PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of digital adherence technologies in improving tuberculosis treatment outcomes in four countries: a pragmatic cluster randomized trial protocol
AUTHORS	Jerene, Degu; Levy, Jens; van Kalmthout, Kristian; Rest, Job; McQuaid, Christopher; Quaife, Matthew; Charalambous, Salome; Gamazina, Katya; Garfin, AM Celina; Mleoh, Liberate; Terleieva, Yana; Bogdanov, Alexsey; Maraba, Noriah; Fielding, Katherine

VERSION 1 – REVIEW

REVIEWER	Iribarren, Sarah University of Washington, BNHI
REVIEW RETURNED	24-Oct-2022

GENERAL COMMENTS	Thank you for the opportunity to review this important trial protocol. The manuscript is well-written and comprehensive. The following are minor recommendations for consideration. Introduction - An overview of all DAT interventions and why only medication sleeve/label and smart pill box was selected would be helpful to readers. Knowing justification for the selection is important as there are a number of other DAT interventions available/being tested. Methods - Justification for why labels were not implemented in Ukraine would be helpful. – now I see a justification later in the methods. Might consider moving this justification up to the study design section? - DS – drug sensitive should be written out on the first instance - There are a number of minor typos that I assume will be identified during the copy-editing phase - Would be helpful to describe the ASCENT digital adherence platform (e.g., features) and how TB teams interact with it (e.g., able to interact with the patients directly?). - Because of the high rate of poor outcomes in Ukraine described in the methods section I feel that there should be more information provided about each country and the known and hypothesized reasons for poor treatment outcomes. For example, why (at the time) did Ukraine have such high rates of poor outcomes compared to the other countries included in the study? - Do all participants in the intervention receive reminder messages or is it opt-in only? - There are a number of validated acceptability and feasibility surveys/questionnaires. It seems that sub-study 3 could benefit from a mixed-methods approach.

REVIEWER	Manyazewal, Tsegahun

	Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa
REVIEW RETURNED	02-Dec-2022

GENERAL COMMENTS	This is an important and timely RCT focusing on emerging digital health technologies that may improve medication adherence and treatment outcomes in patients with tuberculosis. The multi-country nature of the study may facilitate enrolment of a larger volume and diverse set of participants to inform policy and practice more boldly. However, the protocol requires revisions for clarity and reproducibility. Title 1. In the title “Effectiveness of digital adherence technologies in improving TB treatment outcomes in four countries: a pragmatic cluster randomized trial protocol”, it would be more appropriate to clearly write the names of the two DAT interventions. Such technologies start from mobile health and across VDOTs, smart pillboxes, sleeves …. My understanding is that they plan to evaluate 99DOTS medication sleeve and evriMED smart pillbox. 2. Good to revise “in four countries” to “in four high burden countries” 3. “…TB...” as (…tuberculosis...” Abstract 4. Objective: The topic is about “improving TB treatment outcomes” while the 1ry objective here is about “reducing poor treatment outcomes”. I would make sure the two walk in the same way. The one in the title gives more sense. 5. Good to include “medication adherence” as at least a 2ry objective as the main task of the technologies is to ensure adherence. 6. Methods: on line 52, the authors mentioned “two-arm cluster-randomized trial” and then on line 55 “1:1:2 ratio”. Though it is clear that the intervention is DAT in general, the nature, extent, and interpretation of the two DATs are different. Hence, this is a three-arm trial. In fact, that is how the authors have explained on page 8. 7. Countries, where the study will be undertaken, are needed here. Like “The study is operating in Ukraine, Tanzania, South Africa, and the Philippines which are among the top 30 high-burden TB or MDR-TB countries” as stated in the main text. 8. Non-inferiority or superiority? 9. The statement “We will use data from the digital adherence platform and a separate research database of data available from routine data collection.” Is not clear for readers and reproducibility, thus good to rephrase. 10. Some descriptions of the 1ry and 2ry outcomes are important. Treatment success rate seems more a more appropriate 1ry outcome if the Investigators stick to their study title. 11. Ethics: Good to check if “WHO Ethical Review Committee” is correct, as what I know is “WHO Research Ethics Review Committee”. 12. Keywords are missing Strengths and limitations 13. Good enough Introduction

	14. More recent literature have emerged about the DATs that the investigators may use to triangulate their background. 15. Page 6, line 127, “in relation to disease free outcomes”. The statement is not clear. 16. One paragraph summary of the TB status/demography in the 4 countries benefits the background. Methods 17. Again the issue about two-arm vs three-arm shall be relooked at. 18. Write abbreviations in full for the 1st time in the Main Text (DS-TB, MDR, RCT, …) 19. Study population: for an intention-to-treat analysis, Ukraine’s context mentioned “… where patients start treatment as inpatients, participants start the intervention at discharge” will make the analysis, interpretation, and reproducibility of the study very complex. In many DOT facilities in other countries, the SOC requires patients visit facilities daily and swallow the pill in front of a healthcare facility, but this seems not the case in Ukraine, and not sure why this country is included as patients are in good hands. Good to justify/clarify this at least in the Background. 20. Intervention: page 8, line 196, “ASCENT web-based digital adherence platform”. Is this another separate set of intervention beyond the two DATs? What is known is that the two DATs have their own web-based adherence monitoring platform. Any positive or negative outcome emanating from additional arrangements may not count on the DAT and thus may not inform the actual effectiveness of the DAT for an RCT. 21. Intervention Arm 1, 2: Good to clearly describe the source company, country of origin, trademark, and version/key specification (like evriMED1000, 2000, or 500; 99DOTS…) of the two DATs under the RCT. 22. Intervention arm 2: Again the investigators are planning to do some arrangements depending on the nature and capacity of the sites under study. I understand the importance of those additional arrangements but am not sure how such manipulations can be addressed in the analysis of such an RCT, and the reproducibility. Treatment outcomes 23. Page 11, line 50, “The primary endpoint is a poor end of treatment outcome, a composite indicator that includes documented treatment failure, lost to follow-up or death.”I would go for treatment success rate as the primary outcome. And the adverse treatment outcomes (treatment not completed, death, and LFTU) as the 2ry outcomes as they are more prone to confounders including HIV coinfection. 24. Good to consider adherence as mentioned in my comments on the Abstract 25. Smear conversion (following intensive phase) is a very good outcome indicator as well, at least 2ry, as this is the time patients in SOC are subject to daily DOT. Study procedures 26. The medication refill interval is not clear. 27. For a better understanding and reproducibility, the manuscript shall be restructured and strengthened using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial)

	guidelines. This includes replacing Figure 1 with a SPIRIT figure and attaching the completed SPIRIT checklist. References 28. Run through to once again for style uniformity, correctness (1,7,16), and up-to-date information.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sarah Iribarren, University of Washington

Comments to the Author:
Thank you for the opportunity to review this important trial protocol. The manuscript is well-written and comprehensive. Theollowing are minor recommendations for consideration.

Introduction
- An overview of all DAT interventions and why only medication sleeve/label and smart pill box was selected would be helpful to readers. Knowing justification for the selection is important as there are a number of other DAT interventions available/being tested.

We added more information about the overview of DATs based on a recent systematic review (lines 119-125) and added justifications for the selection of DATs (lines 136-140).

Methods
- Justification for why labels were not implemented in Ukraine would be helpful. – now I see a justification later in the methods. Might consider moving this justification up to the study design section?

Justification moved up as suggested.

- DS – drug sensitive should be written out on the first instance
- There are a number of minor typos that I assume will be identified during the copy-editing phase
- Would be helpful to describe the ASCENT digital adherence platform (e.g., features) and how TB teams interact with it (e.g., able to interact with the patients directly?).

We are using the Everwell Hub platform - future plans will accommodate patients having an App on their phone and being able to access the platform to see their data. For the study typically staff at the clinics access the platform via tablet or phone daily and see a summary of their current patients – the display shows missed doses (box not opened/SMS not sent) – actions include phoning patients. These can be logged on the platform. We described the platform more clearly (lines 259-262).

- Because of the high rate of poor outcomes in Ukraine described in the methods section I feel that there should be more information provided about each country and the known and hypothesized reasons for poor treatment outcomes. For example, why (at the time) did Ukraine have such high rates of poor outcomes compared to the other countries included in the study?

We thank the reviewer for this good suggestion. We described characteristics of each country in a new table (Table 2).

- Do all participants in the intervention receive reminder messages or is it opt-in only?

For pill boxes, patients get a verbal/audio reminder – with time set by the health care worker with patient input. For labels, participants make a toll-free call/SMS when dose taken - with their mobile phone linked to the intervention; after call/SMS, patients receive a confirmation text.

By 15:00 if box not opened/SMS not sent participant receives an SMS reminder – only if they a mobile phone or access to one.

- There are a number of validated acceptability and feasibility surveys/questionnaires. It seems that sub-study 3 could benefit from a mixed-methods approach.

We have included quantitative data collection in sub-study 1, but not in 2 and 3. Depending on what emerges during the qualitative interviews, we might consider adding a quantitative component to the other sub-studies.

Reviewer: 2
Dr. Tsegahun Manyazewal, Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa

Comments to the Author:
This is an important and timely RCT focusing on emerging digital health technologies that may improve medication adherence and treatment outcomes in patients with tuberculosis. The multi-country nature of the study may facilitate enrolment of a larger volume and diverse set of participants to inform policy and practice more boldly. However, the protocol requires revisions for clarity and reproducibility.

Title

1. In the title "Effectiveness of digital adherence technologes in improving TB treatment outcomes in four countries: a pragmatic cluster randomized trial protocol", it would be more appropriate to clearly write the names of the two DAT interventions. Such technologies start from mobile health and across VDOTs, smart pillboxes, sleeves …. My understanding is that they plan to evaluate 99DOTS medication sleeve and evriMED smart pillbox.
2. Good to revise "in four countries" to "in four high burden countries"
3. "…TB..." as (…tuberculosis..."

We thank the reviewer for these helpful suggestions. Comments #2 and #3 are well taken and changes made. Regarding comment #3, however, we prefer to keep the wording as is because we plan to evaluate the effectiveness of the whole intervention including the differentiated approach under programmatic condition, not the specific technology.

Abstract

4. Objective: The topic is about "improving TB treatment outcomes" while the 1ry objective here is about "reducing poor treatment outcomes". I would make sure the two walk in the same way. The one in the title gives more sense.

Our primary outcome is reduction in poor treatment outcomes, which in other words means improvement in treatment outcomes.

5. Good to include "medication adherence" as at least a 2ry objective as the main task of the technologies is to ensure adherence.

Medication adherence was part of our secondary objectives. In the revised manuscript, we described our secondary objectives more exhaustively. Note, however we do not have a measure of adherence in the SoC arm – but do have daily measure of a proxy for adherence (box opening/SMS sent) in the intervention arm(s).

6. Methods: on line 52, the authors mentioned “two-arm cluster-randomized trial” and then on line 55 “1:1:2 ratio”. Though it is clear that the intervention is DAT in general, the nature, extent, and interpretation of the two DATs are different. Hence, this is a three-arm trial. In fact, that is how the authors have explained on page 8.

The trials in South Africa, Tanzania and the Philippines were all designed as 2-arm studies with the intervention being “digital adherence technology + differentiated care”, with the type of digital adherence technology not considered being the main issue but that some form of digital capture of adherence is being conducted. The primary analysis will be a comparison on the intervention arm (combination of clinics using smart pill box or labels) vs SoC (1:1 facilities comparison). Secondary objectives include a comparison of each type pf DAT with the SoC: so (i) pillbox versus SoC (1:2 facilities comparison), and (ii) labels versus SoC (1:2 facilities comparison).

7. Countries, where the study will be undertaken, are needed here. Like “The study is operating in Ukraine, Tanzania, South Africa, and the Philippines which are among the top 30 high-burden TB or MDR-TB countries” as stated in the main text.

8. Non-inferiority or superiority?

We are not comparing efficacy of DATs with placebo, and superiority trial is not in our plan.

9. The statement “We will use data from the digital adherence platform and a separate research database of data available from routine data collection.” Is not clear for readers and reproducibility, thus good to rephrase.

Rephrased as “We will use data from the digital adherence platform and routine health facility records for analysis”as suggested.

10. Some descriptions of the 1ry and 2ry outcomes are important. Treatment success rate seems more a more appropriate 1ry outcome if the Investigators stick to their study title.

We have stated treatment outcome as primary outcome with poor treatment outcome being a more appropriate measure (as treatment success rate clearly exceeds 50% in all countries).

11. Ethics: Good to check if “WHO Ethical Review Committee” is correct, as what I know is “WHO Research Ethics Review Committee”.

This is noted and corrected.

12. Keywords are missing

These were included in the online version. Added here as suggested.

Strengths and limitations

13. Good enough

Introduction

14. More recent literature have emerged about the DATs that the investigators may use to triangulate their background.

We added a more recent literature in the background section.

15. Page 6, line 127, “in relation to disease free outcomes”. The statement is not clear.

We are evaluating post-treatment TB free status within 6 months of end of treatment in Ethiopia. Sentence amended.

16. One paragraph summary of the TB status/demography in the 4 countries benefits the background.

Suggestion accepted and summary information added in Table 2.

Methods

17. Again the issue about two-arm vs three-arm shall be relooked at.

This is a two-arm study. Although the intervention arm has two DATs, our primary aim was to detect differences between intervention and control arms including the differentiated response, not necessarily to evaluate efficacy of specific DATs.

18. Write abbreviations in full for the 1st time in the Main Text (DS-TB, MDR, RCT, …)

Done as suggested.

19. Study population: for an intention-to-treat analysis, Ukraine’s context mentioned “… where patients start treatment as inpatients, participants start the intervention at discharge” will make the analysis, interpretation, and reproducibility of the study very complex. In many DOT facilities in other countries, the SOC requires patients visit facilities daily and swallow the pill in front of a healthcare facility, but this seems not the case in Ukraine, and not sure why this country is included as patients are in good hands. Good to justify/clarify this at least in the Background.

We agree with the reviewer that the Ukraine situation is a bit different from the rest of the countries but including a country with a different background is one of the strengths of this pragmatic trial. Each country had its own differentiated approach as explained.

20. Intervention: page 8, line 196, “ASCENT web-based digital adherence platform”. Is this another separate set of intervention beyond the two DATs? What is known is that the two DATs have their own web-based adherence monitoring platform. Any positive or negative outcome emanating from additional arrangements may not count on the DAT and thus may not inform the actual effectiveness of the DAT for an RCT.

We used the Everwell Hub platform, described in lines 259-261.

The overarching aim of the study is to implement and evaluate digital adherence technology (DAT) systems (medication sleeve/label, smart pill box and video supported treatment) linked to a web-based adherence platform and a differentiated response to patient adherence.

Each DAT used can monitor drug dosing/adherence and patient daily dosing histories are then automatically compiled onto the overarching open-source adherence platform (henceforth referred to as the ASCENT adherence platform). All DATs are employed using this platform. Daily dosing histories collected via the DAT are displayed on an Android tablet that is provided to the health facility using Android app and/or using a web dashboard on existing computer infrastructure to enable health care providers to provide counselling and identify good and poor adherence, thus allowing for a differentiated response based on patient adherence. There is no separate set of intervention beyond the two DATs and the differentiated response to patient adherence.

21. Intervention Arm 1, 2: Good to clearly describe the source company, country of origin, trademark, and version/key specification (like evriMED1000, 2000, or 500; 99DOTS…) of the two DATs under the RCT.

We used evriMED1000C-
(Wisepill Technologies https://www.wisepill.com/evrimed) and 99DOTS (99DOTS A low-cost digital adherence engagement tool https://www.everwell.org/99dots). This is added in the revised manuscript.

22. Intervention arm 2: Again the investigators are planning to do some arrangements depending on the nature and capacity of the sites under study. I understand the importance of those additional arrangements but am not sure how such manipulations can be addressed in the analysis of such an RCT, and the reproducibility.

This is a pragmatic trial, and each country will deliver the interventions according to their local context. This is how the study is designed. These changes were made in the preparatory phase, ie. before the main enrolment phase,

23. Page 11, line 50, "The primary endpoint is a poor end of treatment outcome, a composite indicator that includes documented treatment failure, lost to follow-up or death."I would go for treatment success rate as the primary outcome. And the adverse treatment outcomes (treatment not completed, death, and LFTU) as the 2ry outcomes as they are more prone to confounders including HIV coinfection.

We agree that in settings with high treatment success rates, an intervention would not be necessary to improve treatment success. We believe in those settings, however, understanding if the intervention has cost savings (particularly if the SoC is daily DOT by health care worker at the facility) would be of great interest.

Facilities in the ASCENT studies from South Africa, Tanzania and Ukraine have the % with treatment success ranging from 70-88% andn the Philippines it is 91%, based on data from TB cohorts in 2018-19. We therefore believe there is room for the intervention to improve treatment success (reduce poor outcomes).

24. Good to consider adherence as mentioned in my comments on the Abstract

Adherence is part of our secondary outcomes, but only measured in the intervention arm. Our primary aim is to evaluate the impact of DATs with differentiated care approach on treatment outcome, which is the goal of the interventions. Impact of DATs on adherence has been well studied.

25. Smear conversion (following intensive phase) is a very good outcome indicator as well, at least 2ry, as this is the time patients in SOC are subject to daily DOT.

We agree this is an easily measurable indicator which has been studied more widely and our participant population is not limited to smear positive patients. Nevertheless, we are collecting these data from the TB Register so we could add as a post-hoc end point.

Study procedures

26. The medication refill interval is not clear.

The medication refill interval was according to the national guideless as shown in the supplemental information.

27. For a better understanding and reproducibility, the manuscript shall be restructured and

strengthened using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) guidelines. This includes replacing Figure 1 with a SPIRIT figure and attaching the completed SPIRIT checklist.

This is well noted and done.

References

28. Run through to once again for style uniformity, correctness (1,7,16), and up-to-date inform

We thank the reviewer for this observation. This is noted and done.

VERSION 2 – REVIEW

REVIEWER	Iribarren, Sarah University of Washington, BNHI
REVIEW RETURNED	06-Feb-2023

GENERAL COMMENTS	The authors did an excellent job addressing and responding to the issues identified by the reviewers in the revised manuscript. Adding the SPRINT checklist was a good addition. Minor suggestion for the strengths and limitations section: - Consider adding 'pragmatic' to the first bullet point of Strengths - It is important to note the potential confounding effect of the COVID-19 pandemic. It may also be important to note that the ongoing war in Ukraine may also have a confounding effect since recruitment was through August 2022. There are a few places where the Assent platform was changed to the Everwell Hub. Not clear if this should be changed throughout or if the authors want to maintain that it is the Assent platform. Thank you for your thoughtful revisions. The results of this study will be widely anticipated.

REVIEWER	Manyazewal, Tsegahun Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	The authors have satisfactorily addressed the comments I raised in my previous review and I have no further comments.