mHealth application for improving treatment outcomes for patients with multidrug-resistant tuberculosis in Vietnam: an economic evaluation protocol for the V-SMART trial

Qinglu Cheng,1 Tho Dang,2 Thu-Anh Nguyen,2,3 Kavindhran Velen,3 Viet Nhung Nguyen,4 Binh Hoa Nguyen,4,5 Dinh Hoa Vu,3 Chuong Huynh Long,2 Thu Thuong Do,4 Truong-Minh Vu,6 Guy B Marks,6,7 Manisha Yapa,3 Gregory J Fox,2,3 Virginia Wiseman1,8

ABSTRACT

Introduction The Strengthen the Management of Multidrug-Resistant Tuberculosis in Vietnam (V-SMART) trial is a randomised controlled trial of using mobile health (mHealth) technologies to improve adherence to medications and management of adverse events (AEs) in people with multidrug-resistant tuberculosis (MDR-TB) undergoing treatment in Vietnam. This economic evaluation seeks to quantify the cost-effectiveness of this mHealth intervention from a healthcare provider and societal perspective.

Methods and analysis The V-SMART trial will recruit 902 patients treated for MDR-TB across seven participating provinces in Vietnam. Participants in both intervention and control groups will receive standard community-based therapy for MDR-TB. Participants in the intervention group will also have a purpose-designed App installed on their smartphones to report AEs to health workers and to facilitate timely management of AEs. This economic evaluation will compare the costs and health outcomes between the intervention group (mHealth) and the control group (standard of care). Costs associated with delivering the intervention and health service utilisation will be recorded, as well as patient out-of-pocket costs. The health-related quality of life (HRQoL) of study participants will be captured using the 36-Item Short Form Survey (SF-36) questionnaire and used to calculate quality-adjusted life-years (QALYs). Incremental cost-effectiveness ratios (ICERs) will be based on the primary outcome (proportion of patients with treatment success after 24 months) and QALYs gained. Sensitivity analysis will be conducted to test the robustness of the ICERs. A budget impact analysis will be conducted from a payer perspective to provide an estimate of the total budget required to scale-up delivery of the intervention.

Ethics and dissemination Ethical approval for the study was granted by the University of Sydney Human Research Ethics Committee (2019/676), the Scientific Committee of the Ministry of Science and Technology, Vietnam (08/QD-HDDL-NAFOSTED) and the Institutional Review Board of the National Lung Hospital, Vietnam (13/19/CT-HDDD).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will collect detailed patient out-of-pocket expenditure data using a customised cost diary specifically designed for this study.
⇒ A budget impact analysis will be undertaken alongside the cost-effectiveness analysis to determine the costs of scaling up the mHealth application among patients with rifampicin-resistant/multidrug-resistant tuberculosis in Vietnam.
⇒ There is a risk of recall bias since patient out-of-pocket costs and quality of life data are self-reported periodically, with data collected every 3 months.

Study findings will be published in peer-reviewed journals and conference proceedings.

Trial registration number ACTRN12620000681954.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) that is resistant to at least two of the first-line anti-TB medications, isoniazid and rifampicin.1 It can be acquired from improper use of antibiotics during the treatment of TB or person-to-person transmission. Globally in 2021, WHO estimated there were 450 000 incident cases of rifampicin-resistant (RR)/MDR-TB, and the estimated proportion of new TB cases with MDR/RR-TB was 3.6%.2 Vietnam is a high-burden country for MDR/RR-TB, with an estimated incidence of 9.1 per 100 000 people in 2021.3 It is estimated that 4.3% of newly diagnosed patients with TB have MDR/RR-TB.3 Hanoi and Ho Chi Minh City, the two largest metropolitan cities in Vietnam, reported the highest number of MDR-TB cases in 2020 in Vietnam.4 In addition to
morbidity and mortality, MDR-TB is often associated with substantial costs.5–7 The Global Tuberculosis Report 2022 estimated that in Vietnam, nearly 100% of MDR/RR-TB patients and their households faced catastrophic costs, defined as total costs due to the disease that sum to >20% of household annual income.2

In December 2022, the WHO published an update on treatment guidelines for MDR-TB, which recommend a shorter-course regimen with a duration of 6 or 9 months.8 Previous guidelines recommended either a long-course regimen that lasts about 20 months or a short-course regimen with a duration of 9 to 12 months.9 Between 24% and 91% of MDR-TB patients experience adverse events (AEs) during treatment, which can include gastrointestinal disorders, ototoxicity and psychiatric disorders.10–13 Due to the toxicity and long duration of MDR-TB treatment, treating patients with MDR-TB is more difficult than treating patients with drug-susceptible TB. The success rate of MDR-TB treatment remains low, at 60% globally.2 In Vietnam, national data revealed successful treatment outcomes in 70% of MDR-TB patients in 2022, compared with 90% among people with TB that is drug susceptible.4 Previous studies have found that 30–49.5% of cases were lost to follow-up.14–18 Several factors have been identified as associated with non-adherence to MDR-TB treatment, including side effects, financial hardship, history of previous MDR-TB treatment and limited social support.19–21 Failure to adhere and complete treatment not only causes mortality and morbidity for MDR-TB patients but may also lead to the spread of MDR-TB to the wider community and impose increased costs on patients and healthcare systems. Patient-centred management models and the use of digital health technology have been suggested to improve adherence to MDR-TB treatment.22

Mobile health (mHealth) is defined by WHO as “medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices”.22 Designed to provide patient communication, monitoring and education, mHealth has been posited as one potential solution to the problem of medication non-adherence.23–26 However, for MDR-TB, very few adherence interventions have included mHealth technologies27 and there have been no studies to assess their value for money, despite this evidence being vital for future policy making to optimise TB care delivery in Vietnam and other high-burden countries.28 Thus, this economic evaluation aims to evaluate the cost-effectiveness of an mHealth intervention to improve treatment outcomes of MDR-TB patients compared with standard of care in Vietnam from a healthcare provider and societal perspective. In addition to the cost-effectiveness analysis, a budget impact analysis will be conducted to assess the financial impact of wider adoption of the mHealth intervention within the Vietnamese healthcare system.29

METHODS
Study design
This study will be a within-trial economic evaluation alongside a randomised controlled trial (RCT) designed to determine the cost-effectiveness of an mHealth intervention among MDR-TB patients in Vietnam.

Study setting
The public health system in Vietnam is organised across four levels: central, provincial, district and communal.30 Central and provincial health facilities are equipped with specialised healthcare professionals, while doctors at the district and communal level deliver primary care services. The commune health centres (CHCs) are designed as gatekeepers of the public health system. Under the Vietnam National TB Programme (NTP), people with presumptive TB are referred to district or provincial health centres from CHCs for sputum examination and initial treatment. Patients who experience AEs will be referred to provincial or central hospitals for further management. In 2009, NTP began implementing the Programmatic Management of Drug-resistant TB (PMDT) programme. This programme provides treatment and support for MDR-TB patients free of charge at all public sector sites. People can also visit private clinics for diagnosis and treatment of TB but will need to pay out-of-pocket costs for these services. The national health-care insurance reimbursement scheme began to include medications for non-resistant TB from 1 July 2022.

V-SMART trial
This economic evaluation is nested within the V-SMART trial, a community-based, open-label, parallel-group RCT in Vietnam.31 The V-SMART trial will evaluate the effect of an mHealth intervention on MDR-TB treatment outcomes and patient experience. To facilitate the intervention, the trial team developed a smartphone application that allows patients to access information on MDR-TB treatment-related AEs, report potential AEs and receive timely feedback and management of AEs. Treatment adherence support includes push-notified daily medication reminders. The application includes a health worker interface which helps health workers follow up on reported AEs, provide advice on low-grade AEs and arrange assessment of AEs for severe cases. The application also allows health workers to report AEs to the National Drug Information and Adverse Drug Reaction Monitoring Centre. The V-SMART trial commenced recruitment in October 2020 and is expected to complete data collection by August 2025.

Target population
The target population for this economic evaluation is patients treated for MDR/RR-TB from government
PMDT clinics in Vietnam. Trial eligibility criteria are described in the main protocol. The V-SMARt trial will recruit 982 patients across the participating sites. These clinics are located in two cities with the greatest incidence of MDR-TB (Hanoi and Ho Chi Minh City) and five other provinces (Thanh Hoa, Da Nang, An Giang, Can Tho and Tien Giang). Purposive sampling was performed to select the sites from both rural and urban populations across the country.

**Description of standard care**

In the V-SMART trial, patients with MDR/RR-TB treated at participating clinics will be recruited and individually randomised into the intervention or standard-care group. Participants in both groups will receive standard, community-based treatment for MDR-TB; either as a 20-month regimen or a 9-month short-course regimen. Regimen choice will be determined according to the NTP guidelines. Participants in both groups will be monitored for AEs by PMDT staff during clinic visits and will have the opportunity to self-report AEs between scheduled clinic visits via phone calls or visit the clinic for AEs at any time. The diagnosis of AEs is made after patients present to the referral hospitals. After diagnosis, AEs are managed based on both clinical judgement and algorithm provided in the NTP guidelines. A detailed description of AE management procedure was included in the trial protocol.

**Description of the intervention**

In the intervention group, participants will have the ‘Bac Sy Minh’ (‘Dr Smart’) App installed on their smartphones. Participants without their own smartphone will be provided with a smartphone for the study period. Participants will receive monthly credit of 70,000 Vietnamese đồng (VND) to their phones to cover the cost of data. Participants will be trained by a healthcare worker to use the mHealth application. The App is designed to connect patients to their treating healthcare worker, providing daily feedback regarding their symptoms, reporting their adherence and providing patient education about MDR/RR-TB and AEs through a library of frequently asked questions. Healthcare workers can respond to questions on both clinical judgement and algorithm provided in the NTP guidelines. A detailed description of AE management procedure was included in the trial protocol.

**Resource use and costs**

This economic evaluation will take both a healthcare provider and a societal perspective. The healthcare provider perspective will include direct medical costs to the Vietnamese healthcare system. The societal perspective will provide additional costs including patient out-of-pocket payments and productivity losses. Costs to be included in the analysis will reflect the healthcare resources used to deliver the intervention, provide treatment to patients with MDR-TB and all patient out-of-pocket costs. An overview of cost data to be included in the analysis is shown in table 1. All costs will be presented in 2024 US$, using relevant exchange rates and published inflation rates for Vietnam. To value each cost item, a mixed methodology using ‘top-down’ and ‘bottom-up’ costing approaches will be taken.

**Preimplementation set-up costs**

Capital costs and the costs associated with training healthcare workers to use the App will be collected from the

<table>
<thead>
<tr>
<th>Data collection time points</th>
<th>Baseline</th>
<th>M3</th>
<th>M6</th>
<th>M9</th>
<th>M12</th>
<th>M15</th>
<th>M18</th>
<th>M21</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of data collected</td>
<td>Baseline data collection</td>
<td>Telephonic follow-up( cost diary)</td>
<td>Telephonic follow-up( cost diary)</td>
<td>Telephonic follow-up( cost diary)</td>
<td>Telephonic follow-up( cost diary)</td>
<td>Telephonic follow-up( cost diary)</td>
<td>Telephonic follow-up( cost diary)</td>
<td>End of study questionnaire</td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td>SF-36</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Summary of V-SMART trial data collection points. SF-36, 36-Item Short Form Survey.
research project’s financial records. Capital costs will include building, computers and App development. The costs of training health workers will include the costs of training materials, refreshments during training and transportation.

**Intervention costs**

Intervention costs include the costs of providing mobile devices to patients who do not have a smartphone (including monthly phone credits) and will be obtained from research project accounts. Any damage or loss of trial mobile devices will be reported during the study. The costs of replacement phones will be covered by the trial with no limit on the maximum number of replacement per participant, as only a small number of participants may require phone loan for participating in this study. Intervention costs will also include the time of health workers in the participating sites to undertake additional activities including patient recruitment (i.e., counselling, interviewing, data entry and record storage); training patients to use the App and management of AEs through the App. Staff time will be valued using a combination of staff time sheets, App server data and expert opinion (hospital, departmental and clinic managers).

**Healthcare system costs**

Costs borne by the healthcare system will include the costs of treating MDR-TB, the costs associated with reporting

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cost items to be included in the analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost items</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td><strong>Set-up costs</strong></td>
<td></td>
</tr>
<tr>
<td>Capital cost</td>
<td>Building</td>
</tr>
<tr>
<td></td>
<td>Computers</td>
</tr>
<tr>
<td></td>
<td>App development</td>
</tr>
<tr>
<td><strong>Training operating costs</strong></td>
<td>Printing of training materials</td>
</tr>
<tr>
<td></td>
<td>Refreshments during training</td>
</tr>
<tr>
<td></td>
<td>Transportation costs</td>
</tr>
<tr>
<td><strong>Intervention costs</strong></td>
<td>Smartphone for participants</td>
</tr>
<tr>
<td></td>
<td>Monthly phone credit</td>
</tr>
<tr>
<td></td>
<td>Monthly server fees</td>
</tr>
<tr>
<td><strong>Personnel</strong></td>
<td>Staff time allocated to recruitment and enrolment of patients</td>
</tr>
<tr>
<td></td>
<td>Staff time allocated to respond to adverse event reported through ‘Dr Smart’</td>
</tr>
<tr>
<td><strong>Healthcare system costs (direct medical costs)</strong></td>
<td>Treatment of MDR-TB</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Management of AEs</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient costs (direct and indirect costs)</strong></td>
<td>Health service use (public and private)</td>
</tr>
<tr>
<td></td>
<td>Medication</td>
</tr>
<tr>
<td></td>
<td>Transportation</td>
</tr>
<tr>
<td></td>
<td>Other direct (e.g., food, accommodation, laboratory testing)</td>
</tr>
<tr>
<td></td>
<td>Productivity loss</td>
</tr>
<tr>
<td></td>
<td>Funded costs</td>
</tr>
</tbody>
</table>

AEs, adverse events; eTB, NTP’s MDR-TB case management electronic databases; MDR-TB, multidrug-resistant tuberculosis; mHealth, mobile health; NTP, National TB Programme.
of AEs and the costs of managing MDR-TB AEs. Health service utilisation (medical consultation, laboratory test and hospitalisation) and medication administered to patients during the trial period will be elicited from clinical records and NTP’s MDR-TB case management electronic databases (eTB/New Vitimes) by trial officers.

Patient costs
For patients and their families, direct out-of-pocket costs will include the costs of transportation, accommodation, food, medical consultation, medications and non-medical costs (e.g., costs of hiring a caregiver in hospital). Information on patient out-of-pocket costs will be first collected at baseline and then throughout the follow-up period using cost diary. Productivity losses associated with seeking care for TB or needing to take time off work due to TB-related illness will be valued using the human capital approach. For patients who are unwilling to disclose their monthly income in the cost diary, we will assume an average wage rate based on their occupation. The national occupation-income in the cost diary, we will assume an average wage rate based on their occupation. The national occupation-income will be calculated by subtracting PMDT-funded costs (e.g., monthly travel support allowance ranging from 150 000 to 300 000 VND) from total out-of-pocket costs.

Measurement of effectiveness
The primary outcome measure is the proportion of patients with successful treatment after 24 months. We will also include HRQoL as a health outcome measure. The Vietnamese licensed version of SF-36 will be administered to participants at baseline, 6-month follow-up and end-of-study interview to determine their HRQoL. The HRQoL scores will be transformed to a single utility weight, which will be used to calculate quality-adjusted life-years (QALYs) gained for the economic evaluation.

Missing data
We will first perform a descriptive analysis of missing data for key variables, with which we will make assumption about the missing data mechanism. Complete case analysis will be conducted if data are covariate-dependent, missing completely at random. Multiple imputations will be used to deal with data missing at random. The robustness of the results will be tested by conducting sensitivity analyses with alternative assumptions on the missing data mechanism.

Within-trial cost-effectiveness analysis
The time horizon for this economic evaluation will be set to the length of the V-SMART trial (24 months). Both costs and effects will be discounted at a rate of 3% in the baseline analysis. Incremental cost-effectiveness ratios (ICERs) will be calculated using the following formula:

\[
\text{ICER} = \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{control}}}{\text{Effectiveness}_{\text{intervention}} - \text{Effectiveness}_{\text{control}}}
\]

where effectiveness is measured by the proportion of patients with successful treatment and QALYs gained. Currently, there is no standard ICER threshold in Vietnam that reflects how much decision-makers are willing to pay for an additional unit of health outcome. One gross domestic product per capita of Vietnam will be used as the ICER threshold. Currently, there is no standard ICER threshold in Vietnam that reflects how much decision-makers are willing to pay for an additional unit of health outcome. One gross domestic product per capita of Vietnam will be used as the ICER threshold. Currently, there is no standard ICER threshold in Vietnam that reflects how much decision-makers are willing to pay for an additional unit of health outcome. One gross domestic product per capita of Vietnam will be used as the ICER threshold.

Sensitivity analysis
Deterministic (one-way) sensitivity analysis (DSA) will be conducted to examine the impact of changes in key parameters on the ICERs. The results of the DSA will be presented in tornado diagrams. Probabilistic sensitivity analysis (PSA) will be conducted to account for the joint uncertainty across cost and effectiveness data. The results of the PSA will be presented using cost-effectiveness acceptability curves that show the probability of the intervention being cost-effective at varying willingness-to-pay thresholds.

Budget impact analysis
Following international guidelines, the budget impact analysis will take a payer’s perspective. The population eligible for the intervention will be estimated based on the incidence of MDR-TB in Vietnam. A 3-year timescale will be adopted to take into account possible changes in intervention uptake and the fact that the impact of the App may wane over time as has been shown in other studies evaluating the long-term effects of mHealth interventions. Costs will be presented annually to align with the budgeting cycles of the Vietnamese Ministry of Health. By multiplying the unit cost of the intervention (which includes the costs of designing and implementing the intervention) by the number of people affected by the intervention, the analysis will provide an estimate of the total budget required for scale-up. Changes in annual health outcomes will also be reported. Sensitivity analysis will be conducted to reflect the plausible range of circumstances the budget holder may face including changes in the number of MDR-TB cases.

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION
Ethical approval for the study was granted by the University of Sydney Human Research Ethics Committee (2019/676), the Scientific Committee of the Ministry of Science and Technology, Vietnam (08/QD-HDQL-NAFOSTED) and the Institutional Review Board of the National Lung Hospital, Vietnam (13/19/CT-HDDD). Study findings will be published in peer-reviewed journals and conference proceedings.

Author affiliations
1Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia
2Woolcock Institute of Medical Research, Hanoi, Vietnam
Acknowledgements  We would like to acknowledge the various current and previously treated patients with multidrug-resistant tuberculosis who provided input into the study design, application development and piloting phase of the V-SMART project.

Contributors  GJF wrote the proposal for V-SMART project that was awarded funding. VW, GJF, QC and TD conceived and led the design of the study. TAN and KV made important contributions to the design of the study. QC and TD wrote the first draft of the manuscript, TAN, KV, VINN, BHN, DHV, CHL, TTD, T-MX, MV and GBM contributed substantially to manuscript versions. VW supervised the study. All authors revised and approved the final manuscript.

Funding  This work was supported by funding from the Australian National Health and Medical Research Council (NHMRC; APP 1157643) and the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number NHMRC.108.02-2018.01. GF was supported by a NHMRC Career Development Fellowship (APP 1148372) and NHMRC Leadership Fellowship (APP2007920). The trial sponsor is the Woolcock Institute of Medical Research, Australia.

Competing interests  None declared.

Patient and public involvement  Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication  Not applicable.

Provenance and peer review  Not commissioned; externally peer reviewed.

Supplemental material  This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc-4.0/.

ORCID iDs  Jinping Cheng http://orcid.org/0000-0002-3701-8760
Thu Anh Nguyen http://orcid.org/0000-0002-2089-2902
Binh Hoa Nguyen http://orcid.org/0000-0002-1543-4907
Guy B Marks http://orcid.org/0000-0002-8976-8053

REFERENCES


44 Rayward AT, Vandelanotte C, Van Itallie A, et al. The association between logging steps using a Website, App, or Fitbit and engaging with the 10,000 steps physical activity program: observational study. *J Med Internet Res* 2021;23:e22151.
Appendix

Cost diary

Study ID __________
VISIT #______

1. What was the date of the visit (dd/mm/yyyy) __ __ / __ __ / __ __ __ __

2. What type of facility was this? (select one)
   - Central hospital
   - Provincial hospital
   - District hospital
   - Commune health post
   - Pharmacy
   - Private clinic
   - Private hospital
   - Other health facility, please specify___________
   - Don’t recall

3. Was this an inpatient visit (overnight hospitalisation) or outpatient visit (admission, then leaving)?
   - Inpatient → Length of stay (record 0.5 day if less than 1 day) __ __ day(s)
   - Outpatient → Length of visit __ __ hour(s)
   - Don’t recall/ unsure

4. Total cost of medical consultation and hospitalisation (if any) (if unsure, write ‘99’)
   ___________ VND

5. Total cost of medication (if unsure, write ‘99’)
   ___________ VND

6. What was the main mode of transport you used to get to the facility? (select one)
   - Walk
   - Bicycle
   - Public Bus → Bus ticket (if don’t recall, write ‘99’) ___________ VND
   - Someone gave me a lift
   - Motorbike → Distance from home to facility __ __ __ km
   - Taxi, rent car → Taxi fare/ Rent (if don’t recall, write ‘99’) ___________ VND
   - Don’t recall

7. What was the main mode of transport you used to get home from the facility? (select one)
   - Walk
   - Bicycle
8. Total cost of food, accommodation and other non-medical costs (such as gifts and informal payment for healthcare workers, patient lift within the hospital, and communication) related to this visit (if unsure, write ’99’) __________ VND

9. Were you doing any paid work in the past 4 weeks?
   □ Yes → please specify your monthly wage (if prefer not to say, write ’99’)
   __________ VND/month
   □ No

10. Did you take any time off from your paid work to visit this facility?
    □ Yes → Length of time absent from paid work (if don’t recall, write ’99’) __ __ hour(s)
    □ No

11. Total amount paid by health insurance reimbursement (if unsure, write ’99’)
    __________ VND

12. Other comments:
    _______________________________________________________________________
    _______________________________________________________________________
    _______________________________________________________________________