Protocol for a pragmatic randomised controlled trial to evaluate the effectiveness of improving tuberculosis patients' treatment adherence via electronic monitors and an app versus usual care in Tibet

Xiaolin Wei (xiaolin.wei@utoronto.ca)
University of Toronto Dalla Lana School of Public Health https://orcid.org/0000-0002-3076-2650
Joseph P Hicks
Nuffield Center for International Health and Development University of Leeds
Pasang Pande
Shanxi Center for Disease Control and Prevention
Zhitong Zhang
Shigatse Centre for Disease Control and Prevention
Victoria Haldane
University of Toronto Dalla Lana School of Public Health
Xiaoqiu Liu
China National Centre for Tuberculosis Prevention and Control Chinese Centre for Disease Control and Prevention
Tingting Yin
Weifang Medical University
Lixia Wang
China National Centre for Tuberculosis Prevention and Control Chinese Centre for Disease Control and Prevention
Dachun Shi
Shigatse Centre for Disease Control and Prevention
Shiliang Ge
University of Toronto Dalla Lana School of Public Health
John Walley
Nuffield Centre for International Health and Development University of Leeds
Ross Upshur
University of Toronto Dalla Lana School of Public Health
Jun Hu
Shigatse Centre for Disease Control and Prevention

Method Article

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Abstract

Background: Treatment non-adherence is a serious challenge to effective tuberculosis (TB) control in Tibet. In this study, we will pilot and evaluate the effectiveness of using new technologies, including electronic monitors (e-monitors) and a smartphone app, to improve treatment adherence among new pulmonary TB patients in Tibet, China.

Methods: This is a prospective, pragmatic, multicentre, individual-randomized trial with blinded evaluation of outcomes and data analysis, and unblinded treatment. New pulmonary TB patients of Shigatse, Tibet will be randomized to either the intervention or control arm in a 1:1 ration at the time of their diagnoses. All patients will be treated according to the WHO standard TB treatment regimens and China National TB program guidelines. In the control arm, patients will receive their medicines in e-monitors that are deactivated for its reminder function but are able to collect medication adherence history. In the intervention arm, patients will take medications in e-monitors that will record their medication adherence and share with health staff via a smartphone app. Patients will be opted to receive video observed treatment when adherence is problematic. The primary outcome is the rate of poor adherence measured per month during their treatment. It will be calculated from monthly-level data for each patient indicating the number of doses missed per month, with poor monthly adherence defined as the patient having missed ≥20% of doses per month. We will conduct a qualitative process evaluation to explore operational questions regarding acceptability, cultural appropriateness and burden of technology use, a cost-effectiveness analysis and long-term effects on TB control.

Discussion: Our study is one of the first trials to evaluate the use of e-monitors and smartphone app to improve communications between TB patients and health staff in low-and-middle income countries (LMICs). All intervention activities are designed to be embedded into routine practice of TB care with strong local ownership. Through the trial, we intend to understand the effectiveness of our intervention, as well as its feasibility, cost-effectiveness and long-term impact to inform future scale-up in remote areas of China and LMICs.

Trial Registration: Current Controlled Trials ISRCTN52132803, registered on 9 November 2018.

Keywords: Tuberculosis, treatment adherence, mhealth, randomised controlled trial, Tibet

Background

Treatment non-adherence is a paramount challenge in tuberculosis (TB) control and an important driver for the emergence of drug-resistance in Tibet due to its sparse population density, severe weather conditions, long travel distances and shortage of human resources to enable implementation of directly observed treatment (DOT). Similar problems have been identified in other parts of China [1]. Patients either self-administer their treatment or receive inadequate supervision from a health worker, normally the village doctor [2, 3]. This has resulted in poor treatment outcomes and high default rates. Therefore, the

Tibetan TB program urgently requires applicable and affordable alternatives to improve treatment adherence.

Digital technology provides a promising tool to improve treatment adherence. Existing literature suggests that electronic reminder and packaging interventions, such as SMS reminders, electronic device reminders and pager reminders, markedly improve short-term adherence for patients with chronic disease [4, 5]. Typical characteristics of these mhealth technologies include recording of dosing events, storage of records, audiovisual reminders, digital displays, real-time monitoring and performance feedback. Recent studies have included electronic monitors (e-monitors) as they deliver detailed, precise and objective data on daily adherence within a real word setting [6-9]. A trial in Ghana demonstrated that e-monitors and reminders substantially improved patient adherence to diabetic care and their clinical outcomes [10]. However, no studies have shown a long-term effect for patients with chronic diseases [4, 5, 11, 12]. This research gap is particularly apparent for HIV patients undergoing chronic antiretroviral therapy [13, 14]. As such, the existing literature highlights the need to tailor intervention delivery to meet versatile patient demands. That is, the new technologies need to interact beyond the patient-interface to include multi-media technologies, integrating models of patient care delivery and connecting patients with health care professionals [11, 13, 14].

In TB care, e-monitors and automated reminders have emerged to improve the quality of care delivery with accurate, real-time, detailed dosing information, and dedicated communication channels between patients and healthcare workers to discuss their concerns [15]. Real-time treatment adherence can support healthcare workers to identify patients who need help and focused support, rather than having to spread their efforts around all patients. In addition, new apps, such as WeChat, can transmit texts, photos, audio and videos in real-time, and have become popular among Tibetans. This provides the possibility of providing video observed treatment (VOT), an alternative to direct observation using real-time or recorded videos for patients, based on patient treatment histories. Despite the great potential, there is limited evidence supporting using such new technologies to support TB management. To our knowledge, worldwide there has only been one randomized controlled trial that assessed using e-reminders to improve TB adherence, but this used an older e-monitor that could not connect with smartphone apps enabling VOT [16].

After piloting our intervention we will evaluate, via a randomised controlled trial in two districts of Shigatse in Tibet, whether using activated medication e-monitors improves the adherence of new pulmonary TB patients to their medication, compared to usual care that uses inactivated e-monitors. The activated e-monitors will provide patients with automated voice reminders to take their medication, and by linking to a smartphone app will enable patients to receive treatment education and enable clinicians to access real-time patient medication adherence data, and will enable real-time patient-clinician communication, including VOT if necessary. The inactivated monitors will have none of these functions activated. We will also explore implementation questions regarding acceptability, cost-effectiveness and long-term effects to inform future scale-up in remote areas of China and other low-and-middle-income countries (LMICs).

Methods

Study Design

We will use a prospective, unblinded, pragmatic, individual randomized controlled trial design with one intervention and one control arm, using a 1:1 allocation ratio, to evaluate whether the intervention is superior to the control treatment. The study design is informed by the Medical Research Council framework [17] on complex interventions and implementation science principles [18] with an embedded theory-based process evaluation [19] to examine operational questions regarding acceptability, cultural appropriateness and burden of technology use. In addition, we will conduct an incremental cost-effectiveness analysis to inform future scale-up. We also plan here to do a follow-up study to compare the intervention's impact on TB relapse rates after patients' finish their treatment.

Setting

We will implement the study in two districts of Shigatse Prefecture in China's Tibetan Autonomous Region: one urban area called Samzhubze, and one rural area called Sa'gya. Shigatse Prefecture is located west of Lhasa with an average altitude of 4000 meters above sea level. Population density in Shigatse is very low (4/km^2). The prefecture covers an area of 182,000 km^2 of harsh and rugged terrain with paved roads connecting county centres. Over 90% of its 800,000 residents are ethnic Tibetans. The 2014 TB survey revealed the prevalence rate of pulmonary TB was 758/100,000 (0.76%), almost twice China's national average [20, 21].

The two project sites currently face challenges to provide standard DOT to ensure TB treatment adherence. TB care is only available from public health providers including: 1) TB dispensaries located in Centre for Disease Control (CDC) facilities for clinical care and general coordination, 2) township hospital doctors for home visits and supervision of village doctors, and 3) village doctors, often as treatment supervisors. According to China's National TB Programme (NTP) guidelines, new pulmonary TB patients should be treated in the community and should visit the district TB dispensary every month to refill their medicines. However, the serious shortage of health staff, plus the long travel distances and often severe weather conditions make regular home visits often impossible. In practice, patients typically receive self-administered therapy (SAT) with limited calls/visits from health staff, and loss to follow-up rates have been very high. Most patients visit the TB dispensary once every two months, if not longer. Across Shigatse in 2016, only 72% (769/1073) of new pulmonary TB cases completed treatment. Among patients who did not complete treatment 83% (252/304) were lost to follow-up. Treatment completion rates vary greatly by district. In our two study districts a total of 269 patients were registered in 2016, but only 38% (102) completed treatment, while 60% (162) were lost to follow-up and 1% (3) died. Many patients, mostly poor farmers, were lost to follow-up during the intensive phase as they received little education and support from health workers due to a lack of communications.

Eligibility

In the two districts of Shigatse, patients with presumed TB and newly confirmed pulmonary TB will be referred to the TB dispensaries by health workers from other public and private health facilities. Individuals who suspect they have TB can also visit TB dispensaries by themselves. All patients will be diagnosed of TB in the TB dispensary according to national and international guidelines of TB care [22]. All confirmed TB patients will be screened for study eligibility by TB doctors. TB doctors also act as TB coordinators responsible for reporting data to NTP.

Eligible TB patients are those aged 15 years or older, who are starting on standard 6-month short-course chemotherapy, are managed as outpatients, are free from any communication impairment (mental, visual, auditory or speech), and do not have any family members within the same household who have already been enrolled into the trial. We will recruit patients into the study via TB doctors in each TB dispensary, who will explain the study purpose and obtain informed consent. Based on existing routine TB data across the two districts we expect to recruit 300 new pulmonary TB patients in 15 months. We will maximize patient enrollment through fully informed consultations provided by TB doctors.

Randomisation

Following recruitment patients will be randomised to either the intervention or control arms in a near 1:1 ratio, using a computer-generated randomised permuted block design. The design will use random block lengths of 2, 4 or 6, and include an initial unbalanced block, with a maximum of 1 additional patient in either arm, to further hide allocation sequences, which means the ultimate sample size and allocation ratio will vary very slightly from what is planned dependent on the unbalanced block. The allocation will be stratified by district, with one district having approximately 160 patients and another having approximately 140 patients, with a near equal allocation ratio in each. JPH will generate the allocation sequence, and will have no further role in the randomisation or allocation process. The allocation sequence will be used by the study team to print individually numbered allocation cards, which will be placed in sequentially numbered sealed opaque envelopes before delivered to study sites. The TB doctors will allocate each recruited patient after their enrolment by opening the correct envelope in the sequence, and will provide the e-monitor setup according to the patient's allocation. Research team members will educate the TB doctors on the importance of following the correct sequence, and local CDC staff will make monthly visits to the TB dispensaries to carry out spot checks and ensure the randomisation procedures are being correctly followed. It will not be possible to blind providers or patients due to the nature of the intervention.

Treatment processes: all arms

All patients will be treated according to the standard WHO DOTS programme and the China NTP guidelines using isoniazid, rifampin, ethambutol and pyrazinamide for 2 months (3 months for sputum smear-positive patients whose sputum smears have not converted to negative at the end of 2 months), followed by isoniazid and rifampin for 4 months, under daily fix-dose-combination (FDC) for the entire treatment course [22]. According to the NTP guidelines, patients will be given the choice of SAT, or treatment with a supervisor, mostly village doctors but sometime a township hospital staff. The health staff who act as treatment supervisors will receive RMB 60 ($10) from the government when completing 6-months' support to a TB patient. In the two districts, patients should visit the TB dispensary at least every two months to meet with their TB doctor, and refill their FDC medications using the e-monitor box, which will collect data each time they are opened. Patients will also meet with the TB doctor who will count any leftover medicines. E-monitors will be returned to district TB dispensaries at the end of treatment and reused when possible. The township hospital public health staff also have a role of visiting patients' homes, and supervising village doctors.

Intervention arm

Figure 1 shows the framework of intervention strategies. The e-monitors in the intervention arm have two main functions beyond storing the TB medication. First, they will remind patients to take their medicine on time using human voice recordings. Second, they can transmit adherence history to a cloud-based server linking with computers an app. At recruitment the TB doctor will demonstrate how to use the e-monitor box and WeChat app. The treatment supervisor will visit the patient's home within the first week of treatment, and solve any remaining problems. During recruitment or at the first home visit by the treatment supervisor a family member will be chosen to act as a treatment supporter. The family member must live in the same house as the patient, care about the patient, and be literate in using WeChat. Then, using the app, patients or their family members (if the patients are not able to use a smartphone or WeChat) will be invited to setup the WeChat app on their smart phones, and connect with their TB doctor and treatment supervisor. When appointed the family member will be trained about their responsibilities for providing psychological support to patients and facilitating patients use of the e-monitor and the WeChat app.

TB doctors and treatment supervisors will add the patient or the family member into their WeChat. Patients, treatment supervisors and doctors will be able to have direct but distinct communications. In addition, patients will receive audio/video-based health education message through WeChat sent by the treatment supervisor and TB doctor.

Via the WeChat app and also its website, health staff will be able to monitor patient adherence history and outpatient visits. Patients who report consistently taking their medications will continue SAT. TB treatment supervisors or TB doctors will identify patients at high risk of being lost to follow-up based on whether the patient a) expresses serious concerns about maintaining their adherence, b) skips three consecutive doses or c) refuses to start or continue treatment. Treatment supervisors will be trained that

if their patient is considered a high risk of becoming lost to follow-up they should explore with the patient their reasons for non-compliance and what help may be needed. The treatment supervisor or TB doctor will then initiate VOT while trying to provide any help needed. The treatment supervisor will document the start and end time of VOT. Patients who accept the invitation to begin VOT will be given instructions either in the TB dispensary or at home during the visit of their treatment supervisor. Using the WeChat app VOT can be done with the TB supervisor via a live video conversation or via recorded video/pictures showing them taking their medicine. VOT will be provided until three consecutive doses are completed on time, then the patient will switch back to SAT using their e-monitors. Patients who do not agree to VOT will be called daily by treatment supervisors until three consecutive doses are completed. We anticipate less than 20% of TB patients will need VOT, and mostly during the initial phase or at the end of the treatment.

TB doctors, township public health staff and village doctors will receive training on a revised operational NTP guideline that incorporates using the e-monitor box, WeChat, and VOT based on our previous experience [3], as well as communication guidance on using them. In addition to the requirement by the China NTP, all health staff in this study will have to sign an agreement to keep all patient information confidential and only use it for the purpose of TB care. All patient information stored in the WeChat app at the provider's end will be deleted immediately once the patient has completed treatment or been lost to follow-up.

Control arm

The control will practice usual care except that patients will use deactivated e-monitors set into a silent mode to collect treatment adherence data. The data will be encrypted and will thereby not be available to health staff during the study. At each visit to the TB dispensary, patients will refill their medications in their e-monitor boxes every one or two months. Treatment supervisors are advised to visit patients at least once a week according to the NTP guidelines, but this will be at their own discretion. We will not invite patients to connect with their TB doctor or treatment supervisors through the WeChat app. Treatment supervisors will contact patients through traditional means, such as physical visits or phone calls. We will not select family treatment supporters.

Outcomes

The primary outcome will be the rate of poor adherence measured per month across the 6/7 months of the standard WHO DOTS program for new pulmonary TB patients. We will calculate the outcome from monthly-level data for each patient indicating the number of doses missed per month, with poor adherence in a given month defined as the patient having missed ≥20% of doses in that month (equivalent to missing ≥6 out of 30 doses in a given month). This threshold has been commonly used in

other disease areas [23] and in a similar trial as a relevant indicator of treatment adherence [16]. Our secondary outcomes are: 1) the patient-level percentage of total doses missed over the 6/7months of treatment (calculated as a percentage value for each patient based on the total number of doses missed out of the total possible number of doses), and 2) a patient-level binary indicator of overall poor adherence (defined as ≥ 10% of total doses missed, which is the NTP definition of non-adherence). Our remaining secondary outcomes will be the patient-level WHO standard definitions of TB treatment outcomes: 3) treatment completion/success, 4) loss to follow-up, 5) poor treatment outcome (defined as death, treatment failure or patient loss to follow-up) and 6) sputum conversion rate at the end of the 2^{nd} month [24].

Sample size

As there are limited analytical sample size approaches available for longitudinal outcomes we used a simulation approach. We based our subsequent power calculation on our primary outcome of monthly poor-adherence, and assumed a 40% monthly poor adherence rate for the control arm [16]. For our simulations we created 6 binary poor-adherence outcomes (i.e. 1 per treatment month) for patients, varying the total number of patients between simulations to explore power, but always assuming a 1:1 treatment arm allocation ratio. The outcomes were randomly generated from a Bernoulli distribution with a fixed probability of success (i.e. probability of monthly poor-adherence), which was always set to 0.4 for the control arm, but was varied between simulations for the intervention arm. In addition, in each simulation all patients' outcomes were generated with a fixed level of correlation between their monthly outcomes, based on an exchangeable correlation structure. These outcome data were generated using the R package simstudy [25], based on the Emrich and Piedmonte algorithm [26]. We explored the effect on power of assuming an AR1 correlation structure instead, but as our simulations showed this resulted in less conservative estimates of power, and because we had no similar data to explore the robustness of this assumption and no strong reason to assume an AR1 structure, we assumed an exchangeable structure instead. After generating the simulated data we then used the R package geepack [27] to fit a generalized estimating equation (GEE) to the data with binomial errors and an identity link, which allowed estimation of the absolute difference in treatment arm outcome proportions (see *Statistical Analysis* section for more details) [28]. The GEE included a covariate for treatment arm and a categorical variable for month. We then extracted the Wald-based two-sided p-value associated with the coefficient for the treatment effect estimate. Finally, for each set of parameter assumptions we repeated this process 1000 times and calculated the resulting power based on the proportion of p-values ≤0.05. We assumed no missing data due to patients who become lost to follow-up still being able to contribute 100% of their outcomes in the study. Assuming a monthly poor-adherence rate of 40% in the control arm and a moderate within-patient correlation between monthly poor-adherence outcomes of 0.5, we require 300 patients to detect an absolute reduction of 12 percentage points in the intervention arm outcome (i.e. an intervention-arm monthly poor-adherence rate of 28%) with 81.5% power.

Pilot stage

During the preparation period, we will invite four new pulmonary TB patients (two in each district) to be randomized into either intervention or control arm as pilot cases, and will be followed up for two weeks. We will assess the feasibility and acceptability of using the e-monitor boxes, the server for monitoring adherence history, and WeChat for communications. We will pilot the feasibility of VOT in the two patients who are allocated for intervention. We will revise the implementation plan based on experience from the pilot.

Process evaluation

Theoretical framework: We will employ an adapted version of the Unified Theory of Acceptance and Use of Technology (UTAUT) model [29, 30] to guide our process evaluation to assess issues that influence patients' behaviour change in relation to both the technology used, such as acceptance, feasibility, appropriateness, adaptability, as well as adherence behaviours. (Figure 2) The UTAUT has been widely used to understand information technology adoption in general. The adapted UTAUT model has 4 constructs through which to explore technology oriented factors that shed light on user experiences interacting with a given technology. These factors are: 1) performance expectancy, 2) effort expectancy, 3) social influence, and 4) facilitating conditions. Performance expectancy includes the perceived usefulness and personal outcome expectations associated with technology use. Effort expectancy is the perceived ease of use and complexity of the technology. Social influence includes subjective norms and technology use within a user's social context. Facilitating conditions include perceived behavioural control and wider contextual circumstances that support the use of technology. Together these factors provide a comprehensive understanding of the patient's experience with the technology.

We also included adherence relevant aspects of the WHO adherence framework into our theoretical framework [31]. Condition-related factors are the illness-related demands faced by the patient which ultimately impact the patients' risk perception, treatment beliefs and the priority they place on adherence. While, therapy-related factors include side effects, treatment duration, treatment failures and experience of side effects [31]. These indicators may either motivate or dissuade patients from adhering to treatment plans. Though our intervention may satisfy technology-oriented needs of a patient, their treatment plan and their lived experience may pose unforeseen challenges to their behavioural intention and change. All the above factors will be considered with contextual and person-oriented factors including gender, age, socioeconomic factors, experience and voluntariness of technology use.

Our process evaluation is designed to explore factors highlighted by the modified UTAUT model from the perspective of patients, treatment supervisors and doctors. We will record the e-monitor's defects, connectivity, and the operation within existing health and logistics conditions through program logbooks.

We will also record each supervision trip. We will report the proportion of patients having a smart phone, able to enroll in, and their technology use. We will measure the accuracy of patient adherence history collected by e-monitors against anti-TB drug refills/ counting in TB dispensaries at each time of patient refills. District TB doctors will record the persistence of using e-monitors over 6/7 months, the proportion of patients who need VOT, start VOT, and the persistence of VOT (over 3 days until satisfactory adherence).

We will conduct semi-structured in-depth interviews to understand acceptability, cultural appropriateness and burden of technology use. We will recruit and interview 30-40 patients, family members (including 5 from VOT), their treatment supervisors and TB doctors. Questions will explore smart phone literacy, experience and usability of the new technology, overall satisfaction, and any concerns (e.g., understanding, learning experience, time consumption, communication quality, confidentiality, data usage costs). Due to culture norms, we will pay specific attention to females regarding confidentiality/ privacy issues in communications using WeChat and the VOT.

Economic study

We will conduct an incremental cost-effectiveness study that will collect costs of the implementation package including staff, equipment and supplies – 'incremental' to those required in usual (control arm) care. Overall incremental cost-effectiveness ratios for the service intervention and health outcomes, based on our primary and secondary endpoints, will be computed where possible. Simple unit costs of implementing the intervention including cost per district and per patient will be computed. The total per patient cost will be calculated as the sum of three elements: 1) the cost of clinic consultation estimated with doctor's time input and unit salary; 2) the cost of patient follow-up measured with frequency of home visit/using WeChat, average time input for the two approaches and their unit salaries, plus travel cost where applicable; and 3) medication cost including inpatient and outpatient health service charge, and indirect cost (travel, caregiver cost, etc.) when patient is hospitalized. The unit implementation cost will be calculated as the sum of 1) cost of staff time of both trainers and trainees; and 2) preparation of intervention materials including e-monitors and printings. Using published data, as available, we will estimate the benefits to: human health including potentially reduced multiple drug resistance TB or TB death, and productivity gains.

Follow-up study

We plan to follow up all patients using their national ID numbers which will be recorded in the NTP reporting system as a routine practice in Tibet. Follow-up will start from when a patient included in this trial completes his/her treatment with any treatment outcomes including loss to follow-up. We will track any relapse cases reported in Tibet using the national TB reporting systems within 12 months of their

treatment completion. Some patients may travel to other province to work where ID number is not mandatory in reporting TB cases. To mitigate the gap, we will conduct a short survey regarding their TB status and the place of treatment if any by the end of the follow-up study via WeChat. We will also collect any reasons of death using the vital registration. We will compare the relapse rates and mortality rates between the intervention and control arms using similar analysis tools outlined for other trial indicators. This study will be reported separately.

Ethical approval

The trial protocol has obtained ethical approval from the Office of Research Ethics at the University of Toronto (Ref: 36569) and the Ethics Review Committee of the Tibet Centre for Disease Control and Prevention (Ref: 006).

Data collection

Patient information including name, age, sex, address, education, profession, diagnosis and treatment outcomes will be routinely collected by the NTP. We will also collect routinely recorded treatment outcomes data from the two districts, such as conversion at the second months, loss to follow-up, death, and sputum smear results at the 5th and 6th months. All these data will be collected during monthly monitoring visit. Double entry and checking of random subset will be used to ensure data quality. These data will be employed to calculate the secondary indicators, and also be reported to the NTP. The interventions are unlikely to increase potential risks to patients. However, the adverse events and other unintended effects of interventions will still be reported to research coordinators in Shigatse CDC by TB doctors within 24 hours and be recorded in work logs.

For this study, we will allocate a unique participant number for each patient, to mask patient identifiable information such as name and address. Research staff will only have access to the participant number, while the linkage of participant number to patients will be encrypted and access is restricted to the principal investigator. All the patients' national ID number will be recorded in the TB reporting system as routinely required, which will be used to track any relapse cases 12 months after the patient has completed his/her treatment.

Measurement of the adherence indicators will be based on the e-monitor in both intervention and control arms, downloaded from the cloud-based database by the end of the 6-months treatment. We will triangulate the missing doses based on 1) the adherence history recorded from e-monitors; and 2) pill counts at the end of each outpatient visit. We will record the larger number of missed doses which ever is more. The TB doctor will also conduct a short questionnaire survey regarding 1) if patients have had access to and/or used the WeChat and e-monitors, 2) patients' time associated with using the e-monitors and WeChat, and 3) outpatient and inpatient cost. A questionnaire for doctors and treatment supervisors

will be collected at the end of the trial period by researchers to measure their time cost in supporting patient treatment. Implementation cost will be collected using researcher's worklog including number of trainees, trainers' labor and travel cost, cost of training materials and e-monitor boxes.

We will also record and audio tape the interviews with patients and health staff for the process evaluation. Information from the interviews will only be accessed by research staff, and anonymized during analysis.

Statistical Analysis

Full details of all pre-planned statistical analyses will be contained in a statistical analysis plan that will be finalised early in the trial. We will take measures to ensure a blinded outcome evaluation using (1) the "PROBE" design of blinded outcome evaluation [32], and (2) blinding those analysing the data to treatment status. Our primary analysis population will be the "intention-to-treat" (ITT) population, which will include all randomised patients, and all analyses of this population will analyse patients according to their original treatment allocation irrespective of their subsequent adherence or how they were actually treated. The CONSORT guidelines for reporting parallel group randomised trials recommend presenting absolute measures of effect for binary outcomes due to their increased relevance for practice and policy, as well as relative measures of effect. Generalised estimating equations have been shown to produce robust estimates of the absolute difference in treatment effect for binary outcomes from multi-level trial data [28]. Therefore, we will analyse our monthly binary primary outcome of poor-adherence using a GEE, with binomial errors and an identity link, to estimate the absolute average-difference across all treatment months in the proportion of poor adherence between the intervention and the control arms (intervention minus control). This analysis will adjust for month, stratum and a range of covariates, which will be defined in our statistical analysis plan, but we will also conduct a sensitivity analysis of our primary outcome excluding all non-design covariates. For our primary outcome we will also estimate the relative average-difference in the proportion of poor adherence between the intervention and the control arms (intervention minus control) across all treatment months on the odds ratio scale, using a GEE with binomial errors and a logit-link, and adjusting for the same covariates as in the primary analysis. We do not expect any missing data because we are only collecting basic covariate data at baseline, and if patients are lost to follow-up at any point then they will still contribute 100% of their primary outcome data, because their primary outcome would just be recorded as non-adherence from the point at which they were lost to follow-up. However, if their primary outcome data are missing for an unexpected reason (e.g. loss of data), then we will ensure the "intention-to-treat" analysis is maintained in the primary and sensitivity analyses by imputing the missing outcome data assuming the worst outcome of poor adherence for those months where data are missing.

For our secondary outcome of the patient-level percentage of total doses missed over 6-months of treatment, assuming the outcome is normally distributed we will analyse it using a linear regression model including the same covariates as used in our primary outcome analysis. For all remaining

secondary binary outcomes we will use a “logistic regression average-risk-difference” analysis approach (again adjusting for the same covariates as in the primary outcome analysis) to obtain absolute measures of treatment effect. This approach has been shown to provide robust estimates of absolute treatment effects for RCTs [33]. As with our primary outcome we will also conduct sensitivity analyses for all secondary outcomes where we will repeat the above analyses without adjusting for non-design covariates. For all our secondary binary outcomes we will also estimate relative treatment effects on the odds ratio scale using logistic regression models, adjusting for the same covariates as in the primary analyses.

For all secondary outcome analyses if there are any missing data we will follow the same approach to dealing with it as described for our primary outcome, assuming non-adherence or loss to follow-up where appropriate given the outcome (and assuming “yes” for the WHO TB treatment outcome of relapse within 12 months after treatment completion).

We will also conduct a set of “per-protocol” exploratory analyses for our primary outcome and our secondary outcomes of “percentage of total doses missed” and “overall poor adherence”, based on the adherence status of patients to the intervention. Lastly, for selected outcomes we will also conduct a small number of subgroup analyses (which will be fully defined in our statistical analysis plan) to explore whether treatment effects vary by key characteristics.

We will set statistical significance at the 5% level, and base our inferences on the two-sided p-values and associated 95% confidence intervals for the treatment effect estimates. All outcomes will be analysed at the end of the trial, and no interim analyses are planned for this study.

Analysis of process evaluation

Both quantitative and qualitative data will be analysed. Quantitative data will be summarised, described and analyzed using appropriate statistical methods, including multiple linear regression for continuous outcomes, and generalised linear models with identity links and binomial errors for binary data. Qualitative data analysis will use a thematic approach to discover emergent themes. Notes will be reviewed after each interview to identify emergent topics and allow for exploration in subsequent interviews. Data will be translated and transcribed, then analysed using NVivo 10.

Trial management

Prof Xiaolin Wei from the University of Toronto and Dr. Jun Hu from Shigatse CDC will be the co-guarantees of the trial who have full access to the trial dataset. An external member led data management committee (DMC) will be established to 1) safeguard the safety and privacy of patients involved, and to 2) ensure that all data are collected according to agreed ethical guidelines, properly

stored and only used for research purpose. We will also form an external member led trial steering committee (TSC), consisting members from China NTP, Tibetan TB program, key members of the trial team. Annual meetings will be held for both DMC and TSC. Important protocol modifications will be discussed during the meetings.

Discussion

Our study is one of the first trials to evaluate the use of e-monitors and smartphone app to improve communications between TB patients and health staff in LMICs. The study fits well with China NTP's priority to promote new technologies to promote TB care in remote areas. Previous studies revealed that only new technologies that improved communications with patients demonstrated benefits in improving disease control outcomes programs [11, 12]. In our trail, we employ the e-monitor that has been piloted in other geographical challenging areas of China with good usability. Instead of launching a new app, we link patients with health staff through an existing app, WeChat, which has been widely used among Tibetans. Second, we actively involve patient family members who has good literacy in WeChat, and is willing to provide support the patient physically and psychologically. Thirdly, all intervention activities are designed to be embedded into routine practice of TB care with strong local ownership. The project is co-led by Shigatse Centre for Disease Control and University of Toronto, with a trial unit established in Shigatse to coordinate trial activities. We will engage the TB program at the national, provincial and frontline level in developing guidelines and training modules to ensure the materials are ready to be adapted to other remote areas through NTP. Fourthly, the trial is designed to fit into the cutting-edge implementation science principles that include a theory-based process evaluation and economy evaluation to inform scale-up in remote areas with similar challenges.

Several limitations and challenges need to be noted. First, many TB patients in Tibet are illiterate [21], but are able to use a smartphone and WeChat because 1) contacts in WeChat can be recognised by icons and 2) WeChat can enable sending audios and videos recorded by smartphones. We also employ a family member who has good literacy in WeChat to assist the patient. Second, we do not blind the health providers and patients which may lead to reporting bias. Objectivity will be ensured as patient adherence history will be prospectively collected by e-monitors and hard to be interfered by health providers or patients. Third, one health provider, such as TB doctor and treatment supervisor, may deal with patients both from the intervention and control arm. To mitigate the gap, we will ensure correct procedures to be followed up during our training and project supervisions. When patients have to travel for a long time during the treatment, we will coordinate with TB doctors in their influx areas to ensure patients continue to use e-monitors. Fourth, molecular tests such as culture and drug susceptibility test are not available in Shigtase, while GeneXpert only has limited use because of the shortage of cartridges. Thus, we are not able to diagnose drug sensitive or resistance cases.

Abbreviations

TB: Tuberculosis

DOT: Directly Observed Treatment

NTP: National Tuberculosis Programme

SMS: Short Message Service

E-monitor: Electronic Monitor

VOT: Video Observed Treatment

LMICs: Low-and-Middle-Income Countries

FDC: Fix Dose Combination

SAT: Self-Administered Therapy

CDC: Centre for Disease Control and Prevention

UTAUT: Unified Theory of Acceptance and Use of Technology

ITT: Intention-to-Treat

GEE: Generalized Estimating Equation

RCT: Randomized Controlled Trial

DMC: Data Management Committee

TSC: Trial Steering Committee

Declarations

Trial status and timelines

The trial was registered at Current Controlled Trials: ISRCTN52132803 on 09 November 2018 (http://www.isrctn.com/ISRCTN52132803). We started to recruit patients from 26 November 2018. At the submission of the protocol, we have completed pilot studies and have recruited 5 patients.

The study will be done over a 28-month period, with a 3 month preparation and pilot phase, a 15 month patient recruitment phase, a 6/7 month treatment phase, and a 3 month data analysis and write-up stage. We will disseminate trial results through research articles and policy briefs. We also plan a study to follow up all participants in the TB reporting system for relapse in another 12 months. Results of the follow-up study will be reported in a separate paper from the trial results. See Figure 3 for details of the trial timeline.

Ethical approvals and consent to participate

The trial protocol has obtained ethical approval from the Office of Research Ethics at the University of Toronto (Ref: 36569) on 14 September 2018 and the Ethics Review Committee of the Tibet Centre for Disease Control and Prevention (Ref: 006) on 03 August 2018. Informed consent forms with patients' preference of language (Tibetan or Chinese) will be collected before any patient is recruited into the study. The TB doctor will fully explain the information sheet and consent form to the participant in Tibetan or Chinese. Both the participant and the TB doctor are required to sign the consent form. If the participant is not able to sign due to illiteracy, they can use their thumbprint instead. The TB doctor will keep the signed informed consent form and leave a copy to the participants for their reference.

Consent for publication

Not applicable.

Availability of data and materials

Anonymised patient level data will be made publicly available for non-commercial use through a listserv after publication. The corresponding author will grant access upon reasonable request.

Competing interests statement

The authors declared no competing interests.

Funding statement

The trial is funded by TB REACH, a special initiative of Stop TB Partnership (Grant number: STBP/TBREACH/GSA/W6-5). The Beijing FLOW Cloud Data Technology Co., Ltd. who manufacture the FLOW^{â} e-monitors will provide free FLOW^{â} e-monitors for this trial. TB REACH and the Beijing FLOW Cloud Data Technology Co., Ltd. have no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Author's contributions

XW, JH, JPH and ZZ designed the study. XW drafted the manuscript. JPH provided statistical expertise in clinical trial design and will conduct the statistical analyses. VH contributed to the design of the process evaluation and qualitative methods. ZZ, JH, PP, TY and DS conducted the pilot and will conduct trial activities. XL and LW provided critical comments to improve the trial design. SG conducted scoping reviews. JW and RU provided comments to improve the manuscript. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Figures

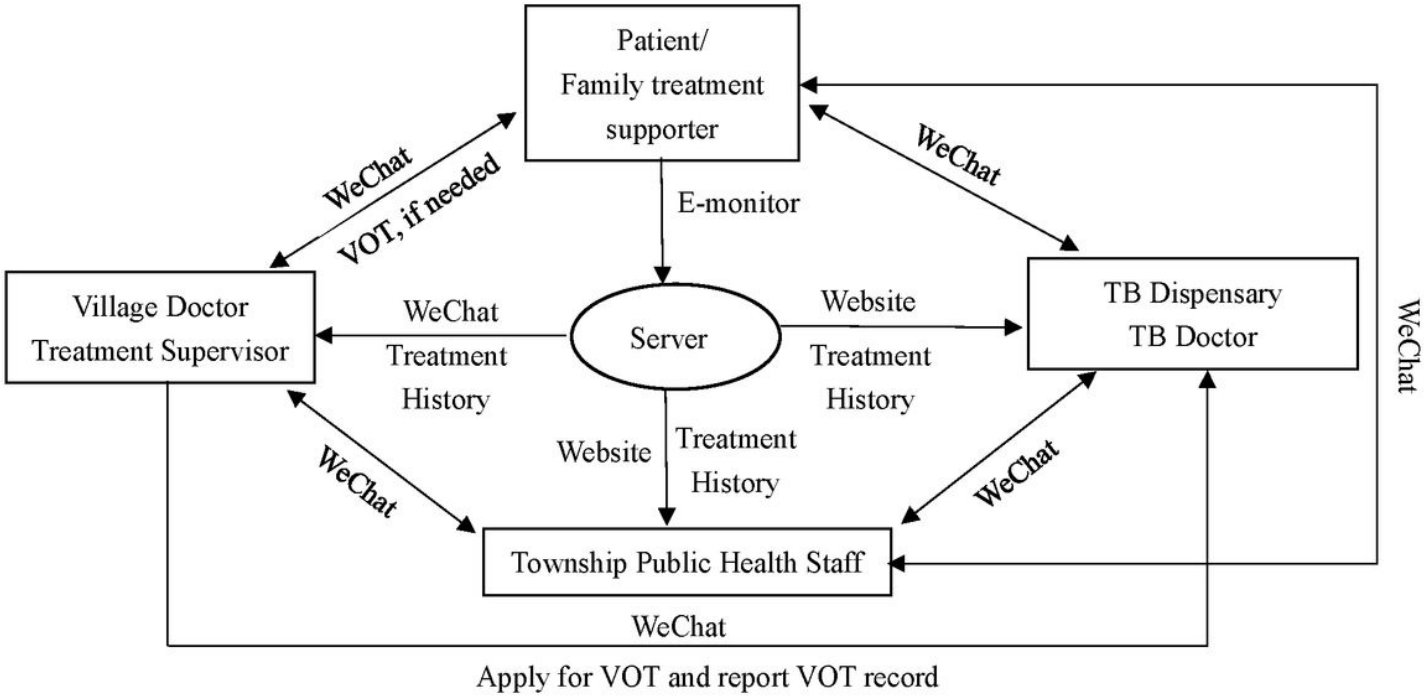

Figure 1

Data flow between patients, health providers and the server using electronic monitors and the WeChat app.

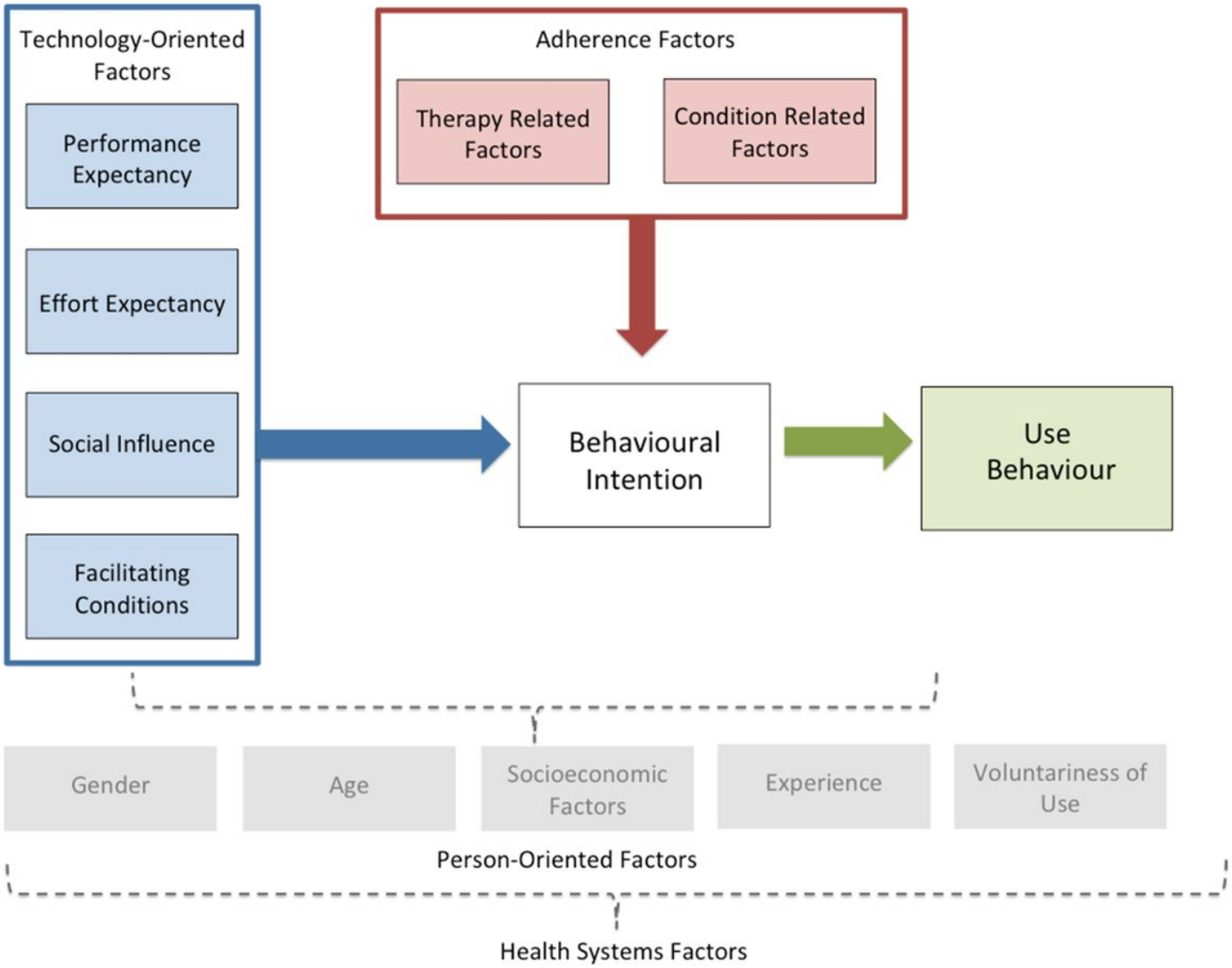

Figure 2

Theoretical framework to examine technology acceptance and use for adherence factors.

	STUDY PERIOD (Month)																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29-37
Preparation																													
Study design																													
Pilot and modify design																													
Interventions																													
Enrolment*																													
Intervention**																													
Control																													
Assessments																													
Treatment adherence data																													
Treatment outcome data																													
Economic evaluation data																													
Process evaluation																													
Data analysis and paper draft																													
Long term follow-up* **																													

Figure 3

Study timeline *Enrolment include eligibility screen, informed consent and allocation which will happened in one day for a patient. **Patients will be followed during their whole treatment period. ***Long-term follow-up will begin when a patient completed his/her treatment or they had a final adverse outcome including loss to follow-up, and will last for 12 months for each patient.

Supplementary Files

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- supplement1.doc