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# Harnessing new mHealth technologies to Strengthen the Management of Multidrug-Resistant Tuberculosis in Vietnam (V-SMART trial): a protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Multidrug-resistant tuberculosis (MDR-TB) remains a major public health problem globally. Long, complex treatment regimens coupled with frequent adverse events have resulted in poor treatment adherence and patient outcomes. Smartphone-based mobile health (mHealth) technologies offer national TB programmes an appealing platform to improve patient care and management; however, clinical trial evidence to support their use is lacking. This trial will test the hypothesis that an mHealth intervention can improve treatment success among patients with MDR-TB and is cost-effective compared with standard practice.

**Methods and analysis** A community-based, open-label, parallel-group randomised controlled trial will be conducted among patients treated for MDR-TB in seven provinces of Vietnam. Patients commencing therapy for microbiologically confirmed rifampicin-resistant or multidrug-resistant tuberculosis within the past 30 days will be recruited to the study. Participants will be individually randomised to an intervention arm, comprising use of an mHealth application for treatment support, or a 'standard care' arm. In both arms, patients will be managed by the national TB programme according to current national treatment guidelines. The primary outcome measure of effectiveness will be the proportion of patients with treatment success (defined as treatment completion and/or bacteriological cure) after 24 months. A marginal Poisson regression model estimated via a generalised estimating equation will be used to test the effect of the intervention on treatment success. A prospective microcosting of the intervention and within-trial cost-effectiveness analysis will also be undertaken from a societal perspective. Cost-effectiveness will be presented as an incremental cost per patient successfully treated and an incremental cost per quality-adjusted life-year gained.

**Ethics** Ethical approval for the study was granted by The University of Sydney Human Research Ethics Committee (2019/676).

**Dissemination** Study findings will be disseminated to participants and published in peer-reviewed journals and conference proceedings.

**Trial registration number** ACTRN12620000681954.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ As the study is embedded within the routine rifampicin-resistant or multidrug-resistant tuberculosis (RR/MDR-TB) management programme, it reflects 'real-world' implementation, which will increase the generalisability of the study findings to other high TB incidence settings, but it also introduces implementation challenges.

⇒ The mHealth application was developed in close collaboration with key stakeholders, including the national TB programme, patients with RR/MDR-TB and healthcare workers, using participatory design.

⇒ Participants with RR/MDR-TB will take standardised regimens of variable duration (9–24 months), allowing additional comparisons based on treatment duration.

⇒ The study will include patients with limited prior experience in smartphone use, which represent an important subgroup to consider given the ageing TB epidemic in many Asian settings.

## INTRODUCTION

Tuberculosis (TB) control is an important global public health priority, since TB remains a leading cause of mortality related to an infectious disease and has major adverse economic impacts.[1] The rise in rifampicin-resistant or multidrug-resistant tuberculosis (RR/MDR-TB) threatens recent gains in TB control, owing to its poor treatment outcomes, risk of epidemic spread and cost to TB control programmes.[2] The complex and

toxic treatment regimens required to treat RR/MDR-TB result in adverse events (AE) that affect most patients. This poses a major challenge for TB control programmes in resource-limited settings, in which the clinical capacity to manage adverse drug reactions is limited. Drug toxicity frequently undermines treatment adherence leading to partially treated infections which translate into poor long-term outcomes for individual patients and increased risk of community transmission.[3 4] Despite a recent shift in WHO guidelines towards recommending better tolerated all oral regimens, serious AEs remain common. New and repurposed drugs used to treat RR/MDR-TB, such as bedaquiline and linezolid, frequently cause bone marrow suppression, peripheral neuropathy and cardiac toxicity.[5] For this reason, the WHO recommends that these new drugs should only be used where adequate oversight of AEs is available.[6]

Even mild AEs can have serious consequences for patients.[7] Non-life-threatening symptoms such as gastrointestinal discomfort and nausea can often lead to treatment interruption if patients are not adequately counselled and supported. Hence, early identification and management of AEs is a key priority for TB programmes, especially for managing RR/MDR-TB cases.[6] This is especially challenging in settings with high case loads and limited human resources to counsel and support the patients. In recognition of the need for more active AE surveillance, WHO issued an 'active TB drug-safety monitoring and management' (aDSM) framework in 2015,[8] comprising (a) active and systematic clinical and laboratory assessment of patients for AEs, (b) timely management of AEs, and (c) standardised data collection and reporting. This policy was developed to strengthen monitoring of patients taking new MDR-TB drugs such as delamanid and bedaquiline, for which limited safety data exist.[5] However, in most settings, including Vietnam, the resources required to scale up aDSM within TB control programmes have been lacking. Barriers to aDSM scale-up in low-income and middle-income countries include a lack of effective processes for AE reporting by patients and TB control programmes, and limited human resource capacity to manage AEs.

Mobile health (mHealth) is defined as the use of mobile and wireless technologies to improve healthcare.[9] A growing body of literature has found mHealth technologies to be feasible and acceptable to patients with TB in resource-limited settings.[10 11] WHO recently issued two policies promoting the use of digital technologies to support global TB control,[12 13] and explicitly highlighted the urgent need for research to guide their implementation,[14] emphasising that their implementation could reduce inequities but should not become another reason people are left behind.[15] Randomised trials evaluating the impact of mHealth interventions on clinical outcomes of TB are lacking. Existing support to scale up mHealth interventions has been mixed, in some instances abandoned due to a lack of alignment and coherence with existing programme infrastructure.[16] 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 optimise TB care delivery. mHealth applications delivered through patients' smartphones may be able to deliver individualised treatment support at scale, while linking patients with early symptoms of toxicity to healthcare providers. The real-time reporting of toxicity by patients will also foster a patient-centred approach to healthcare delivery, while providing data that will help to strengthen TB treatment programmes.

The primary objective of this study will be to evaluate the effectiveness, cost-effectiveness and affordability of a smartphone-based mHealth AE support intervention, compared with 'standard care' (without the mHealth intervention), on treatment success among patients treated for MDR-TB in a programmatic setting.

## METHODS AND ANALYSIS

### Study design

This is an open-label, parallel-group randomised controlled trial. Eligible patients will be individually randomised in a one-to-one ratio to either receive a smartphone-based mHealth application to support their treatment in addition to their routine care (figure 1), referred to as 'standard care', which comprises scheduled patient engagement support during clinic visits (figure 2). Participants will be followed for a total of 24 months after randomisation (figure 3).

### Setting

Vietnam is among the top 30 high-burden TB and RR/MDR-TB countries in the world, with a recent report estimating an annual incidence rate of 176 per 100 000 population. A diagnosis of RR/MDR-TB is made in 3.6% of all new cases.[17] In addition, 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.[18 19] Smartphone use is increasing rapidly—with 84% of mobile users owning a smartphone[19] and 70 % of the population having access to the internet as of 2020.[20]

The study will be conducted within government programmatic management of drug-resistant TB (PMDT) clinics in seven provinces of Vietnam. These are located in two cities with the greatest incidence of RR/MDR-TB (Hanoi and Ho Chi Minh City) and five other provinces (Thanh Hoa, Da Nang, An Giang, Can Tho, Tien Giang). Participating provinces encompass both rural and urban populations from across the country, representative of the population of Vietnam.

### Study population and eligibility criteria

The study population will be patients with microbiologically confirmed pulmonary or extrapulmonary RR/

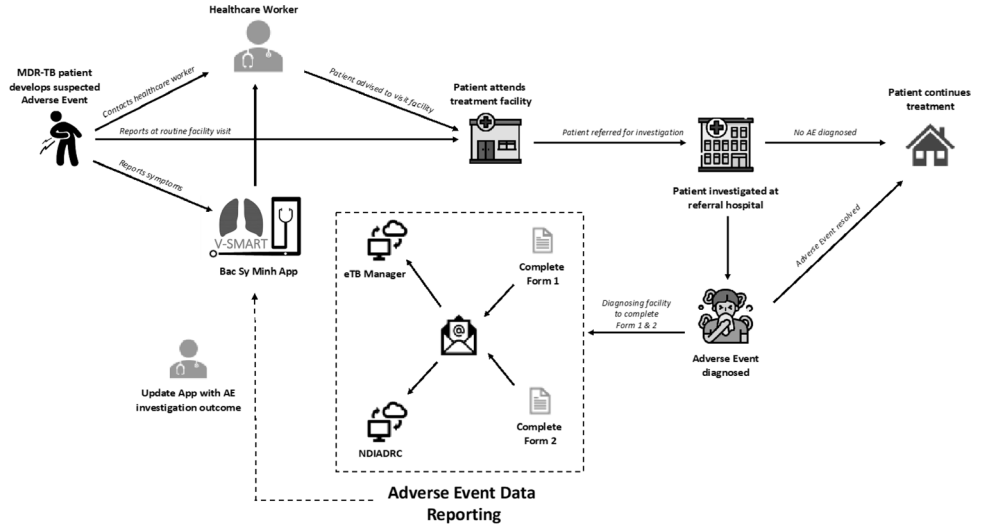



**Figure 1** Process flow for management of patients with multidrug-resistant tuberculosis (MDR-TB), including adverse event (AE) monitoring in the intervention arm. Icons attribution—'Icon made by Freepik from www.flaticon.com'. eTB, electronic TB database; NDIADRC, National Drug Information and Adverse Drug Reaction Centre; V-SMART, Strengthen the Management of Multidrug-Resistant Tuberculosis in Vietnam.

MDR-TB attending participating facilities. RR-TB is defined as a *Mycobacterium tuberculosis* diagnosis by a positive culture and/or molecular test (eg, Xpert MTB/RIF) and genotypic rifampicin resistance detected on PCR, such as Xpert MTB/RIF.[21] MDR-TB is defined as a patient with *M. tuberculosis* confirmed by positive culture and/or molecular test, and phenotypic resistance to both rifampicin and isoniazid (ie, using the proportion method on liquid or solid media).[21] Eligible patients will have commenced treatment for RR/MDR-TB within the 30 days prior to enrolment. Additionally, they will demonstrate their ability to operate simple functions on a smartphone (including entering a passcode, opening an application and making a phone call). Eligibility criteria are presented in table 1.

## Patient and public involvement

The conceptualisation of the mHealth application was informed by a situational analysis performed within the PMDT programme which highlighted current shortcomings in delivery of patient care and management. Patients contributed to the design and finalising of the final application version uploaded to the application stores—this was achieved through focus group discussions and piloting of the application.

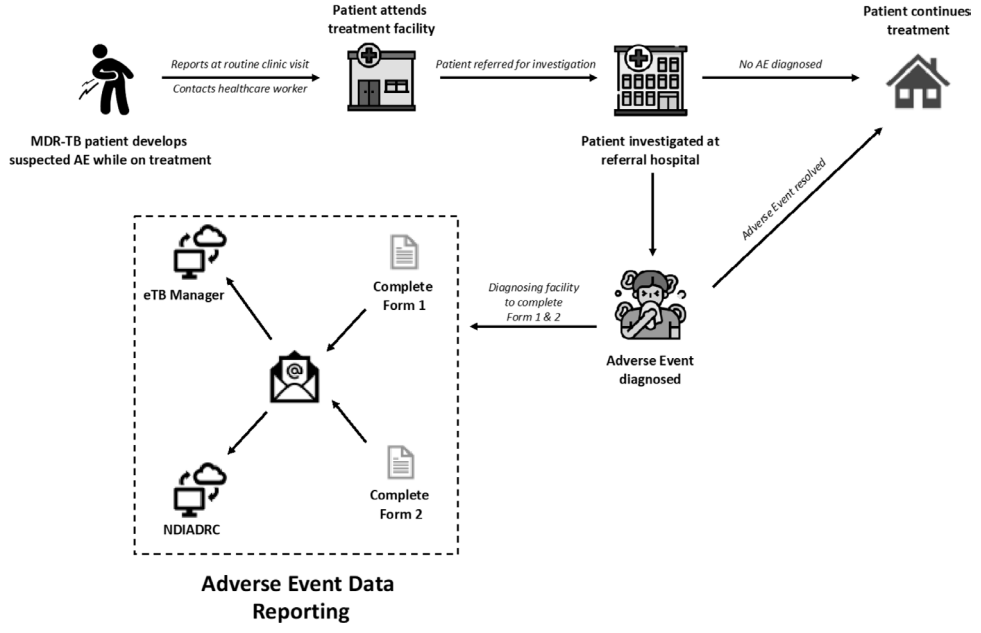
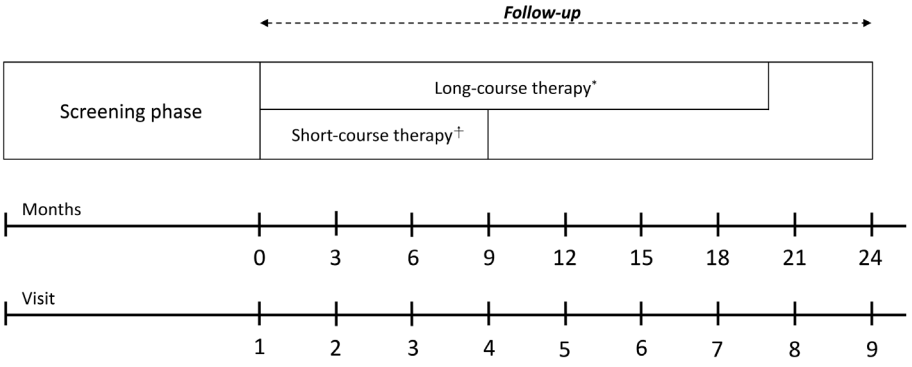



**Figure 2** Process flow for management of patients with multidrug-resistant tuberculosis (MDR-TB) including adverse event (AE) monitoring in the standard care arm. Icons attribution—'Icon made by Freepik from www.flaticon.com'. eTB, electronic TB database; NDIADRC, National Drug Information and Adverse Drug Reaction Centre.




| Data collection timepoints | Baseline | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 |
|---|---|---|---|---|---|---|---|---|---|
| Type of data collected | Baseline data collection<br>SF-36 | Telephonic follow-up | Telephonic follow-up<br>SF-36 | Telephonic follow-up | Telephonic follow-up<br>Facility data Abstraction | Telephonic follow-up | Telephonic follow-up | Telephonic follow-up | Final end of study questionnaire<br>SF36 |

**Figure 3** Summary of V-SMART trial design and data collection points. *Nine-month 'short course' regimen (including bedaquiline). †Twenty-month 'long-course' regimen (including 8 months of an injectable drug antibiotic and at least three other oral antibiotics). SF-36, 36-item Short Form; V-SMART, Strengthen the Management of Multidrug-Resistant Tuberculosis in Vietnam.

## Development of the mHealth application

The mHealth intervention will comprise a smartphone application ('App') for patients and healthcare workers that aims to support timely recognition, reporting and management of AEs for patients treated for MDR-TB. The App was developed using a 'waterfall' framework for software development (online supplemental eFigure 1). Table 2 summarises the steps involved in the App development process. The App will be used by patients in the intervention arm and healthcare workers. The study proposal was reviewed by the Vietnam TB Advisory Committee, a stakeholder group including TB survivors, and App functionalities were refined based on their feedback. In addition, App development incorporated feedback from other stakeholder consultations, including healthcare workers. This participatory 'ground up' approach identified important functionalities to improve 'user friendliness' and to overcome current inefficiencies in routine patient management, with a specific focus on treatment adherence and AE management. A scientific advisory panel provided input into the development of triaging algorithms and patient educational information to be used within the App; these algorithms incorporated local programmatic guidelines as well as international guidelines.[22]

Once a beta version of the App had been developed, it was piloted among patients with MDR-TB and healthcare workers in one urban province and one rural province to test its usability and refine the existing design for 'every day' use. In-depth interviews were conducted with patients with RR/MDR-TB and healthcare workers 2 weeks after enrolment into the pilot; these interviews were used to understand how end users felt about the App functions and ease of use, and also to identify barriers to study implementation from a patient and provider perspective. After incorporating feedback from end users, the App was finalised for both Android (using Java) and iOS operating systems and uploaded to their respective stores for use in English and Vietnamese. The App incorporated end-to-end encryption and password protection to ensure

**Table 1** Participant eligibility criteria for randomisation

| Inclusion criteria | Exclusion criteria |
|---|---|
| ► Aged ≥15 years.<br>► Have a diagnosis of bacteriologically confirmed pulmonary and/or extrapulmonary rifampicin-resistant or multidrug-resistant tuberculosis (RR/MDR-TB).*†<br>► Have commenced MDR-TB treatment within ≤30 days.<br>► Demonstrate the ability to operate simple functions on a smartphone (including entering a passcode, opening an application and making a phone call). | ► Inability to provide written informed consent (eg, due to a significant communication impairment).<br>► Patient does not intend to receive treatment within participating provinces over the subsequent 12-month period.<br>► Another person residing within the same household, at least 1 day/week, has already been enrolled and randomised within this study. |

*RR/MDR-TB defined as bacteriologically confirmed *Mycobacterium tuberculosis* diagnosed on mycobacterial culture and/or nucleic acid amplification test (NAAT) with genotypic rifampicin resistance detected on NAAT, or phenotypic resistance to both rifampicin and isoniazid. †Patients with *M. tuberculosis* bacteria who demonstrate additional resistance to second-line antibiotics used to treat TB (eg, levofloxacin or injectable antibiotics) will also be eligible.

Table 2 Summary of application development using the 'Waterfall' framework[44]

| Requirements and analysis | Design and coding | End user feedback | Finalisation |
|---|---|---|---|
| ► Engagement with PMDT programme to determine needs and gaps within patient management.<br>► Study intervention conceptualised. | ► Application coding performed by external development company.<br>► Application wireframes developed for functions in collaboration with PMDT programme staff and other researchers.<br>► Developed adverse event management algorithms using local programmatic guidelines with input from scientific advisory committee and international guidelines.[45] Obtained additional input from patients with MDR-TB through Vietnam TB Advisory Committee (VTAC), comprising TB survivors from Vietnam. | ► Initial user testing conducted on beta version with research team.<br>► Application piloted among 16 end users in 2 sites (4 patients and 4 healthcare workers per site).<br>► In-depth interviews conducted on 8 end users to refine App and address any implementation issues. | ► Final version of the App incorporating all feedback and refinements completed.<br>► App evaluated by The University of Sydney Cyber Security Department to ensure user cyber safety and data protection.<br>► App uploaded to iOS and Android stores for approval. |

MDR-TB, multidrug-resistant tuberculosis; PMDT, programmatic management of drug-resistant TB.

participant data security. A summary of selected patient and healthcare worker mHealth application functionalities is shown in table 3.

### Randomisation and blinding

Following an informed consent process, participants enrolled in the study will be randomly allocated to either the intervention or 'standard care' arms in a one-to-one ratio. Randomisation will be performed by a member of the research team at the central study office, independent of the healthcare worker enrolling the patient. Healthcare workers will obtain the randomisation code either by phone call or short messaging service. After the participant has been randomised, healthcare workers and participants will remain unblinded to group allocation owing to the nature of the intervention.

Randomisation codes will be generated using a permuted block design, with varied block sizes (4–8). Separate randomisation lists will be created for each province (based on historical RR/MDR-TB case notifications). Randomisation codes will be produced from

Table 3 Summary of selected mHealth application functions for patients and healthcare workers

| Patient* | Healthcare worker† |
|---|---|
| ► Access treatment information including monitoring ongoing progress.<br>► Adverse event reporting through daily check-in.<br>► Treatment adherence support including push-notified daily medication reminders.<br>► Two-way communication with designated healthcare workers from treatment facilities.<br>► Rewards platform to encourage application usage and engagement.<br>► Peer-to-peer support through built-in social media platform.<br>► Frequently asked questions (FAQs) to provide information and support of possible adverse events. | ► Patient management and treatment progress overview.<br>► Weekly push notifications for patient check-ins.<br>► Push notifications from patients requiring adverse event investigation.<br>► Push notifications informing healthcare workers of patients with poor treatment adherence.<br>► Documenting all steps within the adverse event investigation cascade.<br>► Two-way communication with designated patients.<br>► Peer-to-peer support through built-in social media platform to connect with other healthcare workers. |

*mHealth application available on iOS and Android devices.
†mHealth application available on iOS and Android devices AND desktop PC version.

a pregenerated list using a REDCap database accessible only to the central study office.[23] Members of the expert clinical panel, responsible for assigning AE severity, and the trial statistician will remain blinded to group allocation throughout the study.

### Description of the intervention

The intervention comprises an mHealth application which will be installed on patient and healthcare worker smartphones to allow bidirectional communication and support of AE management during the RR/MDR-TB treatment period. Healthcare workers at participating sites will be trained to use the mHealth application. All facilities will have the opportunity to provide patients with either 'standard care' or the intervention, as randomisation will be at the individual level. The perceived risk of 'contamination' through randomisation at the individual level is minimal given the personal nature of the intervention. In addition, initial stakeholder feedback suggested that staff would not be sensitised to side effect monitoring, which would mitigate against contamination.

The functions of the mHealth application are summarised in table 3. The App will allow patients to report changes in their health status to healthcare workers. Patients will be prompted to enter their health status at a fixed time each day (figure 1). Depending on the responses provided by the patients, healthcare workers will be prompted regarding potential AEs that may require investigation and management. Healthcare workers will be reminded through the application to follow-up each step in the cascade of care from notification to resolution of each AE. Healthcare workers will also be reminded to submit a formal notification of all grade 3 and 4 AEs, defined according to the Vietnam National TB Program guidelines (online supplemental eMethod 2), to the National Drug Information and Adverse Drug Reaction Monitoring Centre. Patients will be reminded at a patient-nominated time each day to take their medications. Healthcare workers will also be able to use a computer interface to see in real time which patients have not reported their daily medication intake.

### Participant induction

Participants randomised into the intervention arm will be trained by a healthcare worker on the mHealth application and provide orientation for how to use their own smartphones, or one provided by the study. Where a smartphone is provided, an indemnity is signed by participants to take responsibility for its safe keep and return at the end of the study period. A summary of training activities is described in online supplemental eMethod 1.

### Description of standard care

Participants in both the intervention and standard care arms will receive the same routine clinical care. This comprises standard community-based treatment for RR/MDR-TB according to national guidelines.[24] Typical regimens comprise either a standardised 20-month 'long-course' regimen (including 8 months of an injectable drug antibiotic, and at least three other oral antibiotics), or a 9-month 'short course' regimen; bedaquiline containing all oral regimens is in the process of being implemented. Regimen choice will be determined according to the guidelines of the national TB programme. Patients receiving injectable medication will receive these 5–6 days/week at a healthcare facility. In accordance with local guidelines, and WHO recommendations,[25] patients receiving only oral medications will self-administer their therapy at home, with clinic visits to receive tablets every 2–4 weeks.

During scheduled visits to the healthcare facilities patients will undergo routine clinical assessment; relevant findings will be documented in clinical stationary according to standard practice. The results of all routine sputum tests (eg, smear and culture), HIV tests, blood tests, radiographs and other diagnostic tests will be recorded in routine national TB programme records. Patients who develop AEs will be assessed and managed by existing PMDT staff in accordance with existing national policies.[24] This involves monitoring and investigating AEs by staff during clinic visits or when prompted by patients outside routine clinic visits.

### Enrolment and baseline assessment

At the enrolment visit (baseline), healthcare workers will collect demographic and socioeconomic data from all participants using a structured questionnaire. Clinical and laboratory data will be collected through patient record extraction. A 36-item Short Form (SF-36 v2) survey questionnaire will be completed to assess the quality of life at baseline.[26] The SF-36 form was chosen as it evaluates the 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).[27] Enrolled patients will be provided with health cost diaries for continuously documenting their healthcare utilisation and any associated costs during the follow-up period. This will include the number and duration of visits to tertiary hospitals, district hospitals and clinics. Patient healthcare utilisation will also be evaluated through patient record review, for example, recorded hospital visits.

### Follow-up procedures

Study participants in both groups will be contacted by telephone every 3 months throughout the 24-month follow-up period by study staff to maintain participation in the study (figure 3). Patients will undergo clinical management according to standard programmatic guidelines and AE management will be documented in patients' clinical files, from where relevant information will be extracted. At the 6-month follow-up phone call, the SF-36 survey will be administered for a second time. Twelve months after enrolment, the results of any routine sputum tests (eg, smear and culture), HIV tests, blood tests, radiographs and other diagnostic tests will be extracted from routine national TB programme records.

All AEs will be assessed and managed by PMDT staff in accordance with existing procedures.

When participants complete the treatment, a follow-up interview will be performed by research staff within 7 days of the last scheduled dose of treatment. These interviews will ask patients about their (a) history of AEs; (b) history of any hospitalisations that occurred during treatment; and (c) self-reported treatment adherence. For patients who received at least one dose of an injectable antibiotic at any time during treatment, an audiometry assessment will be performed at the completion of treatment. For participants who do not respond to the 12-month follow-up phone call, research staff will perform a household visit.

A final follow-up interview (in person or telephonic) will be performed 24 months after enrolment, where participants will complete an end-of-study questionnaire and the SF-36 survey will be repeated to assess patient quality of life.[26]

## Primary and secondary outcomes

The primary outcome measure will be the proportion of participants with treatment success after 24 months. This period allows for treatment to be extended for an additional 4 months beyond the 20 months of WHO-recommended long-course treatment, if required. 'Treatment success' is a standard WHO programmatic indicator of treatment outcome, obtained from routine PMDT registries,[28] comprising the sum of treatment completion and bacteriological cure. Treatment completion is defined as treatment completed without evidence of failure. Bacteriological cure is defined as treatment completed without evidence of failure *and* three or more consecutive cultures taken at least 30 days apart that are negative after the intensive phase.[29] Treatment outcomes will be based on programme records that include registration books and patient medical records extracted at defined time points.

Secondary outcome measures include the following:

- *Time to sputum culture conversion.* This is defined as the number of days from diagnosis to the first of three consecutive negative sputum culture results (ideally collected at monthly intervals as per national policy), without subsequent reversion.[28] This measure has been validated as an early indicator of the effectiveness of MDR-TB treatment response[30] and is measured routinely in the PMDT programme and recorded in clinic registries.
- *Reported grade 3 and 4 AEs during treatment.* This is defined as the proportion of patients with grade 3 or 4 AEs occurring from the date of randomisation up to 30 days after the final dose of treatment. This will be based on AEs that are documented in the patient medical records and corresponding formal AE notification reporting to the national AE registry (figures 1 and 2). The criteria for classifying the severity of AEs are described in online supplemental eMethod 2. The category and severity of reported AEs will be assigned by an expert clinical panel consisting of clinicians and MDR-TB programme staff, blinded to group, according to standardised criteria.[31]
- *HRQOL at the completion of treatment.* HRQOL will be evaluated at three time points—at baseline, 6 months and end of treatment—using HRQOL scores from the SF-36[32] and converted to utility scores using the SF-6D and appropriate weights.
- *All-cause mortality.* Mortality will be defined as the proportion of patients dying of any cause between randomisation and the end of 24 months' follow-up. This will be based on a combination of medical records and interviews with surviving household members.
- *Cost-effectiveness.* Taking a societal perspective, we will measure the cost-effectiveness of the intervention by calculating the incremental cost-effectiveness ratios (ICER) for the primary outcome and per quality-adjusted life-year (QALY) gained up to the trial end point (24 months). Details of data collection for the cost-effectiveness are described in online supplemental eMethod 3.
- *Patient and healthcare worker acceptability.* This is defined as the self-reported satisfaction of patients and healthcare workers with the use of the mHealth application. Up to 30 in-depth interviews will be performed to evaluate patient and healthcare worker knowledge, attitudes and practices regarding the technology, its acceptability, ease of use and enablers and barriers to use. This will be assessed using a semistructured questionnaire administered at the completion of the treatment period for patients and at the end of the study for healthcare workers. Details of the qualitative methods are described in online supplemental eMethod 4.
- *Process indicators.* Specific process indicators of the intervention will be measured using routinely collected data from health facilities to inform the fidelity and feasibility of the intervention. Fidelity is defined as the degree to which the mHealth application was delivered in the intervention arm 'as intended'.[33] Feasibility is defined as the ease of implementation and operation of the mHealth application within existing health systems, technology infrastructure and supply chains—assessed by key indicators monitored during the project.

## Censoring

Participants will be censored from follow-up at the earliest date on which one of the following scenarios occurs: (1) complete 24-month follow-up visit; (2) death; or (3) the last documented date when communication between participant and healthcare worker or study staff member occurred prior to the final follow-up visit.

## Sample size

The proportion of patients with MDR-TB achieving treatment success in the control arm is expected to be 75%.[17] We expect an improvement in treatment success

(bacteriological response or completion) by at least 8% (ie, from 75% to 83%), considered the minimal clinically important difference.[34] Using the standard Schlesselman formula for the difference in two proportions,[30] with a power of 0.8, and alpha of 0.05, we require 406 subjects per group. Expecting a 10% loss to follow-up from the study, compatible with our findings in a previous study,[35] we will recruit a total of 902 patients across the participating provinces.

## Trial governance

The study will be managed by a trial steering committee comprising key investigators based in Vietnam and Sydney, who will provide technical and/or operational input on a regular basis. An independent scientific advisory panel will also be created consisting of global TB and RR/MDR-TB experts (external to the study investigators) to help inform study implementation and provide oversight on the safety of patients in the study. An expert clinical panel will classify the severity of AEs, blinded to study arm allocation.

## Ethical issues

The study will be embedded within the routine PMDT programme, that is, healthcare workers will be responsible for the identification and enrolment of study participants. Trained healthcare workers will complete a written informed consent process with eligible patients using patient information sheets and informed consent forms available in Vietnamese. Participants unable to read or write will be asked to make a mark or provide a thumbprint in the presence of a witness who can sign on their behalf. Only written informed consent will be allowed for study participation. All study records will be stored at the participating clinics in locked cabinets. Access to the records will be restricted to specified study team members. Case report forms (CRF) and case management documents will be identified using the participant's study number only, with locator information stored separately. Data privacy will be maintained, with secure transfer of encrypted data between smartphones and servers and storing data on password- protected servers. Smartphone data will be password protected.

## Dissemination

The study findings will be presented at international conferences and submitted to peer-reviewed journals. In addition, we will provide ongoing feedback to various stakeholders within Vietnam such as staff of the PMDT programme and the national TB programme through meetings and presentations. Deidentified participant data will be made available for additional analyses by external collaborators on request to the study investigators. Study participants will be informed of the main study results via email or post, after the study has been concluded.

## Data analysis

The primary effectiveness analysis of the mHealth intervention will be assessed by comparing the treatment success rates[22 28] between patients in the intervention and 'standard care' arms, 24 months after treatment initiation. We will use a marginal Poisson regression model estimated via a generalised estimating equation (GEE) to test the effect of the intervention on treatment success. The model will be estimated via a GEE, as this is robust to mis-specification of the correlation structure, and we will use empirical SEs. Analysis of all quantitative outcomes will be conducted in a manner blinded to the study team.

### Time to sputum culture conversion

We will compare time from treatment initiation to sputum culture conversion at month 6 of treatment[22] between the two arms by conducting a survival analysis, using a Cox proportional hazards model adjusting for potential confounders.

### Proportion of patients with grade 3 and 4 AEs during treatment

The proportion of patients with any grade 3 or 4 AEs during 24 months of follow-up will be defined according to Common Terminology Criteria for Adverse Events[36] and compared between the two arms. We expect the proportion of reported grade 3 or 4 AEs will be greater in the standard care arm, due to delayed identification and consistent with barriers in the routine programme. The effect of the intervention on incidence of severe AEs will be estimated using a marginal logistic regression model estimated via GEE. We will also investigate the predictors associated with this outcome using the same approach.

### Health-related quality of life

Patient quality of life will be evaluated using the SF-36 survey, a measure of health status that enables evaluation of the effect of an intervention on quality of life. The scale has been validated in Vietnamese[26] and used to evaluate quality of life in Asian settings.[37]

### All-cause mortality

All-cause mortality will be evaluated by research staff 24 months after randomisation. The mortality status of study participants will be evaluated in two ways: (1) through existing patient information collected and maintained by the national PMDT programme; and (2) through dedicated study staff who will maintain regular contact with participants and/or their designated family members during and at the end of the follow-up period following treatment (including patients who drop out of treatment). We will perform a verbal autopsy for patients who die during the study. This will require detailed assessment by our study staff, using clinical records, death certificates and multiple interviews with family members and other community members using standardised WHO tools.[38]

We assume that less than 10% of patients will die during the course of their treatment. The study has not been powered to detect a difference in this outcome, so mortality findings will be largely exploratory and hypothesis generating. The relative risk of mortality during 24 months of follow-up in the intervention arm, compared with the 'standard care' arm, will be estimated using a

marginal logistic regression model estimated by a Poisson marginal model estimated via GEE.

### Economic evaluation

The cost and cost-effectiveness analyses will be presented in terms of ICERs for the primary outcome of the trial (ie, treatment completion). Population data will also be used to extrapolate the cost-effectiveness of the intervention to a scenario where the programme is scaled up nationwide. We will also model the incremental cost per QALY gained using utility values derived from the SF-36 health survey delivered at baseline, 6 months and 24 months. Discount rates of 3% will be used to discount both costs and effects in the primary analysis, following international reference case recommendations.[39 40] Discount rates, study perspective and any other uncertain variables will be tested using deterministic and probabilistic sensitivity analyses. Costs will be converted into international dollars (Int$) using purchasing power parity conversion factors published by The World Bank.[41] Results will be presented using cost-effectiveness acceptability curves for a range of willingness to pay thresholds.

## Data management and quality control

Data for analysis will be collected from three separate sources: (1) paper CRFs during enrolment and follow-up visits with participants; (2) MDR-TB programmatic reports including laboratory data; and (3) the mHealth application. The paper CRFs will be entered into a customised electronic database by study staff. All fields will have automatic range checks, reducing data entry errors. In addition, a data monitor will compare approximately 10% of paper CRFs with the electronic database. This will help to identify systematic data entry errors, and may lead to a review of a larger proportion of CRFs. Biweekly electronic checks for inconsistencies within and across forms will be performed followed by CRF review of any data queries that are generated. Selected investigators will have access to the final study data.

Monitoring and evaluation will be undertaken by research study staff within participating healthcare facilities every 3 months. In-service training and review of paper CRFs during these visits will ensure consistency of practice with programme guidelines and the study protocol and the quality of data collected.

## DISCUSSION

Vietnam has made a significant progress in recent years in controlling TB; however, high and rising rates of RR/MDR-TB among new and previously treated patients[17] indicate that new approaches to ensuring successful treatment outcomes are urgently required. Patients with MDR-TB often experience significantly more AEs from longer more toxic treatment regimens compared with patients with drug-sensitive TB (DS-TB). Unmanaged AEs often result in treatment interruption or discontinuation, with adverse outcomes for the patient and the community. A recent retrospective cohort study in Ho Chi Minh City confirmed international experience, with at least 50% of patients with RR/MDR-TB reporting treatment-related AEs.[42]

Timely AE reporting is a high priority among all patients treated for MDR-TB[22]; however, inadequate systems and human resource limitations remain a major barrier to timely reporting. In addition, the lack of feedback to clinicians by health authorities serves as a disincentive to submit reports, at the expense of good surveillance data and improved patient care. As a rapid adopter of modern digital technologies, Vietnam is well positioned to lead the way in identifying pragmatic mHealth interventions that may improve TB patient care. The use of an mHealth application can play various roles within the End TB Strategy[43] and can support patients with RR/MDR-TB with AEs, while also providing strong synergies with other TB control components. This would ultimately enable better use of programmatic data and foster a more patient-centred approach to TB care.

The V-SMART trial will evaluate the effect of an mHealth intervention on RR/MDR-TB treatment outcomes and patient experience. The evidence generated by this trial will provide immediate impact to the Vietnam National TB Program and other settings where patients with RR/MDR-TB are managed.

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