**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | Harnessing new mHealth technologies to Strengthen the Management of Drug-resistant Tuberculosis in Vietnam (V-SMART trial): a protocol for a randomized controlled trial |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS            | Velen, Kavindhran; Nguyen, Viet Nhung; Nguyen, Binh Hoa; Dang, Tho; Nguyen, Hoang; Vu, Dinh; Do, Thu; Pham Duc, Cuong; Nguyen, Huu; Pham, Huu; Marais, Ben; Johnston, James; Britton, Warwick; Beardsley, Justin; Negin, Joel; Wiseman, Virginia; Marks, Guy; Nguyen, Thu Anh; Fox, Greg |

**VERSION 1 – REVIEW**

| REVIEWER         | Chaiyachati, Krisda |
|------------------|---------------------|
| University of Pennsylvania Perelman School of Medicine, Medicine |

| REVIEW RETURNED | 30-Aug-2021 |

| GENERAL COMMENTS | Overall, this is a well-written and transparent protocol paper. My comments are the following: |
|------------------|----------------------------------------------------------------------------------------------------------------------------------|
|                   | My major comment is related to the heterogeneity of the treatment group. Given the authors will have a mixture of rifampin-resistant and MDR-TB patients who will experience a variety of treatment modalities (some injectables and some oral only), I would recommend the authors consider subgroup analyses based on the treatment program. In particular, injectable medication-based regimens vs. oral-only medication-based regimens may signal differences in disease severity and monitoring intensity (e.g., injectable regimen requires close monitoring because patients present to the clinic/hospital for multiple injections per week). Additionally, the authors may consider this a key covariate if there are imbalances in the randomization. |
|                   | A semantics comment – why not call it both rifampin-resistant and MDR-TB in the title, seeing how both groups are included? Or simply “drug-resistant TB”? |
|                   | Formatting-wise, sometimes the superscript citation is before the period, sometimes it is after. |
|                   | The authors may consider referencing a manuscript published in 2013 about the use of mHealth among healthcare workers in rural South Africa. Acceptance of the manuscript for publication, in my eyes, should not be made contingent upon citing this work given it is mine, the reviewer. Citation is here: |
|                   | Chaiyachati KH, Loveday M, Lorenz S, Lesh N, Larkan LM, Cinti S, Friedland GH, Haberer JE. A pilot study of an mHealth |
application for healthcare workers: poor uptake despite high reported acceptability at a rural South African community-based MDR-TB treatment program. PLoS One. 2013 May 28;8(5):e64662. doi: 10.1371/journal.pone.0064662. PMID: 23724075; PMCID: PMC3665589.

REVIEWER
Ibeneme, Sunny
Federal Ministry of Health, ICT Department

REVIEW RETURNED
02-Oct-2021

GENERAL COMMENTS

The manuscript speaks to the literature on mHealth and TB health outcomes, contributing an incremental contribution to the empirical understanding of macro-level relationships between TB health outcomes and mHealth in Vietnam. The proposed analytical approach is useful and promises to add understanding to this topic of continued interest.

In the introduction, please note that discourses around technology and development has changed since the 2014 WHO report. For example, consider the following statements about the downsides of technological change, by the World Health Organization and the Pathways for Prosperity Commission on Technology and Inclusive Development:

"We must make sure that innovation and technology helps to reduce the inequities in our world, instead of becoming another reason people are left behind [sic]." (WHO, 2019:v) (2019). WHO Guideline: recommendations on digital interventions for health system strengthening. Geneva: World Health Organization. Retrieved from https://www.who.int/reproductivehealth/publications/digital-interventions-health-system-strengthening/en/

"If the same social norms that prohibit girls from walking longer distances to attend secondary school also limit their access to mobile technology (which could offer an alternative education medium), inequalities will not merely remain but may even be exacerbated." (Pathways for Prosperity Commission on Technology and Inclusive Development, 2019:37)

Pathways for Prosperity Commission on Technology and Inclusive Development. (2019). Positive disruption: health and education in a digital age. Oxford: University of Oxford.

Please also do not limit references in the introduction to positive cases of ICT uses for health, but also include some critical literature for balance – many problems stem in this field from a one-sided and uncritical treatment of the topic, focusing solely on positive potential of ICT. For counter-example, consider that Uganda in 2012 halted all projects involving the use of ICT for health due to a lack of coherence and alignment. Researchers such as Day (2014:184) in Sierra Leone and Glik et al. (2014:8) in Senegal problematize for instance the role of digital technology as pathway to pornography (with likely consequences for sexual health and violence). The quantitative studies by Haenssgen (2018) and Haenssgen & Ariana (2017) also provide evidence that the spread of mobile phones in India and China can increase inequities in access to healthcare. More generally, the medical literature around digital technology contains a problematic pro-technology bias at the
expense of balanced and critical considerations of technological change and interventions.

Republic of Uganda. (2012). Coordination and harmonisation of eHealth initiatives [ADM 45/273/01]. Kampala: Uganda Ministry of Health.

Day, A. (2014). Getting the 'blues': the existence, diffusion and influence of pornography on young peoples' sexual health in Sierra Leone. Culture, Health & Sexuality, 16(2), 178-189. doi: 10.1080/13691058.2013.855819

Glik, D., Massey, P., Gipson, J., Dieng, T., Rideau, A., & Prelip, M. (2014). Health-related media use among youth audiences in Senegal. Health Promotion International. doi: 10.1093/heapro/dau060

Haenssgen, M. J., & Ariana, P. (2017). The social implications of technology diffusion: uncovering the unintended consequences of people’s health-related mobile phone use in rural India and China. World Development, 94, 286-304. doi: 10.1016/j.worlddev.2017.01.014

Haenssgen, M. J. (2018). The struggle for digital inclusion: phones, healthcare, and marginalisation in rural India. World Development, 104, 358-374. doi: 10.1016/j.worlddev.2017.12.023

Other areas to consider revisions are

- Page 5: "Research evaluating both the effectiveness and cost-effectiveness of mHealth interventions to support patients with TB is urgently needed"……put add a justification sentence as to why this is needed?......the justification may be save healthcare cost, optimize service delivery or inform policy on intervention mapping protocols….just state what yours is.

- “access to mobile technology has expanded rapidly in Vietnam over the past decade. A recent survey showed that 93% of urban dwellers and 89% of rural dwellers own mobile phones – among the highest worldwide. Smartphone use is increasing rapidly – with 84% of mobile users owning a smartphone”………talking about mobile/smartphone access without mentioning internet penetration rates in Vietnam sounds biased. Please I suggest you add a sentence or two on internet penetration rates in Vietnam.

- There is need to reference sections where RR-TB and MDR-TB were defined (lines 152 and 155) respectively.

- Please add a sentence as to why you choose to use the ‘SF-36’ survey tool over ‘EQ-5D’ tool or other related tools for assessing patient quality of life measures?.......that will be good practice.
Reviewer 1

Comment 1: My major comment is related to the heterogeneity of the treatment group. Given the authors will have a mixture of rifampin-resistant and MDR-TB patients who will experience a variety of treatment modalities (some injectables and some oral only), I would recommend the authors consider subgroup analyses based on the treatment program. In particular, injectable medication-based regimens vs. oral-only medication-based regimens may signal differences in disease severity and monitoring intensity (e.g., injectable regimen requires close monitoring because patients present to the clinic/hospital for multiple injections per week). Additionally, the authors may consider this a key covariate if there are imbalances in the randomization.

Response 1: Thank you for highlighting an important aspect to the study i.e., heterogeneity of the treatment group. The approach to including both RR-TB and MDR-TB patients was considered for the study on the basis that it would broaden the pool of eligible patients for enrolment. Given variations in regimens prescribed for RR-TB and MDR-TB including differences in treatment duration, we anticipate these will influence the development of adverse events. As such, we agree with your suggestion and plan to perform sub-group analyses on the duration of treatment and type of drug-resistant TB.

Comment 2: A semantics comment – why not call it both rifampin-resistant and MDR-TB in the title, seeing how both groups are included? Or simply “drug-resistant TB”?

Response 2: We deliberately used the ‘multi-drug resistant’ wording in the title to complete the V-SMART acronym. However, we acknowledge your comment and have changed the wording to ‘Drug-resistant’ to reflect the inclusion of both RR-TB and MDR-TB as suggested.

Comment 3: Formatting-wise, sometimes the superscript citation is before the period, sometimes it is after.

Response 3: Thank you for identifying this discrepancy. We have reformatted the manuscript to ensure consistency throughout i.e., the citation after the period.

Reviewer 2

Comments 1: In the introduction, please note that discourses around technology and development has changed since the 2014 WHO report. For example, consider the following statements about the downsides of technological change, by the World Health Organization and the Pathways for Prosperity Commission on Technology and Inclusive Development.

Response 1: We agree that it is important to present a balanced argument for mHealth interventions to frame our research study. We have thus included the following sentence to highlight the specific reference by the WHO: “WHO recently issued two policies promoting the use of digital technologies to support global TB control, and explicitly highlighted the urgent need for research to guide their implementation, emphasizing that their implementation could reduce inequities and should not become another reason people are left behind.”

Comment 2: Please also do not limit references in the introduction to positive cases of ICT uses for health, but also include some critical literature for balance.

Response 2: Following on from the previous comment, we have included further language to indicate that mHealth has not always succeeded programmatically and critically, needs to be aligned with existing health systems to be impactful and adopted. The following sentence has been included: “Existing support to scale-up mHealth interventions have been mixed, in some instances abandoned due to a lack of alignment and coherence with existing programme infrastructure.”
Comment 3: Page 5: “Research evaluating both the effectiveness and cost-effectiveness of mHealth interventions to support patients with TB is urgently needed”…….put add a justification sentence as to why this is needed?…..the justification may be save healthcare cost, optimize service delivery or inform policy on intervention mapping protocols….just state what yours is.
Response 3: We have not completed the sentence by including the justification in the afore-mentioned sentence. It now reads as follows: “Research evaluating both the effectiveness and cost-effectiveness of mHealth interventions to support patients with TB is thus urgently needed to determine its potential impact on patient and programmatic outcomes, and importantly, to optimize TB care delivery.”

Comment 4: “access to mobile technology has expanded rapidly in Vietnam over the past decade. A recent survey showed that 93% of urban dwellers and 89% of rural dwellers own mobile phones – among the highest worldwide. Smartphone use is increasing rapidly – with 84% of mobile users owning a smartphone”…….talking about mobile/smartphone access without mentioning internet penetration rates in Vietnam sounds biased. Please I suggest you add a sentence or two on internet penetration rates in Vietnam.
Response 4: We agree with your comment and have now include internet penetration rates for Vietnam in the specific sentence. The sentence now reads as follows: “Smartphone use is increasing rapidly – with 84% of mobile users owning a smartphone and 70% of the population having access to the internet as of 2020.”

Comment 5: There is need to reference sections where RR-TB and MDR-TB were defined (lines 152 and 155) respectively
Response 5: We have now included a reference for these definitions.

Comment 6: Please add a sentence as to why you choose to use the ‘SF-36’ survey tool over ‘EQ-5D’ tool or other related tools for assessing patient quality of life measures?…….that will be good practice.
Response 6: The following sentence has been included to explain why the SF-36 form was chosen: “The SF-36 form was chosen as it evaluates patient’s health status across eight dimensions, making it suitable for an in-depth assessment of the patient’s health-related quality of life (HRQOL).”

Sincerely,
Dr Kavindhran Velen

VERSION 2 – REVIEW

| REVIEWER       | Chaiyachati, Krisda  
| University of Pennsylvania Perelman School of Medicine, Medicine |
| REVIEW RETURNED | 01-Feb-2022 |

| GENERAL COMMENTS | The authors have sufficiently responded to the reviewers’ comments and suggestions. |

| REVIEWER       | Ibeneme, Sunny  
| Federal Ministry of Health, ICT Department |
| REVIEW RETURNED | 05-Feb-2022 |

| GENERAL COMMENTS | The authors have incorporated the necessary revisions that were suggested in the last submissions. However, the final edit they need to effect now will be to revise the keywords. |
They had included “mobile health and mHealth” as part of the keywords. These are repetitive and mean the same thing. I suggest they use either of those words. They could add “Randomized Controlled Trial” as part of the keywords.

### VERSION 2 – AUTHOR RESPONSE

**Reviewer 1**

**Comment 1:** The authors have sufficiently responded to the reviewers' comments and suggestions.

**Response 1:** No further changes required.

**Reviewer 2**

**Comments 1:** The authors have incorporated the necessary revisions that were suggested in the last submissions. However, the final edit they need to effect now will be to revise the keywords.

They had included “mobile health and mHealth” as part of the keywords. These are repetitive and mean the same thing. I suggest they use either of those words. They could add “Randomized Controlled Trial” as part of the keywords.

**Response 1:** We have made the suggested changes to the keywords.

Thank you again for giving for consideration to our manuscript.

Kind Regards

Dr Kavindhran Velen