PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Perceptions of drones, digital adherence monitoring technologies and educational videos for tuberculosis control in remote Madagascar: a mixed-method study protocol
AUTHORS	Nouvet, Elysée; Knoblauch, Astrid; Passe, Ian; Andriamiadanarivo, Andry; Ravelona, Manualdo; Ainanomena Ramtariharisoa, Faniry; Razafimdriana, Kimmerling; Wright, Patricia; McKinney, Jesse; Small, Peter; Rakotosamimanana, Niaina; Grandjean Lapierre, Simon

VERSION 1 - REVIEW

REVIEWER	Dr. Kevin Schwartzman McGill University, Canada
REVIEW RETURNED	11-Dec-2018

GENERAL COMMENTS	Thank you for the opportunity to review this protocol, which I found well-written, timely and informative. The attention to perceptions and experiences of patients, community members, and health staff is important and commendable. The study design, including choice of respondents, is appropriate to the stated objectives. I do have a few suggestions for improvement. 1. In the discussion section, a brief description of potential limitations and challenges, and how these may be mitigated, would be useful. 2. In the ethics section, could there be concerns about stigmatization as a result of participation in some study activities, notably the individual interviews? In other words, could perception that individuals are participating in interviews related to TB treatment experiences (even if the interviews in fact include people with and without TB) lead to stigma for participants? 3. The reference list could be updated to include the most recent WHO handbook on the use of digital technologies for TB adherence and treatment support: https://www.who.int/tb/publications/2018/TB_medication _adherence_handbook_2018/en/ 4. Introduction, p. 7, line 84: please change to "10 million people developed active TB in 2017." The number who acquired latent infection is likely much higher. 5. Same page, line 93: I would suggest less emphasis on DOT per se; instead focus on treatment support and supervision.

| | 6. Same page, line 104: It would also be useful to comment on HIV prevalence in this setting/context. |
| | 7. I believe there is a typographical error in table 1: no numbers are provided for the target number of focus groups with elderly men and women in villages 2 and 3. I believe the correct numbers should be 1 each. |

REVIEWER	Dennis Falzon
	World Health Organization, Geneva, Switzerland
REVIEW RETURNED	10-Jan-2019

GENERAL COMMENTS	Authors propose to publish the protocol of a mixed-methods qualitative study of user perceptions on the involvement of unmanned aerial vehicles (drones) equipped with tools to facilitate the administration of TB medication in sites that are difficult to reach. As per the protocol the collection of data was expected to start before the article submission. The submission of study protocols is highly commendable and newsworthy. Minor changes are proposed before further consideration.
	Line 46: the abstract intro needs to clarify which specific challenges to achieve the End TB targets are drones advantageously positioned to address. You can state that poor medication adherence and inadequate HCW skills are important bottlenecks and DrOTS could thus improve both in places where access by road and good communications are otherwise a major barrier. This needs to be spelt out.
	Line 50: the word "Observed" should give way to ""Supported" in an era of greater patient-centered care and shared decision making. This may allay resentment that many patients increasingly express towards constant, intrusive surveillance. You can still retain DrOTS as an acronym of course.
	Line 57: how will questionnaires be applied? better to indicate the type of study, as done for other methods in the same line, rather than specify the tool used to collect data (e.g. anonymous polling)
	Line 70: evriMed is not a standard term and needs to be replaced. You should include "medication support" the word "tuberculosis" here; aim to have 1-2 keywords at least that are proper MeSH terms
	Line 72: it's very unlikely that the reader of this article will know what evriMED is so it is best to remove it here or define it very briefly. In this summary you should make it clear that tuberculosis care is being used as a pathfinder for other application of the DrOTS intervention
	Lines 77, 160 and 295: data is in plural, so "Data are ..."
	Line 84: there were 10 million new TB cases of disease in 2017 and not infections. Please correct this.
	Line 95: apart from the number of TB cases you should also highlight the problems with treatment adherence. For instance, among the 27k new and relapse cases starting treatment in 2016 11% were lost to follow up or not evaluated in Madagascar. This justifies measures to improve compliance, such as the intervention that you describe
	Line 104: are you sure that the study you reference at 11 here should not be the one presently at 12?
	Line 107: what is the national TB programme position on this intervention?

Line 123: it would be helpful to describe other barriers here that will not be uncovered by your survey, such as permissions to operate the drones by the local regulator or possibilities to sustain funding of the programme into the future (servicing equipment, recharging etc).

The Introduction assumes that the reader knows about the application of drones to health care and what evriMed is; I suggest that you describe these at some length here and give some background and citations for further information.

Line 143: whose "prevalent perceptions"? will you also poll the opinions of health policy decision makers and regulators? Please add a para on target audience for your studies and list them out clearly there.

Line 159: FGD not FDG

Line 171: there is no mention of the total number of subjects to be surveyed, the mix of patients, selection strategy and how the sample size will be estimated (on what assumptions?). How would you ensure that the "large sub-population sampling size" mentioned in line 185 will be achieved?

Line 190: can you add a sentence in this para to support the decision that FGDs in 3/61 participating villages would suffice to get a good sense of prevalent perceptions?

Line 204: selection of participants in FGDs is commonly done using convenience sampling. Random selection is likely to identify subjects who are far between and who would be obliged to join a group of other subjects whom they do not know and may take time to interact usefully together. This is more likely to overburden the conductors of the study rather than lighten their task, as implied in lines 207-208. Please clarify.

Line 252: how many of these ethnographic studies will be done ? how will you ensure that you get a good cross section of the individuals or settings that are relevant to the objects of your study ?

Lines 304 and 305: you provide here information about the number of studies that was not previously presented in the respective sections describing these studies. can you please fix this?

Para starting line 306: can you state here or elsewhere about any other studies that exist which could shed light on the findings that you expect? did you undertake a literature review to see what exists already, at least for electronic medication monitors if not for UAVs. This is critical to comment about here because you need to contextualise what you will eventually discover among patients in this country with what is known from elsewhere.
Also in this section bring in a discussion about other barriers that could impede the scale-up of DrOTS in Madagascar and elsewhere and which will not be elucidated by the findings of this study (e.g. licence/regulations to operate the UAVs in many countries)

Line 309: replace "are" with "is"

	Line 314: replace "fronts lines" with "front lines"
	Line 338: under competing interests can you state any/absence of relationship or funding with evriMed developers?
	Table 1: are the elderly men and elderly women in Villages 2 and 3 being redistributed into the respective 4 groups along homosocial lines?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments to Author:

1. In the discussion section, a brief description of potential limitations and challenges, and how these may be mitigated, would be useful.

Response: We have included a new Limitations and potential challenges section in the discussion.

2. In the ethics section, could there be concerns about stigmatization as a result of participation in some study activities, notably the individual interviews? In other words, could perception that individuals are participating in interviews related to TB treatment experiences (even if the interviews in fact include people with and without TB) lead to stigma for participants?

Response: This is an important point. We now flag the possibility of stigma, situating it in the literature on TB, and describe strategies being used to mitigate risk of stigma to participants in our TB-focused study. We have addressed these issues in the Ethics and Dissemination section.

3. The reference list could be updated to include the most recent WHO handbook on the use of digital technologies for TB adherence and treatment support: https://www.who.int/tb/publications/2018/TB_medication_adherence_handbook_2018/en/

Response: This was emphasized in the text and a reference was included.

4. Introduction, p. 7, line 84: please change to "10 million people developed active TB in 2017." The number who acquired latent infection is likely much higher.

Response: We have changed the first sentence in the introduction according to the reviewer's suggestion.

5. Same page, line 93: I would suggest less emphasis on DOT per se; instead focus on treatment support and supervision.

Response: This section was rephrased to better represent the lack of resources not only for DOT implementation but also those control activities the reviewers refer to.

6. Same page, line 104: It would also be useful to comment on HIV prevalence in this setting/context.

Response: Low rates of HIV in Madagascar, together with low rates of MDR-TB were mentioned in the manuscript and appropriate references were included.

7. I believe there is a typographical error in table 1: no numbers are provided for the target number of focus groups with elderly men and women in villages 2 and 3. I believe the correct numbers should be 1 each.

Response: Thank you for catching this. We have made the correction.

Reviewer 2 Comments

Reviewer Name: Dennis Falzon

Institution and Country: World Health Organization, Geneva, Switzerland

Please leave your comments for the authors below

Authors propose to publish the protocol of a mixed-methods qualitative study of user perceptions on the involvement of unmanned aerial vehicles (drones) equipped with tools to facilitate the administration of TB medication in sites that are difficult to reach. As per the protocol the collection of data was expected to start before the article submission. The submission of study protocols is highly commendable and newsworthy. Minor changes are proposed before further consideration.

Comment 1 - Line 46: the abstract intro needs to clarify which specific challenges to achieve the End TB targets are drones advantageously positioned to address. You can state that poor medication adherence and inadequate HCW skills are important bottlenecks and DrOTS could thus improve both in places where access by road and good communications are otherwise a major barrier. This needs to be spelt out.

Response: Thank you. The abstract has been adjusted to more clearly stress the importance of DrOTS in such contexts.

Comment 2 - Line 50: the word "Observed" should give way to ""Supported" in an era of greater patient-centered care and shared decision making. This may allay resentment that many patients increasingly express towards constant, intrusive surveillance. You can still retain DrOTS as an acronym of course.

Response: This is a very interesting point. Of course, the initial name was chosen in reference to the well-known DOTS acronym. Indeed, implementation of the DrOTS project already reveals that all its technological component are better implemented if individually tailored to patient realities. This includes drones and evriMED devices which certainly do not replace well-functioning alternatives and for which there is not a one size fits all solution. This being said, given that IRB approval has been obtained under this appellation, it difficult to modify the project's name on paper at least. Another important aspect is that since implementation includes significant community sensitization activities, modifying the name of the approach to which CHWs and local authorities identify the field team and certain NTP officers would generate an important amount of confusion.

Comment 3: Line 57: how will questionnaires be applied? better to indicate the type of study, as done for other methods in the same line, rather than specify the tool used to collect data (e.g. anonymous polling)

Response: The start of the section about the questionnaire/survey has been revised. It now includes the rationale underlying use of this method in this study (this sentence was previously at the very end of the section). It also specifies to whom the questionnaire survey will be administered. Both these statements precede a description of the tools, in accordance with the reviewer's recommendation.

Comment 4: Line 70 (keywords) evriMed is not a standard term and needs to be replaced. You should include "medication support" the word "tuberculosis" here;

Response: All keywords except evriMEDTM and medication support (suggested by Reviewer 2) are now MeSH terms. We propose keeping evriMEDTM as it is a first study to the best of our knowledge on perceptions of this particular technology, and this may facilitate consultation of the article by others interested evriMED use and acceptability. Of note, evriMEDTM (along with 2 other adherence technologies) were subject of the last TB REACH call for proposals because of its anticipated

potential in supporting remote treatment and adherence monitoring. It is anticipated that evriMEDTM will receive increased attention in the near future and will become a well-known and used term in the TB field.

Keywords are now:

"drones, tuberculosis, biomedical technology, global health, patient care management, medication adherence, medication support, eHealth, evriMEDTM, Madagascar, video"

Comment 5: Line 72: it's very unlikely that the reader of this article will know what evriMED is so it is best to remove it here or define it very briefly. In this summary you should make it clear that tuberculosis care is being used as a pathfinder for other application of the DrOTS intervention

Response: The highlighted text has been added to this "Strength" bullet point

☐ "This study is one of the first to assess acceptance and perceptions of drones and evriMEDTM pillboxes (medication reminder and remote treatment adherence monitoring devices), technologies currently being considered for scale-up in several health systems around the world."

We now speak of evriMEDTM pillboxes (instead of devices – which is less descriptive a term) throughout the paper.

Finally, with reference to the last point in Comment 5, we have:

(a) Added the following to Strengths and Limitations section: "The bundle of technologies at the core of this study is one that could be applied in response to other health needs in other contexts."

(b) State in the paper introduction: "Such technologies may strengthen TB control activities within challenged national tuberculosis treatment and control programs (NTPs), and also may be adapted to address other public health challenges."

Comment 6: Lines 77, 160 and 295: data is in plural, so "Data are ..."

Response: Corrections made.

Comment 7: Line 84: there were 10 million new TB cases of disease in 2017 and not infections. Please correct this.

Response: Corrections made.

Comment 8: Line 95: apart from the number of TB cases you should also highlight the problems with treatment adherence. For instance, among the 27k new and relapse cases starting treatment in 2016 11% were lost to follow up or not evaluated in Madagascar. This justifies measures to improve compliance, such as the intervention that you describe

Response: This was clarified in this specific section which now reads:

"Treatment adherence and success rates are reported to be highly variable between regions of the country respectively averaging 60% and 84% in the DrOTS intervention area and at national level"

Comment 9: Line 104: are you sure that the study you reference at 11 here should not be the one presently at 12?

Response: Correct. This was adjusted in the revised version.

Comment 10: Line 107: what is the national TB programme position on this intervention?

Response: Madagascar's Ministry of Public Health and the NTP were consortium partners of this project. In a desire to assess new ways to overcome the intrinsic challenges of TB care in remote settings which are listed in the manuscript, the NTP collaborated with IPM and SBU on this project. This is mentioned in the manuscript. We do not think this specific item needs to be further described in this article at this stage.

Comment 11: Line 123: it would be helpful to describe other barriers here that will not be uncovered by your survey, such as permissions to operate the drones by the local regulator or possibilities to sustain funding of the programme into the future (servicing equipment, recharging etc).

Response: This was included in the manuscript which now reads:

"Given the novelty of this new approach we designed and here present a study protocol for the DrOTS perception study, a mixed-method cultural acceptability sub-study embedded within the DrOTS project. This study will shed light on cultural and individual perceptions and barriers and facilitators to implementation. To facilitate the implementation of such innovative technologies, other challenges such as sustained funding, creation of a LMIC-friendly market environment for drone supplies and aviation regulation approval also need to be overcome and those will not be addressed in this study."

Comment 12: The Introduction assumes that the reader knows about the application of drones to health care and what evriMEDTM is; I suggest that you describe these at some length here and give some background and citations for further information.

Response : A brief review of current uses and expected contributions of drones and digital treatment support and adherence technologies has been added to the introduction:

"Several organizations are exploring the economic and practical feasibility of using drones for healthcare purposes including: support to rescue missions in disasters; enhanced epidemiological monitoring for disease outbreaks and vectors; delivery of critical resources such as blood or defibrillators in emergencies; delivery of other routine and occasional medical payloads such as samples for laboratory analysis, vaccines, medication and supplies for community healthcare centres (13-18). Medication reminder and remote treatment adherence monitoring devices, such as the EvriMEDTM pillbox, may augment treatment adherence and facilitate more effective allocation of limited HCP resources in contexts where populations are hard to reach, or health systems under-resourced (19-21). While the potential of new digital technologies to transform healthcare is enormous, this potential is contingent on user- and context-specific needs, engagements with technologies and digital health strategies, and may imply different impacts and challenges in different contexts (22)."

Further reference to pertinent literature has also been added to the discussion section (see Response to Comment 20).

Comment 13: Line 143: whose "prevalent perceptions"? will you also poll the opinions of health policy decision makers and regulators? Please add a para on target audience for your studies and list them out clearly there.

Response : We have added the target/participant groups to the objective with this wording.

Comment 14: Line 159: FGD not FDG

Response: This was adjusted in the revised version..

Comment 15: Line 171: there is no mention of the total number of subjects to be surveyed, the mix of patients, selection strategy and how the sample size will be estimated (on what assumptions?).

How would you ensure that the "large sub-population sampling size" mentioned in line 185 will be achieved?

Response: The total number of subjects to be surveyed results form the '10-15 individuals aged ≥15 years in each of the DrOTS-participating villages'. Hence, 10-15 individuals times 61 villages, amounting to 610-915 filled questionnaires. The median value of 750 completed questionnaires was added to the main text. The sample size was calculated based on (i) a total population size of 27,000 in Androrangavola commune, (ii) on the assumption that 50% reply 'Yes' to one main question on drone perception (i.e. "Do you think that the drones bring something positive to your community?", (iii) a 95% confidence level, and (iv) a 10% drop-out rate. This resulted in a sample size of 417. However, the overall DrOTS-project design, lifespan and geographic coverage allowed us to sample a larger population. The sample size considerations were added to the revised.

Comment 16: Line 190: can you add a sentence in this para to support the decision that FGDs in 3/61 participating villages would suffice to get a good sense of prevalent perceptions?

Response: Done. We have added the sentence: "While there is a possibility that gathering perceptions in only three of 61 villages may result in the study failing to capture all perceptions, this focus aligns with our interest in generating detailed insight into DrOTS, by ensuring we have the time needed in each village to conduct several FGDs."

We re-acknowledge this potential limitation in the new Limitations and Potential Challenges section.

Comment 17: Line 204: selection of participants in FGDs is commonly done using convenience sampling. Random selection is likely to identify subjects who are far between and who would be obliged to join a group of other subjects whom they do not know and may take time to interact usefully together. This is more likely to overburden the conductors of the study rather than lighten their task, as implied in lines 207-208. Please clarify.

Response: Random or purposive or a combination: what is best depends on many factors. Individuals not knowing each other can be as conducive to a successful FGD as individuals knowing one another, in the primary author's experience. In the Malagasy context of this research, random sampling does not involve strangers being in dialogue. All participants in FGDs know each other ahead of the FGD: villages are small, some livestock is raised in common, many families will head out to and return from their fields together, and there is a tradition of all villagers attending regular village council meetings.

Convenience sampling is only used by the primary author if it is the only option (few volunteers or individuals with relevant experience, for example), and never when the purposive and randomized approach described here is possible. Why? Even amongst people who know each other well, one cannot expect a good FGD if it goes against social norms, such as (but not limited to) gender, age, class distinctions. For perceptions studies aiming to learn from individuals who are diversely positioned in relation to a healthcare program, and in contexts where conversation may be easier amongst individuals of the same age or gender, it is very important to be purposive. As noted in the manuscript, there is a random dimension also to participant selection in this study when volunteers to one category of FGD exceed participants needed. Random inclusion in such scenarios reduces risks of anyone feels unfairly excluded.

Comment 18:

Line 252: how many of these ethnographic studies will be done ? how will you ensure that you get a good cross section of the individuals or settings that are relevant to the objects of your study ?

Response: We believe we created some confusion as the heading for this section was plural, when it should have been singular. We have revised the description of this method to clarify this method

involves one two-week period of ethnographic observation. Note: We are not aiming with this method to learn from a cross section of individuals or settings; rather, our objective is to enhance an already robust study with ethnographic observation in one DrOTS-enrolled village focused on one DrOTS patient, towards building our awareness and understanding of meanings, attitudes towards, or engagements with DrOTS.

Comment 19: Lines 304 and 305: you provide here information about the number of studies that was not previously presented in the respective sections describing these studies. can you please fix this?

Response: Thank you for seeing that. The summary of data to be collected is now included in the abstract (methods and analysis) and in the first sentence of the Methods and Analysis section.

Comment 20: Para starting line 306: can you state here or elsewhere about any other studies that exist which could shed light on the findings that you expect? did you undertake a literature review to see what exists already, at least for electronic medication monitors if not for UAVs. This is critical to comment about here because you need to contextualise what you will eventually discover among patients in this country with what is known from elsewhere.

Also in this section bring in a discussion about other barriers that could impede the scale-up of DrOTS in Madagascar and elsewhere and which will not be elucidated by the findings of this study (e.g. licence/regulations to operate the UAVs in many countries)

Response : We have made significant additions in terms of references within the introduction pertinent to this comment (Response to Comment 12). We have also revised the discussion section to summarize key concerns raised in the literature related to drones and remote adherence and monitoring devices that may or may not align with eventual findings from our study:

"This study responds to a current gap in knowledge on the feasibility and cultural acceptability of using a new suite of technologies including evriMED™, drones and tablet-mediated video education to support improved TB diagnosis and treatment in remote populations. Digital technologies that enable remote monitoring and faster delivery of medical care and supplies are potential game changers for healthcare landscapes struggling with long-standing or temporary (as in the case of disasters) barriers to healthcare delivery. Still, the development of innovative healthcare technologies does not guarantee their enthusiastic and rapid adoption in diverse settings (26-28). Perceived benefits and risks, use, and challenges of adopting such innovation is not likely to be uniform across distinct socio-cultural, health system, and economic settings. These may vary depending on any number of factors, including (to name just a few) the presence or lack of alternative options for care, association of use with a context-specific stigmatized condition, as well as prior direct or rumored experiences with interventions deemed to be similar in some way to the new ones. There is inherent ethical complexity in using devices such as drones for "surgical strikes" on "wicked" global health challenges, if key determinants of poor health remain unaddressed (29). Recent studies conducted with intended users and 'beneficiaries' of new digital health systems in LMIC contexts reveal other context- and culture-specific concerns or limitations of these technologies, such as concerns these could dehumanize assistance (30), infringe on private spaces (31), and be too expensive for some governments (31). Findings from the DrOTS cultural acceptability study may or may not reveal similar concerns in the Malagasy context, and will be situated within growing literature on perceptions and acceptability of TB remote digital medical monitoring and adherence strategies."

Comment 21: Line 309: replace "are" with "is"

Response: This has been corrected.

Comment 22: Line 314: replace "fronts lines" with "front lines"

Response: Done.

Response: This has been corrected.

Comment 23:

Line 338: under competing interests can you state any/absence of relationship or funding with evriMed developers?

Response: We have added the following sentence: "The authors have no relationship and obtained no funding for this study from the developers of evriMED."

Comment 24:

Table 1: are the elderly men and elderly women in Villages 2 and 3 being redistributed into the respective 4 groups along homosocial lines?

Response: I believe this question emerges from an error in Table 1 in the previous version. We were missing indication of 1 elder women and 1 elder men group in villages 2 & 3. This has been corrected.

VERSION 2 – REVIEW

REVIEWER	Dr. Kevin Schwartzman McGill University
REVIEW RETURNED	01-Mar-2019

GENERAL COMMENTS	In my view the authors have addressed earlier comments very well. There are a few very minor typographical errors in the manuscript which can be remedied at the copy editing and proofreading stages.