must be completed once permission of the parent or guardian has been obtained to do so.


References 10-12 describe the triangular test and analysis. Additional citations of these references have been placed more prominently near the start of the ‘Analysis and sample size’ section.

12. P 5, p 5. The sample size does not justify any of the choices the investigators made to choose the sample size, and they are not referenced. Was a software package used to compute the sample size and will the same one be used to do the analysis? These should be specified.

The methods are now more clearly cited and the relevant section has been reworded and expanded, including software references. The lower and upper values ($p_0$ and $p_a$ respectively) were set to 75% and 90% based on efficacies of currently available therapies. For example, 90% would be an acceptable proportion cured, in terms of current options in public health use.

13. P 5, p 7, l 3,4,5. Make the upper case [N] into lower case [n], times 3. Samples are always lower case while populations are upper case.
These Ns have been changed. Please note, however, that we have not consistently followed this convention on upper & lower case. For example, to be consistent with the literature on the triangular test, $Z$ & $V$ retain upper case despite being sample quantities.


This has been done.

15. P 6, p 3, last l. Insert a [.] after [210] to read [210.].

Inserted.

16. P 6, p 4, l 5. Choosing the constant as $[1.96]$ suggests that the distribution is normally distributed. Can this be documented in the literature?

We now highlight the use of a normal approximation. The analysis of this secondary endpoint is described at length and without citations because we could not find the problem addressed to our satisfaction in the literature and the approach is of our own devising.

17. P 7, p 1, l 2,3. Replace [range] by [interval]. A range is the length of an interval. Also on l 3, was a method that does not need truncated values looked for instead of using truncation?

We have replaced ‘range’ with ‘interval’.

In terms of alternative methods, we did consider the two other approaches.

a) Estimate the day 210 $\theta$ by adding the day 28 $\theta$ to the log-odds ratio between days 28 & 210, adjust the CI width (for $\theta$) by the ratio of the $\sqrt{n}$‘s on the two days. However we were concerned that this approach, in particular the CI part, would not be very accurate if there were many changes in status between the days.

b) More analogous to the method in the MS, but based on odds rather than probabilities. However this ‘blew up’ in the case of no changes from day 28 to 210.

We felt that the stated disadvantages of these approaches were more serious than those of estimation on the probability scale.

18. P 7, p 2, l 3. Rewrite as [# 90].

Done.

   Replaced.

20. P 7, p 3, l 3. What level of significance will be used here?

   We have added that a 5% significance level will be used when comparing
   the primary and efficacy endpoints between sites.

21. P 7, p 8. Are you planning to measure compliance with usual as well as study
medications?

   Compliance (e.g vomiting, missed dose) will be measured for all study
medications, as all treatments will be observed or administered by site
staff. Compliance with other concomitant treatment will not be assessed.
A sentence has been added to the interventions section for clarity.

22. P 7, p 9, l 6. Rewrite as [# 7].

   Inserted space before 7.

23. P 8, p 1, l 10. These covariates should be specified either here or in the data
analysis section. How does one know they are appropriate?

   We have removed the word ‘appropriate’ and explained in a separate
sentence the procedure to evaluate base models and also the suggested
covariate models for PK. Covariate models for body size are exemplified
as much as possible in the new sentence, but remain dependant on the
final base model which is a priori unknown.

24. P 8, p 6, l 13. What will be done about unusual values detected at the time of
analysis?

   Range checks have been implemented to detect unusual values at data
entry, before analysis. These are then verified with the investigator at the
sites. This will also be captured in the data management report prior to
database lock.

25. P 9, p 4, l 8. Suggest inserting [completed] between [and] and [CRFs].

   Inserted.

26. P 9, p 5. Mention is made here of a [DSMB]; however, its composition and
powers are not outlined or referenced.
Reference provided for the DSMB charter (based on WHO-TDR operational guidelines) and composition of membership has been added to the manuscript. The DSMB will seek advice from an external statistician when necessary.

27. P 10, p 1, l 10. Drop [In order] and capitalize [To] as the words are redundant in English.

Changed as suggested.

28. P 11, p 3 twice, 5 twice 6 once and 7 twice. There is no plural in metric units, so drop the [s] on [mls] to read [ml].

Dropped 's' in ‘mls’.

29. P 11, p 5, l 1. Delete [only] as it implies an unstated expectation.

Deleted.

30. P 11, p 7, l 1, 2. Will all these measurements be done by the same clinicians?

No.
Data will be collected as per standard operating procedures (SOP’s) by laboratory technicians, medical doctors, clinical officers and nurses trained in GCP under the investigator who ensures the accuracy, completeness, legibility and timeliness of all data reported to the sponsor in the CRFs and any other additional information that is required.


Replaced.

A random sample of 10 R(ference)s was checked for accuracy. This reviewer also likes to have issue numbers on Rs as it makes it easier to find the paper.

Updated as suggested (added issue number to all references).

32. P 12, R 3. There are many more authors. Trials likes to publish all authors.

We had followed EndNote’s BMC Medicine style. Looking at previous issues of Trials indicates that all authors are not always listed, but we will follow editorial guidance either way.

33. P 12, R 5. Insert [(3)] after [10].
Inserted (added issue number).

34. P 12, R 7. There are 6 more authors and on l 3, insert [(4)] after [196].

Inserted (added issue number). See response above (point 32) on list of authors.

35. P 12, R 10, 12, 13, 16, appear to be accurate.

No change required.

36. P 12, R 11. The last author is [Chastang] and on l 2 insert [(8)] after [9].

We have updated the last author to ‘Chastang’ and added issue number.

37, R 17, l 3. Insert [(12)] after [100].

Inserted (added issue number). This is now reference 19.

38. P 13, R 20, 21, 22 appear to be accurate.

No change required.

39. P 15, Make the numbers on the y axis rotate clockwise 90 degrees to make the labels easier to read.

Changed.
We have also changed figure 1 with more details added on trial flow.