TB Treatment Support Tool Interactive Mobile App and Direct Adherence Monitoring on TB Treatment Outcomes

ID: 12112019

NCT 04221789

Version 2.0: 8/11/2021
Last IEC approval: 01/07/2022

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Sponsor: Institute of Clinical Effectiveness (IECS), Argentina

RESEARCH PROTOCOL

Summary

1. TITLE OF THE STUDY

TB treatment support tools: design and evaluation of an interactive mobile application for direct adherence monitoring of TB treatment outcomes.

2. DESIGN OF THE PROPOSED STUDY

Mixed-approach study: Qualitative design in the initial phase of the final development of the application and a two-arm randomised controlled clinical trial for the phase of evaluation of the impact of the intervention on treatment outcomes, mainly treatment success and drop-out.

3. RESEARCHERS

	Name and surname	Position and Institution	Contact email	Contact telephone number
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4. FUNDING

Proposal for a grant application to the National Institutes of Health (Grant Application: R01AI147129-01 **NIAID - NIH).**

5. SCOPE OF THE STUDY

The study will be carried out in public hospitals in some districts of the conurbation of the Province of Buenos Aires (to be designated) where patients with tuberculosis are treated a self-administered treatment modality.

6. DATE OF SUBMISSION TO THE ETHICS COMMITTEE

Version 1.0: 07/05/2019

Version 2.0: 08/11/2021

Last IEC approval:

01/07/2022

7. INTRODUCTION

Tuberculosis (TB) remains one of the top ten causes of death worldwide.[1] The more than 4,500 deaths per day associated with TB are unacceptable, given that almost all deaths are preventable.[2] TB patients face multiple barriers to treatment , including stigma and lack of education about the disease and its treatment and medication side effects. Poor adherence to medication, along with challenges in monitoring patients and re-engaging those who drop out of treatment, are important factors contributing to disease persistence and the development of drug resistance. If left unchanged, it is estimated that by 2050 multidrug-resistant TB could kill an estimated 2.5 million people per year and cost the global economy up to US$ 16.7 trillion.(3) To address the global health emergency that TB represents, the World Health Organization's (WHO) TB control strategy has set targets to reduce deaths and incidence levels by 95% and 90% by 2035, respectively, compared to 2015.[5] To support these targets, there is substantial interest in the use of mobile health (mHealth) interventions to help reduce the challenges and support patients to complete their treatment.[6,7]

Of the mHealth approaches being investigated for TB adherence monitoring, drug metabolite testing has been identified as the most promising, ethical and accurate, and less intrusive and stigmatising strategy compared to other mobile solutions (e.g. video observation, SIM card-containing drug vials, ingestible sensors), yet its potential remains largely unexplored.[8] Mobile applications could provide personalised treatment monitoring, increase patient self-management and improve patient-health system communication by offering advanced functionalities for treatment support and monitoring. However, available TB-related apps have not focused on patients as end-users or been fully evaluated.(9)

Tuberculosis (TB) remains a global health threat and one of the 's most deadly infectious diseases, ahead of HIV/AIDS. Globally, approximately 1.7 billion people are infected with the bacillus, and this latent TB infection has a 5-10 percent chance of developing active disease in the course of a lifetime.[10] In 2017, an estimated 10 million people developed active TB and 1.6 million died from the disease.[11] The

spread of TB is compounded by a myriad of challenges for patients and health systems to adhere to prolonged treatment due to social stigma, fear, discrimination, poverty, lack of knowledge about the disease and its treatment, drug side effects and lack of system support.[12-14] Health care systems are overburdened by patient volume, the HIV epidemic, lack of resources and lack of advanced technology for monitoring and follow-up.[15,16] Treatment abandonment is a known cause of adverse individual and societal outcomes, including prolonged infectivity, relapse, increased morbidity and mortality, and the development of drug resistance,[12,17,18] which threatens to reverse the progress achieved by TB eradication efforts to date.[19] Resistant tuberculosis (MDR) is more contagious, costly and deadly.[20] As a result, preventing the spread of the disease and the development of resistance is a global public health priority.[21]

To achieve this goal, health systems must ensure completion of treatment.

A long-standing World Health Organisation (WHO) recommendation to ensure adherence to treatment has been the Directly Observed Treatment (DOT) strategy. A key component of DOT is the direct monitoring of medication intake by a treatment supervisor.[22] While it is an ideal strategy to reduce adherence problems, it is also recognised as resource intensive (human and financial) for both the patient and healthcare systems.[7,23-25] As a result, DOT has been inconsistently implemented and, in many settings, self-administered treatment (SAT) remains the most widely used standard treatment.[23] Incomplete implementation of effective control measures has resulted in TB incidence and mortality rates being sustained or declining more slowly than expected in recent years.[26] The current WHO recommended rate for treatment success is 90% of all identified cases.[21] The WHO Region of the Americas has the lowest treatment success rate (approx. 75%), one of the highest rates of loss to follow-up and a high percentage of TB deaths compared to other WHO regions.[27]

In Argentina, treatment success rates have been among the lowest in the region, between 44 and 66% according to WHO reports, and consistently high treatment drop-out rates of close to 20% have been reported.[28,29] It is also one of the five countries in the Americas with the highest estimated number of MDR-TB cases. Therefore, Argentina is one of the countries where the health system needs to implement more effective TB treatment strategies.

Current strategies are recognised as insufficient to meet the goal of TB elimination in this century.[21,30] In response to the challenges of DOT implementation, current developments in treatment management involve the use of technology (eHealth, mHealth), such as the use of mobile phones, tablets, smartphones and other wireless devices, to explore more efficient and effective ways to ensure that patients complete their treatment.[6] The availability of smartphones is rapidly increasing in our setting. Maximising mobile tools for patient support

treatment may be a promising alternative to increase patient engagement in care, improve adherence, monitoring, communication and delivery of evidence-based interventions.[6,8,31] However, more evidence is needed to develop, adapt and validate these tools in various conditions and models of care.[6,7]

Mobile health approaches to TB treatment monitoring being tested include video-observed therapy (VOT), 38,39 and other strategies (e.g. self-reporting, drug vials containing a SIM card, direct monitoring via integrated sensors[32] or testing for metabolites,[33,34] although these interventions have been questioned on the basis of their accuracy and costs.[8] For example, while direct video monitoring may avoid stigmatisation issues, patients may fake ingestion. Drug metabolite testing is potentially superior to DOT or VOT because it requires actual drug ingestion and has been identified as the most promising, ethical, accurate, least intrusive and stigmatising of these mobile strategies; however, its potential remains largely unexplored.[8] Preliminary reports outside the peer-reviewed literature highlight the potential for drug metabolite testing[35], however, there is a need for further development of the technology and rigorous research to assess its impact on treatment outcomes. On the other hand, as smartphones rapidly replace less sophisticated phones, tools such as mobile apps offer more advanced functionalities for patient support and monitoring, as they can facilitate real-time adherence monitoring or side-effect tracking, more personalised education and two-way communication with care teams.[36] In a systematic review of TB-related apps, most were geared towards health professionals (e.g. dose calculations or treatment recommendations) or provided very general information about TB.[9] Few apps have been developed directly oriented towards patient use and none were developed to support TB patients' engagement in their own care, limiting the potential of these apps to facilitate patient-centred care.

This TB treatment support intervention (TB-TST) will engage and support patients throughout the course of treatment and provide a platform through which a treatment coordinator (e.g. a TB nurse) can interact with patients, monitor their progress and identify needs for additional support. In our previous studies, patients on active treatment identify the following priority components for the implementation of a mobile app: simple and reliable TB information, medication reminders, interactivity with a treatment coordinator, monitoring of treatment and side effects, and the ability to incorporate social networking.[37]

The base model of the application includes: medication reporting (self-reporting of intake and periodic urine testing (presence of INH metabolite) and monitoring of medication side effects, education based on priority patient issues and reliable sources (CDC, WHO). Additional modifications will be needed to integrate the

patient recommendations, e.g. simplifying reporting steps, improving visualisation of treatment progress, and developing a more user-friendly test strip. The refinement will address these issues and others based on the initial phase of the study. This development will use non-proprietary open source components that can be interoperable with current and future infrastructure and integrate data with the health information systems of the national TB programme.

The intervention is supported by a biochemical test that detects the TB drug metabolite in the patient's urine. The paper-based colorimetric test uses a classical chemistry (the Arkansas Method) that changes the colour of the strip to purple when an isoniazid drug metabolite (INH) is present in the urine.[33,38] INH, one of the main first-line TB drugs, is considered an ideal target for daily adherence monitoring because it is often combined in the same pill with other anti-TB drugs and its pharmacokinetics make it a good biomarker as it is detectable in urine for 24 hours.[39] By up with bioengineers, work will be done to improve the test (faster, simpler and improved sensitivity), which is specifically designed for patient self-assessment and mobile app image capture. This innovative work reveals exciting opportunities to greatly improve the test by redesigning the strips with features specifically for use in the patient's home.

7.1. Preliminary Investigations Conducted

Previous research studies conducted by the authors include: exploration of barriers and facilitators to TB treatment success at the individual, societal and system level in regions with high TB burden in Argentina[16], development and pilot testing of an interactive text message-based mHealth intervention;[40-42] literature review of mobile device applications used in TB patients;[9] an evaluation of different treatment modalities and health system and patient factors on treatment success and dropout rates,[43,44] and development and field usability testing of a functional prototype.[37]

A first step to improving consistently low treatment success rates is to identify and understand the barriers in this context. To this end, we conducted in-depth interviews and focus groups composed of patients, TB care team members, and programme and hospital managers at local, regional and national levels.[16] Barriers included a shortage of TB-trained staff, lack of trust in local health facilities, paper-based follow-up systems that varied across systems, and a lack of resources for TB care. Most barriers were concentrated at the health system level. Treatment delivery strategies varied, with TSS being the usual strategy in large health facilities, where a large number of cases are concentrated. Therefore, there is a need to focus on efforts to support those receiving unsupervised treatment in an appropriate manner and to strengthen patient-health worker relationships through a strategy that facilitates patient and family interaction with the health system.

In response, we developed TextTB, a text message-based intervention, with patients and experts to help people receiving SAT.[40-42] Educational test messages were developed based on patient-reported information needs identified in qualitative interviews and guided by the Information-Motivation-Behavioural Skills model.[45,46] A mixed-methods pilot study was conducted to assess the feasibility and acceptability of TextTB with newly diagnosed patients who were 18 years or older and had access to mobile phones.[41] An open source, text messaging platform (FrontlineSMS)[47] was used to send, receive and view messages, and turned a computer into a 'hub' for managing interactions. The final intervention allowed patients to learn about medication administration, receive theory-based/appropriate staged educational messages twice a week, and receive individualised support remotely. Although successful as a pilot programme, and patients reported that they 'provided the necessary support', areas for improvement were identified in a larger cohort: developing strategies to reduce manual review of data by the treatment supervisor (e.g., increasing automation to alert which patients needed follow-up), expanding educational messages, and improving patient adaptation[(41,48).] In addition, after pilot testing, healthcare staff noted an increase in the use of communication apps, such as WhatsApp, rather than text messaging as individuals transitioned to smartphones. From this research, primarily, we have established that the intervention should be interactive and responsive to the individual, while incorporating design efficiencies to support the care team and minimise burden.

To better understand the situation, we conducted a prospective cohort study of 963 newly diagnosed TB patients (R01AI083229, PI: Rubinstein) and identified that 68% received SAT compared with 19% who received DOT and 12% mixed treatment monitoring.[44] Success rates were lower (70.2%, 85%, 84.2%) and default rates were higher (20%, 8.5% and 7%) in SAT, DOT and mixed groups, respectively. The high non-compliance rates in the SAT group are a cause for concern, as most patients receive this treatment modality. Increasing the level of patient contact, even without formal supervised treatment, was associated with a significant improvement TB outcomes, particularly among high-risk individuals (drug and alcohol users, young, low-income). These findings highlighted the continued need for action to develop tools to support people in unsupervised treatment.

In our current research, we have converted the functionalities of TextTB into a mobile application (app) and seek to extend its functionalities based on patient-centred design with input from TB experts. User-centred design principles and agile methods will be employed to develop and initially pilot test TB-TST to identify refinement needs prior to rigorous testing to assess the impact on treatment outcomes (treatment success and dropout rates) in a pragmatic clinical trial.

The pilot will also serve to create an actual dataset of patient-created images of metabolite test strips needed to build an algorithm for automatic detection of direct adherence results. Further refinement is anticipated meet the needs of the TB-TST patient and healthcare team, such as expanding functionality, improving customisation, simplifying navigation between screens, and making the test strips more user-friendly. The results of the pilot test will be the starting point for assessing its potential impact in a clinical trial in the second stage of the study.

7.2. Theoretical Framework for the Proposed Study.

Rapid or agile methods for software development and intervention allow for flexibility and adaptability, close collaboration between developers and end users, and short iterative product cycles to support the development and validation of technology-based tools.[49,50] Information System Research (ISR) is a framework that applies these user-centred design and system development methods in a rigorous and standardised way to incorporate end-user design preferences and has been shown to be useful in guiding the design of mHealth applications.[51] The cycles of relevance (to understand end-user needs), rigour (identifying technology-based interventions to meet needs) and design cycle (usability evaluation methods to iteratively develop and refine the application). The framework considers the environment, design science and the knowledge base that grows through experiences and expertise as a recommended method to support the efficient creation and validation of mHealth applications. Considerations for this application include interoperability, compatibility with local and remote health data storage, user-friendly data visualisation and modular development for future extensible technologies. According to this framework, the refinement of the application component (Objective 1) will follow an iterative process in which feedback from end-users and stakeholders will be used to optimise the intervention.

The *Information, Motivation, Behaviour Change* (IMB) model will be used for behaviour change content, development of educational material and to guide the coding of qualitative focus group data.[42,45,46] The IMB model supports the hypothesis that initiating and maintaining a behaviour, such as medication adherence, must be provided with adherence-related information and motivation, along with appropriate tools and strategies to maintain the behaviour.

Our proposed study is timely and relevant, as there is currently a paucity of evidence on the use of digital health technologies to improve TB adherence and clinical outcomes. In a recent systematic review of studies to assess the impact digital health technologies on TB treatment, the authors concluded that the evidence remains limited and that better quality studies are needed.[52] Given the lack of evidence for digital technologies in TB research, in particular, patient-centred applications for TB treatment adherence[53], the need to improve medication adherence, recognition of drug metabolite testing, and the need to improve TB adherence, the proposed study is timely and relevant.

as the most ethical and accurate direct treatment monitoring strategy,[8] TB-TST promises to improve TB treatment outcomes and have a sustainable public health impact.

The feasibility of TB-TST is supported by data showing that mobile device use is almost ubiquitous and smartphone use is high in Argentina.[54] It is important to understand how different strategies perform in real-life practice settings, as limitations of health systems and services for TB control are often responsible for lack of progress in control efforts.[55,56] Our team proposes to revisit a classic laboratory test, the Arkansas test, and modify it for use in the patient's home.

The current trial is important in representing the first study to systematically construct, evaluate and apply together with a test strip to monitor and improve anti-TB treatment outcomes. In summary, our proposed study to refine and test an interactive mobile intervention (TB-TST) builds on the results of our preliminary work,[9,16,40-42] a theory-based approach to design[51] and content construction16 to improve treatment adherence. Our long-term goal is to improve treatment outcomes for patients diagnosed with TB, particularly for those in resource-limited settings, by developing a tool to support patients, monitor adherence to treatment and identify whether they require additional support. This outcome will support global efforts for EndTB by 2035 and reduce the growth rates of MDR-TB.(2)

8. RESEARCH STRATEGY: INNOVATION

There are four innovative aspects of our proposed study to address critical barriers to TB treatment adherence.

1. This study is the first to our knowledge to design a patient-centred mobile app for TB that uses an iterative user-centred design, which has been shown to improve quality, functionality and engagement with patient health apps. However, this claim has not been tested in an active TB population in a low-resource setting. There is a need to provide continuous feedback and support for patient-centred approaches. The intervention will provide two-way messages, including personalisation based on participants' responses and outcomes (e.g. side effects, compliance reports). We will use real-time data collection and provide participants with feedback on their compliance performance in graphical and text form. One-way messages may provide reminders or motivations for patients to play a more active role in their management, however, bidirectionality can maximise the potential of interventions.

2. Both the re-engineering of a classic paper-based test to detect a drug metabolite in urine for home use and the image capture of the results on the mobile phone allow for a new direct monitoring of adherence in real time. The test confirms drug intake in approximately the previous 24 hours, ,

avoids the inaccuracy of self-reporting. This may enhance a treatment coordinators ability to provide personalised or accurate feedback to promote positive health behaviours and ensure adherence to treatment. Self-reporting or other methods of surveillance are considered less accurate, increase stigmatisation or are intrusive to the patient.[8]

3. The collection of repeated, longitudinal data on the side effects of anti-TB drugs by telephone, over the course of treatment, is novel in Argentina and may lead to new insights into side effects and adherence to treatment over time.

4. Building the application and provider interface in a modular fashion using open source software and open standards allows for future integration into healthcare systems (e.g. electronic health records and surveillance systems) and expansion of future functionality based on end-user needs. The mobile-optimised web application allows for use on any patient's smartphone rather than relying on an operating system or type of phone. The success of this effort could inform opportunities for treatment adherence and symptom management for other populations with complex care needs.

9. OBJECTIVES

9.1. Objective 1

Refine TB-TST according to the results of the pilot study based on user-centred design principles.

9.1.1. Technological refinement of the TB-TST application

For the refinement of the TB-TST application, the findings of the pilot study approved by the ethics committee of the Centrándolo Chest Hospital, where the study was conducted, will be synthesised. Priority changes will be identified and recommendations will be provided as technical requirements to the software engineers. Dr. Iribarren will work with the University of Washington's information technology team to convert the recommendations into actionable review plans. We will enhance the application's functionalities to meet the needs of the healthcare team and the patient, through improvements to interfaces facing both the patient and the provider. The developers believe that six months, divided into four design/development/testing cycles of six weeks each, will be sufficient to refine this application to sufficient levels of function and usability for the ECCA.

We will refine the home drug metabolite test based on patient feedback. Ideal chemical conditions will be evaluated to improve the sensitivity and speed of the test. Design considerations will include: ease of use (easy to use by users without prior experience or training, quick to perform, easy to understand results); the test should be effective (specificity and sensitivity), efficient (the amount of effort and cost required is proportional to the target value achieved), and satisfactory (given the

context and type of user); using affordable and accessible manufacturing techniques (usable and marketable to people with varying abilities, can be manufactured locally using technologically appropriate manufacturing [57].

Further improvements will include automating the reading of test results. We will use the test strip images captured during the pilot to implement an algorithm for the application to automatically read and send test . Algorithms from open source colourimetric analysis software are available, but will require adaptation and testing. Adding image capture guidance within the application can improve image quality, complementing the test improvements.

Once the modifications to the TB-TST components have been completed, we will invite 5-10 participants from the previous pilot study to review the refined TB-TST application. This step aims to ensure that the changes are responsive to patient needs and that usability issues have been addressed, test the refined TB-TST functionality, feedback and interactivity of the software, and identify any technical bugs. At the end of this technological refinement phase, the application will be ready for implementation in the ECCA (Objective 2).

9.2. Objective 2

To assess the impact of TB-TST on treatment outcomes compared to usual care.

9.2.1. Design

We will conduct a pragmatic, two-branch, randomised controlled clinical trial (RCT) with equal numbers of individuals randomised to intervention and control groups. We will patients throughout their entire treatment course (6 months) comparing the TB-TST intervention with usual care. The unit of analysis will be the participant and randomisation of the intervention will be to individual patients seen in hospitals where they receive TB care through self-administered treatment.

We hypothesise that managing adults with drug-sensitive pulmonary TB using the TB-TST intervention will result in better clinical and adherence outcomes and improve patient satisfaction with care.

9.2.2. Study environment, selection of study sites and population

The study will be conducted in hospitals in CABA and the Province of Buenos Aires, Argentina, where half of the more than 10,000 cases per year in the country are diagnosed and treated. Most patients are concentrated in specialised public hospitals where they receive self-administered treatment. We will select public hospitals with different geographical coverage areas in high TB burden areas defined by the criteria established by Argentina's National Tuberculosis Programme (NTP). NTP reports from the last 5 years and our cohort study showed that more than 60% of patients were treated in public hospitals and 65% received self-administered treatment. Of these, 85% were of low socio-economic status,

50% were unemployed, 25% were smokers and 20% reported alcohol or drug use.[28]

9.2.3. Eligibility criteria for participants

Participants must be at least 16 years old, have a new diagnosis of TB sensitive to regular drugs, have regular access to a smartphone and be able to operate the phone or have someone who can help them. It is estimated that more than 75% of the population has smartphones.[59]

Severely ill patients requiring hospitalisation will be excluded, as well as patients with known drug resistance and those with HIV co-infection as their treatment is administered separately. Selected patients who do not meet study eligibility will have specific screening data (including sex, age and reason for exclusion) entered into the study database to examine reasons for exclusion and feasibility of enrolment criteria.

Case definition: TB confirmed by positive sputum smear or diagnosis of pulmonary TB based on radiological findings and clinical signs and symptoms, but with negative sputum smear. The diagnosis can be confirmed by other methods such as MGIT960, BACTEC 9000 or MB Bact, nucleic acid amplification (PCR) or ELISA.

9.2.4. Standard of care

TB treatment and care are provided free of charge in the public health system. The standard of care includes routine clinical and laboratory tests. In self-administered treatment patients receive a 1-2 month supply of medication and are asked to return monthly for follow-up appointments, or earlier if they have problems. Treatment of drug-susceptible TB consists of a 6-month regimen consisting of: a two-month intensive phase of four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol or streptomycin), followed by a four-month continuation phase of isoniazid and rifampin daily or 3 times a week.77 Three of the four drugs are given in a combination pill that includes isoniazid, so urine tests for isoniazid metabolites are an indicator that the combination pill was taken within the last 24 hours.

9.2.5. Statistical power and sample size.

Argentina's WHO report on TB in the country indicates that treatment success rates have ranged from 44% to 66%.35 These rates include cases lost to follow-up. For those with known outcomes, the Argentina SOP and our previous cohort study estimated the treatment success rate among patients on self-administered treatment was approximately 70%, with a dropout or default rate of 20%.[28] To detect a success rate of at least 85% in the experimental group with 90% power, we will recruit 360 individuals (180 subjects per arm). Power calculations are based on the analysis of the primary outcome, the treatment success rate. All calculations are based on a 2-tailed test with alpha at the 0.05 level.

9.2.6. Recruitment Plan

The research team and coordinators at each hospital will introduce the study to the members of the health care team to whom newly diagnosed patients are referred for registration and treatment. Trained clinic staff will notify all newly diagnosed patients who meet the age inclusion criteria (16 years or older) the study and refer them to the site study coordinator for further information. The site coordinator will: (1) discuss the nature of the study with patients and answer questions; (2) review eligibility criteria; (3) obtain informed consent; (4) administer initial questionnaires; and (5) collect standard PNT follow-up information from the patient's treatment record.

The research team will conduct training for coordinators to ensure that this process is the same at each recruitment site. Signed informed consent will be obtained for all participants. A recruitment register will be maintained to document patients selected and reasons for declining participation (if willing to share the reason). Patients will be enrolled consecutively and recruitment is estimated to be completed within the third year of the trial.

9.2.7. Randomisation

Randomisation of the intervention to participants will be done sequentially with a 1:1 allocation, using randomised permuted blocks of different sizes between 6 and 10 and stratified by hospital to ensure that numbers are balanced by centre and group. Once the patient signs the consent form, the study coordinator will call the Institute for Clinical and Health Effectiveness (IECS) to receive allocation instructions. The randomisation sequence will be generated using available software such as http://www.randomization.com/ or similar. Sequentially numbered and sealed opaque envelopes will be used for treatment allocation masking.

Due to the nature of the intervention, complete blinding of group assignment to research staff or patients cannot be achieved. Professionals in charge of patient care will not be informed of the group assignment unless their patient informs them. Data managers and analysts will be blinded to the Hospital and group assignment of participants, who will be identified by an alphanumeric code. To limit contamination bias, all participants, regardless of the group to which they are assigned (intervention and control), will receive standard instructions, educational materials and booklets on TB treatment from the National Tuberculosis Programme (NTP). Since the primary outcomes, treatment success and treatment dropout are objective and not based on self-reported adherence, we believe that the risk of bias is minimised.

9.2.8. Procedures

Upon enrolment in the study, participants will be asked to complete a baseline questionnaire that includes socio-demographic characteristics, habits, self-care measures and a TB knowledge test. After completing the baseline survey, all participants will be asked to complete a baseline questionnaire that includes socio-demographic characteristics, habits, self-care measures and a TB knowledge test.

Study participants will receive written educational materials and will be instructed to follow the treatment plan by their primary provider.

Study participants in the TB-TST intervention group will receive assistance in gaining access to the app and will receive verbal and written instructions as well as a personalised demonstration of the app features by the study coordinator. Participants in the TB-TST group will also receive drug metabolite test strips and verbal and written instructions on how to complete the test and upload the image into the app (instructions also within the app). To assess whether patients are taking their medications, a request to complete the drug metabolite test will be sent periodically and randomly as an app alert 2-3 times per week during the intensive phase and 1-2 times per week during the continuation phase. The image will be automatically synchronised with the web interface via the application. A member of the TB team (e.g. a TB nurse) from each of the selected hospitals will act as study coordinator to interact with patients assigned to TB-TST and monitor treatment progress through the provider portal. The coordinator will be trained on the use of the application and provider portal, research objectives and protocols by the principal investigator and collaborating members of the regional TB programme team. Participants in the intervention group will be informed that interaction with the study coordinator through the app will be provided within office hours and that any emergencies should be addressed through standard routes.

Study participants in the control group will be asked to complete the Simplified Medication Adherence Questionnaire (SMAQ), a validated 6-item questionnaire to assess adherence when they return for their monthly visit.[60] The control group will not receive the TB-TST (neither application nor direct adherence test).

Compensation for time and expenses: all participants will be given the equivalent in Argentine pesos of $20 USD for the baseline survey and $20 USD upon completion of data at the end of treatment or at the last follow-up. Patients in the intervention group will be asked to complete an exit survey. We will pay for 1 Gb of data per month to cover data usage from the application.

9.2.9. Operationalisation of outcome measures

The primary outcome will be treatment success according to WHO definitions.[61] Treatment outcomes are defined as: success (cure or completion of the 6-month treatment regimen), dropout (discontinuation of treatment for at least 2 months), transfer, death, or other. Secondary outcomes include dropout rate, technology use as measured by actual use of the application, and technology usability as measured by Technology Usability Assessment Scale information.

9.2.10. Data Management

The data collection forms will be developed using RedCap, a secure web-based application with interactive data capture controls designed to support the

data capture for research studies, providing an intuitive interface, audit trails and automated export. RedCap is a free service offered through UW SoN and IECS is a Redcap partner through Vanderbilt University.

9.2.11. Data Analysis

All analyses will be based on intention to treat. Statistical analyses will be performed using STATA version 13.1. A t-test or Wilcoxon test will be performed for continuous numerical variables and a chi-square test for dichotomous or categorical variables. Standard descriptive statistics of frequency, central tendency and dispersion will be used to describe each sample. A p-value of less than 0.05 will be set to detect a statistically significant difference for all analyses. We will compare baseline characteristics of the group, including age, sex, education, travel time to the centre, adherence to medication regimen and basic TB knowledge. The primary endpoints will be Although we do not expect differences in the groups, logistic regression analysis can be used to adjust for possible confounding factors if necessary.

9.3. Objective 3

Assess patient and provider perceptions of facilitators and barriers to TB-TST intervention implementation and synthesise lessons learned.

9.3.1. Design and procedures

Exploratory qualitative study based on focus groups that will have a duration of 60-90 minutes. We will include the equivalent in Argentine pesos of $20 USD to compensate for participants' time. Once the informed consent process is completed, all focus group sessions will be audio-recorded. Focus group guides will be informed by the Mobile App Rating Scale (MARS) to assess acceptability (perceived usefulness and ease of use)[62]. The MARS has proven to be a highly reliable tool for assessing app quality.[62-64] The scale includes three sections and a modifiable app-specific section. Questions include identification of challenges, bottlenecks, whether the intervention meets needs, satisfaction with care, confidentiality concerns, and post-intervention perceptions and recommendations. We will use a socio-technical perspective that considers Structure-Process-Outcome with a socio-technical perspective to understand, for example, workflow issues and altered practice and service delivery.[48]

9.3.2. Sampling and sampling

After the intervention, through non-probability convenience sampling, we will conduct 3 focus groups of 8-10 people randomly assigned to the TB-TST group and 2 focus groups with TB care coordinators and TB team members to assess their experience using the application and the accompanying case management platform.

9.3.3. Qualitative data analysis

All focus groups will be transcribed verbatim for coding.[65] Transcripts will be entered into qualitative data management software, such as Nvivo, to organise and facilitate analysis. We will code iteratively using qualitative thematic and thematic methods.

[66,67] Specifically, we will use an inductive approach that provides a systematic set of procedures for analysing and deriving reliable and valid findings from qualitative data.[68] The following steps will be used for the analysis: 1) Preparation of raw data files: clean data; 2) Thorough reading of the text to understand the issues discussed by the participants; 3) Creation of categories (codes): identification and definition of categories, themes and sub-themes; 4) Continuous review and refinement of the coding scheme: within each category, search for sub-themes, including contradictory views and ideas and selected appropriate quotes that conveyed the themes; and 5) Application of the final coding scheme to the full data set and assessment of inter-coder reliability.

10. DISSEMINATION OF RESULTS TO STAKEHOLDERS.

The findings will be presented and discussed with key stakeholders and participants (patients, TB teams, regional and national TB programme officers). The study team will present the findings to health professionals at recruitment sites that are open to the community, to disseminate the findings, encourage feedback and participation for wide dissemination and use, and further adaptation to meet local needs. Members of the study team will attend the annual regional and national TB conferences to present the findings and discuss the benefits and limitations of this intervention identified in this study. The purpose of knowledge transfer and capacity building of mHealth tools is to strengthen local capacity to support leaders who can scale up and adapt these interventions to meet the needs of their communities. The team will also disseminate the results of the study through traditional academic channels, such as scientific conferences and peer-reviewed journal publications.

11. POTENTIAL PROBLEMS AND ALTERNATIVE STRATEGIES

Adherence and dropout: We will measure application usage using log files downloaded from the provider's web interface and embedded usage analytics (using http://piwik.org, a privacy-protective web analytics system run by the University of Washington (UWCIRG) to monitor their clinical applications. As part of the algorithms to be established, the study coordinator will contact the participant directly. We will request a second phone number of the contact (family member, support person) who will be contacted as an alternative.

In addition to communicating with the patient, personalised/conditional messages, such as: go to clinic, inform healthcare provider, will be sent automatically through the app if the patient has a problem and sends an alert. Potential IT/app/mobile phone issues: participants may lose or change phones, have a flat battery after power outages, or lose service while travelling during the intervention, all of which occurred in the TextTB pilot study. These factors will be documented in exit surveys and interviews to understand the extent to which they might affect a larger-scale intervention. If participants have trouble taking the direct compliance test at home, we will conduct the test when the participant comes for their visit.

monthly or have a community health worker conduct random inspections and send a photograph directly to the intervention coordinator and record it as data collected by a health worker.

12. EXPECTED IMPACT

The goal of this study is to improve treatment outcomes by designing and testing tools to support patient-centred care and to empower healthcare teams with a strategy to more easily monitor and support a cohort of patients. The application is being built using current design and interoperability standards and in a modular system. This allows us to modify the application and adapt it to user and system needs identified along the way and in the future. As technology is changing rapidly, it is important to maintain a flexible development environment to ensure that rapid changes can be made while remaining mindful of cost constraints and the particular needs of low-resource environments. The system needs to maintain flexibility to reach those most in need who may not have access to the most advanced phones or technology. In addition to disseminating and presenting the results to key stakeholders and participants in the community and national programmes, as described above in Objective 3, our team will also disseminate the results of the study through traditional academic channels. We will: 1) seek to publish results in high-impact scientific journals; 2) provide results in an annual and final report to NIH; 3) present results at major national and international meetings for TB and public health; 4) build code in an open source configuration for others to benefit; 5) register and publish findings on clinicaltrials.gov.

13. PUBLIC HEALTH IMPLICATIONS

The findings have wider implications and will improve our understanding of how to support patients on challenging treatment regimens. Poor medication adherence to TB regimens, along with challenges in monitoring patients and re-engaging them in treatment, are important determinants of poor outcomes and the development of drug resistance, contributing to the vicious cycle that makes TB control difficult. The main objective of this study is to refine and evaluate the impact of a treatment support tool (TB-TST) that links a user-centred app design to improve treatment outcomes in TB patients. We believe that mHealth tools, such as mobile apps, hold the promise of providing personalised treatment monitoring, increased self-management of care and improved patient-provider communication, as well as a means to record vital information across different groups, not only for TB but for a range of other chronic diseases.

14. ETHICAL CONSIDERATIONS IN RESEARCH

The fundamental mission of the central ethics committee (CEC) of the Province of Buenos Aires will be respected, and this research will be conducted with due respect for the dignity, integrity of personal rights and well-being of the participants involved in the research.

The interests and welfare of each study participant will prevail over the interests of science and society. The accepted ethical and scientific principles and the physical and mental integrity of the research participants, as well as their privacy and the protection of their personal data in compliance with the laws of the Province of Buenos Aires will be honoured. The study will be supported by the basic postulates proposed in the Belmont Report. This includes the principles of respect for persons, beneficence and justice.

"The basic principle of research involving human subjects is that the person decides to participate in the project voluntarily, by free choice, after being informed and understanding the significance of the research, its foreseeable risks and its potential benefits". This principle is to be implemented through the Informed Consent Process. In addition, all the administrative documents required by the CEC are attached.

Both the principal investigator and the research associate declare that there is no conflict of interest related to the conduct of the proposed study.

15. TRIAL REGISTRATION

ClinicalTrials.gov ID: NCT04221789
Unique Protocol ID: 12112019

16. FINANCING

Proposal for grant application to the National Institutes of Health (Grant Application: R01AI147129-01 NIAID - NIH).

17. TIMETABLE FOR THE STUDY

Table 1: Timeline of the study		Time in months										
Stages	Activities	0	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60
			01/06/19 01/11/19	01/12/19 01/05/20	01/06/20 01/11/20	01/12/20 01/05/21	01/06/21 01/11/21	01/12/21 01/05/22	01/06/22 01/11/22	01/12/22 01/05/23	01/06/23 01/11/24	01/12/23 01/05/24
Preliminary	Evaluation of the protocol by the Ethics Committee	X										
	Register on clinicaltrials.gov	X										
High School	Refinement of the TB-TST app (Objective 1)		X	X								
	Preparation of materials, development of technical manuals and operational.			X	X							
	Selection of hospitals and approval by each institution's Ethics Committee		X	X	X							
	Training of coordinators of the sites.			X	X							

Table 1: Timeline of the study		Time in months										
Stages	Activities	0	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60
			01/06/19 01/11/19	01/12/19 01/05/20	01/06/20 01/11/20	01/12/20 01/05/21	01/06/21 01/11/21	01/12/21 01/05/22	01/06/22 01/11/22	01/12/22 01/05/23	01/06/23 01/11/24	01/12/23 01/05/24
Execution	Recruitment of patients: eligibility, consents, questionnaire baseline and randomisation					X	X	X	X			
	Implementation of the clinical trial (objective 2)					X	X	X	X	X		
	Data collection					X	X	X	X	X	X	
	Trial data analysis clinical					X		X		X	X	X
	Conducting focus groups (objective 3)								X	X		
	Qualitative data analysis								X	X	X	
	Presentation of results to key stakeholders (Objective 3)										X	X

Table 1: Timeline of the study		Time in months										
Stages	Activities	0	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60
			01/06/19 01/11/19	01/12/19 01/05/20	01/06/20 01/11/20	01/12/20 01/05/21	01/06/21 01/11/21	01/12/21 01/05/22	01/06/22 01/11/22	01/12/22 01/05/23	01/06/23 01/11/24	01/12/23 01/05/24
Monitoring	Progress reports to NIH, the Ethics committee and the staff of the study.					X		X		X		X
	Data Safety Monitoring Board meetings			X		X		X				X
	Preparation and submission of manuscripts									X	X	X
Closing	Submission of Final Report to NIH, Ethics Committee and study personnel.											X

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