Author’s response to reviews

Title: Using electronic medication monitoring to guide differential management of tuberculosis patients at the community level in China

Authors:

Ni Wang (wangni@chinacdc.cn)
Hui Zhang (zhanghui@chinacdc.cn)
Yang Zhou (zhouyang@jscdc.cn)
Hui Jiang (zjmbk@sina.com)
Bing Dai (414898078@qq.com)
Miaomiao Sun (msun@path.org)
Ying Li (liying@chinacdc.cn)
Amelia Kinter (akinter@path.org)
Fei Huang (huangfei@chinacdc.cn)

Version: 1 Date: 12 Sep 2019

Author’s response to reviews:

The number of pages used below is based on the document of using track changes.

Editor Comments:

Responses to Reviewer 1:

1. Comment regarding Line 137 - The authors failed to adequately address this comment. The reviewer requested clarification on the meaning of "patient management organization", but the authors simply provided a new term without any clarification.
Response: I have clarified the meaning of BMU in lines 158-159.

2. Last comment under Methods - Response was added in lines 136-138; however, the new text is a run-on sentence that is difficult to understand. Recommend revising the sentence.
Response: I have delete the sentence in lines 128-130, because this sentence is a superfluous explanation.

3. Comment regarding Line 230 - The authors' response does not adequately address the reviewer’s comment. By definition, patients were switched from EMM to DOT if low adherence was detected when providers reviewed the data on the EMM device. Thus, it isn’t clear when providers would have had the opportunity to use the data to provide support to improve adherence before being switched back to DOT.
Response: I have explained the interventions more specifically in lines 142-146.
Responses to Reviewer 2:

1. Major critique #1 - This comment was not fully addressed. How were providers assessed (interview vs. self-administered questionnaire)? Also, could responses have been biased due to their relationship to the person collecting their data? (e.g., If asked by superiors, respondents might have felt compelled to provide positive responses).

Response: the providers were assessed by a self-administered questionnaire, we have taken some measures to reduce bias: first, the research group fully explained the purpose of this study; second, the questionnaires were asked sent to a given email by anonymous, and the research group would not give the result to their direct superiors. I have revised this part in lines 113-117.

2. Major critique #2 - this comment was only partially addressed because the authors do not define "acceptability".

Response: The definition have been described in lines 94-99.

New comments:

1. There are numerous grammatical and typographical errors throughout the paper in the original and revised text. Recommend a thorough editorial review of the paper by a native English speaker.

Response: Sorry for the inaccuracy, a native English speaker have reviewed the manual.

2. Some acronyms are not defined the first time they are used (e.g., FDC).

Response: We have checked it again.

3. In the data analysis section (lines 182-184) the authors use odds ratios for "refusal to use EMM" and rate ratios for "switching from EMM to DOT", but do not explain why these measures differ even though the modeling methods are the same.

Response: Sorry for the mistake, the two analyses used the same methods, it’s should be used odds ratio, I have revised it in line 176.

4. Table 1 - column headers include "RR", but the footnote refers to "OR".

Response: Sorry for the mistake, I have revised it in table 1.

5. Table 2 - "RR" is defined as "relative ratio", which is not a recognized epidemiological measure. I assume the authors meant "rate ratio" or "relative risk".

Response: Sorry for the mistake, I have revised it in table 2.

6. Tables 1&2 - footnotes are needed that indicate what variables are adjusted for in the multivariable models.

Response: I have add the footnotes in tables 1 & 2.
7. Line 299-301 - The authors state that a positive bacteriological result was a "risk factor" for refusal to use the device, which implies that there is a causal link between these measures. Although the factors were "associated" in this population, this study was not capable of determining whether there was a causal link. Other examples of lax use of epidemiologic terminology were observed throughout the paper. Recommend thorough review by a biostatistician.

Response: Sorry for the inaccurate use of the epidemiologic terminology. We have checked it again.

8. Line 324 - should "medium" be "median"?
Response: Yes, sorry for the misspelling.

Reviewer reports:
Richard Garfein (Reviewer 1):
Line 106 - Was age considered in the eligibility criteria? No lower age limit was mentioned in the Methods.
Response: Age was not a criteria in this study, as long as the patients could express clearly and have no communication impairment.

Line 111 - The abstract states that patients who refuse to use EMM were offered DOT, but that is not described in the Methods section; only that the physician would record the reason for refusing EMM.
Response: I have described the interventions more specifically in lines 142-147.

Line 138 - It would be helpful to define "basic management unit" for readers who are not familiar with the Chinese healthcare system.
Response: I have clarified the meaning of BMU in line 158-159.

Line 153 - Logistic regression models produce "odds" ratios, not "rate" ratios.
Response: I have revised it throughout the manual.

Line 155-156 - This type of analysis would ordinarily exclude variables from the multivariable analysis that were not statistically significant on univariate analysis. Therefore, justification should be given for including all variables in the multivariable analysis.
Provide justification for the strata used to analyze age. Also, would age have been statistically significant if treated as a continuous measure?
The Methods section does not describe how the health care work assessments were performed or analyzed. Also, it is important to specify whether the health care worker questionnaires were self-administered or interviewer-administered, and if the latter, who conducted the interviews (i.e., potential for socially desirable responding).
Response:

1. I have given the justification under the table1 and table2. Even some variables didn't show statistical significance in univariate analysis, considering the important influence of patient’s background and diagnosis in the treatment management, we included all the variables in the multivariable analysis.

2. In ordinary, age will be divided into 4 groups: <15; 15-44; 45-64; >=65. But in this study, only one patient under 15 years old, so we merged the first two age groups.(in table1 and table 2). And there is no statistically significant even if treated age as a continuous measure.

3. The method of the assessments for the health care workers have been revised in lines 113-117.

Line 177 - Include the min/max age of participants. Inclusion of children is not adequately addressed in the paper.
Response: I have revised it in line 200-201.

Line 185 - It is important to know whether adherence differed while using the EMM between patients who were withdrawn and patients who completed treatment.
Response: Thanks for your comment, I agree it’s an important result, but the aim of this study is to evaluate the acceptability of the EMM, so I think this analysis could be in the future study.

Figure 1 - To be consistent with the narrative of the paper, "Offered Consent" could be changed to "Offered EMM", and "Did not consent" cold be changed to "Refused EMM".
Response: I have revised it in figure 1.

Line 225 - Can the authors provide further insight into the 15 patients who were switched to DOT for poor adherence? Simply stating that "the results need to be studied further" is inadequate.
Response: I have revised this sentence in lines 251-257.

Line 253 - Unclear what the authors are referring to by "…increased by 1.2%."  
Response: The purpose of citing this literature is to support the result that most patients who stopped using EMM in the last two months of treatment, so more interventions were needed to enhance medication adherence.

Discussion - Another limitation that should be considered is the fact that this study did not collect data from patients about their perceptions of EMM use—only refusal at the start and during treatment. Such data would be important to collect in future studies.
Response: Thanks for your comment and I have add this limitation in lines 311-312

Discussion - There is a substantial body of literature on electronic pillboxes similar to the EMM
described in this paper (https://www.wisepill.com/research-news), yet this paper seems to ignore those other studies.

Response: thanks for your comments, I have read these literatures, some have already been cited in this paper. But most of the study about electronic pillboxes is on HIV/AIDS, so these literatures were not cited.

A thorough editorial review is needed to fix typographical errors and clarify confusing wording. Below are some examples noted while reviewing the paper.

Paragraph beginning on line 100 - This paragraph is awkwardly written and difficult to follow. Consider rewording.
Line 106 - insert "who" after "participants".
Line 139 - typo: "newt" should be "new".
Line 149-150 - the sentence starting, "The proportion of eligible…" is confusing. Consider rewording. Also, in the next sentence, the comma should be moved in front of the word "patients".
Line 187 - Insert "were" after "Patients".
Table 1 - "RR" is used in the column headings, which should be "OR".
Table 2 - Should also use OR, not RR.
Line 234 - Replace "could" with "were".
Line 240-242 - this sentence is awkward and difficult to understand. Also, "medium" should be "median". Consider rewording for clarity.
References are not formatted consistently (see #25).
Response: thanks for the comments. A native English speaker have reviewed the manual.