Author's response to reviews

Title: Community-based directly observed therapy (DOT) versus clinic DOT for tuberculosis treatment: a systematic review and meta-analysis.

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Author's response to reviews: see over
Dear Dr Harris

RE: MS: 2690893511427064 - Community-based directly observed therapy (DOT) versus clinic DOT for tuberculosis treatment: a systematic review and meta-analysis.

Thank you for assessing the manuscript named above and to the reviewers for their comments. Amended sections of the manuscript are highlighted in red and we would like to respond to the comments as follows:

Reviewer # 1

• Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

Line 107: How many studies included family member based DOT? Please comment on this.

Response: We have provided references for studies of DOT provided by family members in the introduction (on line 79). Studies with family member DOT supervision were only included in our review if treatment outcomes were separately reported for patients undergoing DOT supervised by a community health worker (CHW) or community volunteer (CV). Specific mention of how the exclusion criteria were applied with respect to DOT provider is given on lines 183-184 and 188-190. Line 262 mentions that only one of the included studies also had family DOT as an option (Kamolratanakul et al. reference 13).

• Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Line 54: May want to add more detail re: barriers to clinic and community-based DOT

Response: Some examples of barriers have been added to line 56-59 of the introduction and readers can refer to the references provided for more detail. The discussion (lines 399 to 401) also mentions some of the barriers to DOT and how CB DOT may help to address these.

Line 130: there is no mention re: the WHO outcome “not evaluated” (which includes transfer of care). This may significantly alter results. I would at least
comment on this, or perform a secondary analysis including transfer of care as an unsuccessful outcome to see if this significantly changes your results.

Response: It is possible that some of the patients assigned as lost to follow-up in the included studies were ‘not evaluated’ according to WHO definitions. However, all but one of the studies in which loss to follow-up (or default) was not specifically defined (Nirupa et al. reference 31) reported results for patients ‘transferred out’. Thus the impact of this possibility on the secondary outcome (loss to follow-up) meta-analysis should be limited. As events where treatment success was not achieved were considered ‘unsuccessful’ outcomes (whether death, treatment failure, loss to follow-up, or not evaluated) there should be no impact on the primary outcome (treatment success) meta-analysis result. This has been mentioned in the discussion on lines 441 to 447.

Line 183: I am concerned about criteria 6 (i.e. your definition of major selection bias). This seems somewhat arbitrary as there is not a fixed definition/criteria for this. In addition, I do not see a criteria for study quality, and note that several studies were of low quality. I would devote a bit more discussion to this issue and would recommend that you perform analysis by study quality as you did not exclude studies based on this.

Response: We thank the reviewer for his comments regarding selection criterion 6. Additional information on how this exclusion criterion was applied has now been added (line 193 onward). The detailed rationales for the studies excluded under criterion six are provided in additional file 2, with further justification added and highlighted in red for some studies in this revised submission. As most of the reviewed studies were not randomized controlled trials, the use of stringent exclusion criteria for selection bias was imperative for this systematic review of comparative effectiveness of two different DOT strategies. To emphasize that only studies were included that allowed comparison of the two DOT strategies we have also added to the title that this is a systematic review and meta-analysis of comparative effectiveness. The word ‘treatment’ has also been removed from the title to avoid redundancy, given the word ‘therapy’ is already in the title. Additional explanation has also been added to criterion 5 has also been added (lines 187-190), to explain specifically how this was applied during study selection. Upon final review of studies excluded under each criteria, the study by Arora et al. (reference 47) has been reallocated to criterion 6a, as opposed to 5 as it was in the original submission.

The quality of the studies overall was low, and this has been mentioned as a limitation of the systematic review results in the discussion (lines 355 and 356). The sub-analysis with only (relatively higher quality) prospective studies decreased heterogeneity, while the pooled result for treatment success was approximately the same as for the meta-analysis of all eight included studies for treatment success (lines 317 to 320 and figure 3).

Discussion: I would suggest discussing the value of patient preference, as some patients may prefer to attend clinic, rather than have a community health worker
visit them at home (stigma).

Response: The role of patient preference in DOT allocation has now been added to the discussion from lines 393 to 398. That stigma may be an issue for some patients receiving CB DOT is highlighted by one of the included studies (Miti et al. reference 27) and this has been mentioned in this section of the discussion (lines 410-414).

Reviewer # 2

Major Comments

Comment 1. Conclusion: The authors conclude that: our meta-analysis showed a significant benefit from CB DOT compared to clinic DOT for treatment success, but not difference between the two DOT strategies for loss to follow-up. The authors do not say anything about patients who failed treatment between the two groups. Examining the TB treatment outcomes, that includes treatment success (cured plus complete treatment), treatment failure and loss to follow. The authors’ findings indicate that since there was no difference in the loss to follow-up between the two treatment strategies (CB-DOT and Clinic-DOT), the differences in treatment successes between the two strategies may be explained by the treatment failures that occurred during treatment, which might indicate that the patient populations were different as far as sensitivity to treatment. Given that majority of the studies were observational, might this be related to the reason why patients were put on a given treatment strategy? Authors should explain why they think that CB-DOT was more effective than Clinic-DOT and not because the populations who received the interventions were different.

Response: Possibles explanations of differences in treatment success for the CB DOT and clinic DOT groups include: different treatment adherence; differing drug-resistance profiles (though all included studies assessed patients undergoing treatment for presumed drug-sensitive TB), or; differences between the patient groups (e.g. confounders based on socio-economic status such as malnutrition). While different patient and disease characteristics in Clinic-DOT and CB-DOT groups may have impacted on treatment outcomes to a certain degree, we believe that the strict inclusion criteria for this systematic review (excluding studies with apparent selection bias) make it unlikely that these factors explain the difference in treatment outcome. Lines 416 to 429 of the discussion raises these points.

Minor Comments

Comment 2. Abstract Key words: Instead of repeating directly observe therapy in words and also as an abbreviation DOT, the authors should add clinic-DOT as it is the other comparison arm

Response: Clinic DOT has been added as a keyword. DOT has been left as a keyword as an acronym due to DOT being a common term in its own right in the field (line 40 to 41).

Comment 3. The question the reviewers are addressed was clearly stated
Line 114, definitions, it should read CHWs were defined as not CHWs are were defined as written ..... 

Response: Grammatical error, now corrected (line 124).

Comment 4. Line 193 The primary outcome was the proportion of patients who successfully completed treatment .......... To avoid confusion with patients who completed treatment versus the composite of patient who completed treatment and those who cured I suggest that the authors rewrite the statement to read that: The primary outcome was the proportion of patients who were successfully treated and the secondary outcome .......... 

Response: The primary outcome for the analysis was treatment success: patients completing treatment with or without confirmation of cure. This has been reworded (line 214) to match terminology used in the definitions section (line 133 and 134).

Comment 5. Figures should be titled 
Response: The figure titles have been added. Note that exact p-values have been added to the results section (lines 311 and 327) and to the abstract, rather than in the forest plots (figures 2 to 4) as in the original submission.

Yours sincerely 

Cameron Wright, Lenna Westerkamp, Sarah Korver and Claudia Dobler