Cover page

Official Title of the study: Development and Evaluation of an Interactive Mobile Health Intervention to Support Patients with Active Tuberculosis

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STUDY PROTOCOL

Aim 1. Convert and expand TextTB into a mobile optimized app based on stakeholder feedback and engagement. 1.a Preliminary App version will be built with the following components based on prior research: educational component, communication tool, side-effect/symptom reporting, and self-administration tracking. Drug metabolite testing will be added for enhanced adherence monitoring. Further options for expansion will be explored in Aims 2 and 3. To improve patient engagement, patients will be able to curate their information, monitor and share their symptoms, contact health care team, tailor reminders or alerts for medication or follow-up appointment. See Appendix B for modular feature options. Platform will support texting component for non-smartphone users as done in pilot study. The app mPOWEr©[22] is an example of a deployed system (led by mentor Dr. Lober) that came from a participatory design process (Fig 5) (http://mpowercare.org/).

Table 5. Base app components and features

Component	Features
Educational material	Educational material can be uploaded through a webpage including topics and content Application triggers notification of new content
Communication tool	Encrypted, HIPAA compliant chat between patient and health care worker within app
Side-effect reporting	List of symptoms and checkboxes for users to select and report side-effects/symptoms
Treatment administration tracking	Participant confirms self-administration Reminders for can be set up Screen for program manager to see participants on track with treatment and others lacking confirmation (Fig 2)

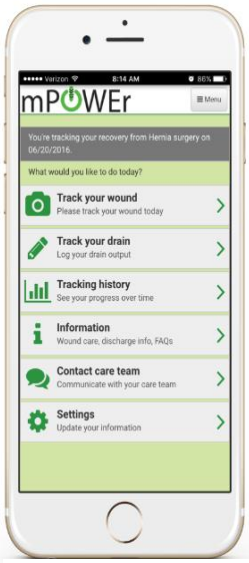

Figure 5. Example of deployed system

1.b Expand educational messages for full treatment course and patient tailoring. Educational messages for TextTB focusing on information needs for the intensive treatment phase (first 2 months) were developed using patient topic recommendations, suggested messages, TB expert input, and by compiling and coding patient-directed TB education from WHO, departments of health and Argentina's patient education material and guided by the Information-Motivation-Behavior skills (IMB) model.[49,50] Educational messages will be expanded ongoing to full treatment course based on user and stakeholder feedback throughout Aims 1-3. Educational material can be easily uploaded through webpage and notifications can be sent to participants when new and relevant material is added. Branching logic will be used to increase individual message tailoring based on baseline characteristics/profile conditions (e.g., current smoker) or request for further information.

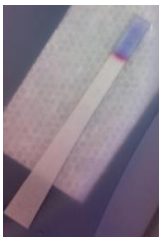

Figure 6 Positive result

1.c Add drug metabolite testing component. Photo imaging, similar to that used in mPOWEr©[22] for surgical wound monitoring, will be added to report drug metabolite results. Amlabu et al. reported the Arkansas colorimetric test reliably predicted isoniazid ingestion at 4 hours after ingestion.[54] Figure 6 displays purple positive result. After reporting self-administration participants will be requested to test and submit photo within 4-6 hours.

1.c Refine app with information technology (IT) and TB experts. IT and TB experts will test and provide critique of the app. IT experts will be from the DUB (Design, Use, Build) alliance of faculty and students across the UW exploring Human-Computer Interaction and Design; TB experts will be from the Firland Northwest Tuberculosis Center and collaborator Dr. Chirico. Dr. Demiris, my primary mentor, is an active member of the DUB alliance. Rapid app refinement will be based on written and verbal critiques. All suggestions will be maintained in a study log.

Aim 2. Refine and enhance product during pilot deployment following principles of iterative design. App will be tested in the field with two design iterations aimed to identify technical glitches, potential problems, or needed modifications to enhance and prepare app for pilot testing.

Participants: Five patients and five health care team members will be recruited from the public pulmonary specialized hospitals located in Health Region V (see letter of support Dr Chirico). Health Region V serves a large geographic region with a population of 3.13 million and accounts for about one third of the TB cases (incidence 49.2/100,000) within the province of Buenos Aires.[55] Patients will have completed TB treatment or are within the last month of completion, have regular access to a smartphone, and be 18 or older. Health care team members (eg, nurse, social worker, pulmonologist, nutritionist) will be those who are responsible for care or care management of patients with active TB, have regular access to a smartphone, and 18 or older. Potential patients will be introduced to the study by clinic staff through collaboration with Dr. Chirico, regional director. Informed consent will be obtained at start of testing.

Procedure. App will be field tested for 10 days. Participants will be asked to use all features and review all app content material. This is expected to take 2-3 hours over the course of field testing. After the first five days we will conduct focus groups with the end-users. Individual sessions will be conducted for those who cannot join

focus group and will include the "think-aloud" approach where process of use will be recorded and participant will be observed using the system to study how easy it is to execute the tasks.
The following are examples of questions for TB patients:

- What additional functionalities could help you manage your TB treatment? What educational information would you have liked to receive throughout treatment (e.g., at initiation, at four months)? What form of information do you prefer (e.g., text, video, links to websites)? At what time of day are you most likely to read educational messages and what content best matches what time of day? What are your biggest barriers to taking medication daily and what features/functions could address them? What are your concerns using an app for support (e.g., privacy and confidentiality)? What local resources would you want to have links to or more information on? What name would you recommend for the app?

Examples of provider questions:

- What features and functionalities could better help you support patients throughout their treatment? What information do you see as critical to provide to TB patients throughout their treatment? What functions would facilitate you managing a large patient cohort effectively? What name would you recommend for the app?

Method and analysis: All focus group sessions and interviews will be audio-recorded and transcribed verbatim for analysis. Identified glitches, feedback, recommendations will be synthesized for programmers. Steps will be repeated after refinements made.

Aim 3. Assess feasibility, usability, perceived usefulness, and initial efficacy of the resulting product in a pilot RCT. By conducting a pilot RCT, mimicking all of the major essentials of definitive trial, I will determine the feasibility, usability, perceived usefulness, and further refine intervention in congruence with iterative framework and estimate effect size for a future definitive evaluation. The goal is to increase TB treatment success rates to WHO minimum 85% target and reduce rates of poor outcomes (e.g., default, drug resistance).
Sample size: To detect a 15% increase in treatment success with 80% power and an α of 0.05 (two-tailed) a sample size total of 348 is required. Based on recommended sample size calculations for pilot RCT,[56] 9% of sample size of main planned trial is needed, 35 participants. The power calculation is only applicable to the primary outcome of treatment success and not for the subgroup analyses. To be cautious and account for an estimated 20% attrition, the recruitment target was increased to 46.
Setting: Health Region V described above.
Recruitment: All patients newly diagnosed with TB meeting inclusion criteria will be notified of the study by clinic staff and referred to research staff to receive full explanation and have questions answered. Signed informed consent will be obtained for all participants. A recruitment log will be maintained to document screened patients and reasons for declining participation. Patients will be enrolled on an ongoing basis, and recruitment is estimated to be completed in 4 months after start of recruitment.
Inclusion/Exclusion criteria: Patients 18 years of age or older starting TB treatment for the first time, with no known TB drug resistance, HIV negative, owning or having regular access to a smartphone, and who are able to operate the mobile phone to communicate or have someone able to assist. Excluded will be patients who are severely ill (i.e., requiring hospitalization) or reside in the same household with another study participant. Patients with known drug resistance and those with HIV co-infection will be excluded because their care is managed separately and the treatment regimens and duration differ. Screened patients who do not meet study eligibility will have specific screening data (including gender, age and reason for exclusion) entered into the study database which data will be helpful in examining the patient population and feasibility of enrollment criteria.
Randomization: Participants will be randomized to usual care and usual care plus app-based intervention at a ratio of 1:1 in blocks of 10 to ensure balanced representation in both arms. Random allocation sequence will be generated using http://www.randomization.com/. Opaque envelopes sequentially numbered and sealed will be used for treatment allocation concealment. Due to the nature of the intervention, blinding to the group allocation cannot be achieved for research staff. Clinicians will not be made aware of the group allocation unless their patient informs them.
Usual care: Drug treatment and patient monitoring are provided free of charge in the public health system. Usual care consists of outpatient treatment management from the time of diagnosis (unless symptoms are severe and hospitalization is recommended), routine clinical and laboratory tests, and follow-up appointments determined by the clinician. In general, patients receive 1-2 month's supply of medication and are asked to return monthly for follow-up appointments, or earlier if experiencing any problems. Patients with first treatment receive 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 with isoniazid and rifampin daily or 3 times a week.[57] Three of the four medications are provided in a combined pill, therefore testing isoniazid urine metabolite is an indicator of all medications ingestion except for ethambutol.
Procedures: A local health care professional (i.e. nurse) with expertise of TB treatment protocols and the healthcare system will be sought to manage and monitor the messaging system/intervention, and follow-up with participants. The health care professional will be trained on app and platform use, research goals and protocols

by the PI and the regional TB director, Dr. Chirico. Participants will be informed that interaction with the healthcare staff through the app is provided within a clinic-based system and available during office hours (Monday-Friday) and that emergencies must be directed through standard routes. Participants randomized to intervention will receive verbal and written instructions as well as one-on-one demonstration of app features.

Duration and follow-up period: This study is estimated to take about 1 year and will be conducted during years 2 to 3 of this award. Participants will be followed for their full treatment course (approximately 6 months) after entering into the study. Therefore, data collection will be completed about 6 months after the last participant is enrolled into the study.

Outcomes: Table 5 provides an overview of primary and secondary outcomes, hypotheses, operationalization, data collection and analysis methods. **Treatment outcomes** will be measured using standard definitions set by the WHO Standards of TB treatment.[58] The primary outcome for initial efficacy will be *treatment success* based on WHO definitions: *completed* (without bacteriological confirmation) or *cured* (negative sputum smear at 6 months and at least once prior to 6 months). Other treatment outcomes include: failed (sputum smear positive at 5 months or later), died, defaulted (treatment interruption for ≥ 2 months), lost to follow-up (diagnosed, treatment outcome not documented), or transferred out (transferred to another reporting unit and treatment outcome is unknown).[32] To assess **acceptability** (perceived usefulness and ease of use), we will use the Mobile Application Rating Scale (MARS).[59] The MARS has been shown to be highly reliable tool to assess app quality.[59-61] The scale includes three sections and a modifiable app-specific section: classification, quality and satisfaction classification section provides descriptive information about the apps. The objective app quality section includes 19-items divided into four scales: engagement, functionality, aesthetics and information quality. The subjective quality section contains 4 items evaluating the user's overall satisfaction. MARS items are scored using a 5-point Likert scale. The final MARS scores include four subscale scores, a total mean score, subjective quality score and an app-specific subscale that assesses perceived impact on the user's knowledge, attitudes, and intentions to change as well as likelihood of changing targeted behaviors. The MARS total mean score describes the overall quality of an app, while the mean engagement, functionality, aesthetics, and information quality subscale scores can be used to describe its specific strengths and weaknesses. Participants will be asked questions similar to those in Aim 2 and specifically about urine test strip use.

Table 5. Overview of variables, hypotheses, operationalization & data collection

Outcome/Variable	Hypothesis	Outcome measure	Analysis	Measurement point			
				T0	T1	T2	T3
Primary outcomes							
Treatment outcomes	I > C success I < C other	Treatment success rate (%) Other outcomes (failed, default, died, lost to follow-up)	χ^2 test				X
Acceptability*		MARS scale (Likert scale)	Descriptive/ qualitative				X
Program evaluation		Feasibility, ease of use, home drug metabolite testing, recommendations	Descriptive/ qualitative				X
Secondary outcomes							
Global Health PROMIS SFv1.1 WHOQoL-BREF measures	I>C	CDE outcome for self-management		X			X
Level of engagement*		# of messages: notification, side effects, questions	Descriptive	X	X	X	X
TB knowledge	I > C	Change in TB knowledge score	t-test	X			X
Appointment attendance	I > C	Mean proportion	χ^2 test		X	X	X
Cost accounting		Log of intervention costs	Descriptive	X	X	X	X
Subgroup analyses							
Gender	Female>male		χ^2 test				
Age	Older>younger						
Mobile phone access type	Personal>shared						
Time to clinic	≤30> >30 min						

Note: I=intervention, C=control; PROMIS= Patient-Reported Outcomes Measurement Information System; CDE=common data elements; T0 Screening, T1 Baseline, T2, 2 months, T3 6 months, * = data collected from intervention group only

Secondary outcomes include the Global Health Patient-Reported Outcomes Measurement Information System (PROMIS) short form,[62] TB knowledge, level of tool engagement, appointment attendance and cost accounting. The Global Health SF is a recommended outcome measure for self-management, includes 10 items, is available in the Spanish language, and can be integrated into REDCap. TB knowledge will be assessed using items from the Tuberculosis Knowledge Assessment Questionnaire at pre and post-intervention.[25] Items include questions focused on exploring knowledge about: causes and symptoms of TB (5 items), TB transmission (4 items), TB treatment (2 items), and TB prevention (5 items)(Appendix C). The questions are structured to answer (yes, no, I don't know). For those randomized to app, I will evaluate the level of engagement with the intervention (e.g., percentage of notification without a reminder, number of questions, number of reported side effects).

Data collection methods: **Baseline survey** will use NINR common data elements of main and form administration and demographics using the Computer Assisted Interview.[62] The **web based interface** will collect all incoming and outgoing messages and capture instances of participants not notifying. **Medical records or national registry** will be reviewed to collect treatment outcomes, including sputum sample results if collected or rationale why they samples were not ordered (e.g., patient without cough/sputum). Data convergence will be used to assess treatment adherence: notification of self-administration, sputum sample, report of no symptoms, and drug metabolite test results. Metabolite tests will be done in home and time-stamped through app. An **exit survey** will be given to all intervention group participants via app survey or text message and will include: Likert scale questions on acceptance (e.g., was intervention helpful in you completing your treatment, would you recommend to others), open ended questions for problems and recommendations, and 10 item Global Health PROMIS SFv1.1. I will conduct **in-depth semi-structured qualitative interviews** with a minimum of 10 intervention group participants and 5 healthcare team personnel (director, clinician, social worker, nurse, and ancillary staff). I will attempt to interview participants from each of the following groups: had abandoned treatment, had difficulties, and those who completed successfully. Interviews questions include identifying challenges, bottlenecks, if intervention meet needs, confidentiality concerns, and recommendations. Interviews will be recorded and transcribed verbatim.[63]

Data Analysis/Interpretation: All analyses will be based on intention-to-treat. Statistical analyses will be performed using IBM SPSS, version 20 (Chicago, IL). Independent-sample *t*-tests will be conducted for continuous outcomes and 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 less than 0.05 will be set to detect a statistically significant difference for all analyses. I will compare group baseline characteristics including: age, gender, education, travel time to center, take other medication on a regular basis, and baseline TB knowledge. For qualitative data, the transcripts will be entered into Nvivo to organize and iteratively code using thematic and descriptive qualitative methods.[64,65]

Potential Problems and Alternatives: ***Potential IT issues***: Participants may lose or change phones, have dead battery after power outages and loss of service while traveling during the intervention, which occurred in the pilot study. One participant later notified the study team that his phone was stolen. These factors will be documented to understand the degree to which they might affect a larger scale intervention. *Access to mobile phones*: Smartphone access is rapidly increasing globally. Although there are more mobile phone subscriptions than people in Argentina, all potential participants may not have access to a smartphone. In our pilot study there were only 2 (2.2%) who did not qualify for mobile phone access reason. I do not plan to give potential participants mobile phones and will record the reasons for ineligibility into study. Likewise, in a real world situation mobile phones would likely not be allocated to newly diagnosed patients. *Social desirability bias*: Self-reporting adherence by texting-in raises concern for assurance of medication adherence and social desirability bias. When patients receive treatment by self-administration, treatment completion is extrapolated from returning to healthcare visits and picking up ordered medication, conducting sputum smear tests, and reporting of no symptoms. To mitigate social desirability of reporting adherence, we will use data convergence of sputum samples, report of no symptoms, and metabolite test results. *Confounding factors: nonspecific effects of the intervention*. We considered the option of the comparison group to be attention control one; however, because this does not mimic usual care and requires additional resources, we decided against this option.

Feasibility: ***Spanish language/Investigator***: With my experiences living in South America for extended periods (nearly 3 years total) I am proficient in reading, writing, and communicating in Spanish. I will be able to successfully communicate with the healthcare team and participants; however, if language issues arise, Dr. Rubinstein is bilingual with Spanish as his first language and Dr. Chirico is proficient in reading and comprehension of English. The regional TB director and regional TB social worker, with whom I will collaborate, will also be available and will serve as local coordinators, TB experts, and Spanish language verifiers. *Recruitment*: There are over 10,000 new TB cases per year in Argentina, half of which are identified in the Province of Buenos Aires. Health Region V had 1020 cases in the last analyzed cohort. During recruitment phase, in the event that there are insufficient number of subjects, I will enroll additional study sites such as another regional public hospital with the assistance of onsite co-mentor Dr. Rubinstein. He recently completed a prospective cohort study recruiting from 47 different healthcare facilities from 16 different departments. The proposed study will take place at one large public hospitals where there is a higher concentration of cases. *IT logistics:* Refining and adding features to an open-source software is realistic and achievable. Given Dr. Lober's (co-mentor) experiences with successfully implemented apps and international mHealth interventions, he will supervise the IT component of app refining, implementation and trialing.

Timeline: Table 6 provides timeline of the proposed research activities under this award.

Table 6. Timeline of Proposed Research Activities

Activity	Year 1		Year 2		Year 3	
6month increments	1	2	3	4	5	6
Coursework						
Aim 1						
Aim 2						
Aim 3						
Analysis						
Submit R01						
Result dissemination						

Future Directions: If intervention is found to be feasible, acceptable, and efficacious in pilot RCT, a subsequent R01 application will propose a comparative effectiveness evaluation comparing app to mixed strategies and directly observed therapy. The ultimate goal is to plan for a sustainable, scalable, and easily adaptable intervention managed by local healthcare teams. Because of a significant percentage of foreign born TB cases in the US originated from a Spanish speaking country the intervention could be trialed in other Spanish speaking settings where treatment support is limited or could be adapted for latent TB infections in the US (with rates of abandonment over 50%)[66] or other chronic or long term treatment regimens where patients self-administer, have poor adherence, and limited treatment support.

Statistical Design and Power

Sample size: To detect a 15% increase in treatment success with 80% power and an α of 0.05 (two-tailed) a sample size total of 348 is required. Based on recommended sample size calculations for pilot RCT,[55] 9% of sample size of main planned trial is needed, 35 participants. The power calculation is only applicable to the primary outcome of treatment success and not for the subgroup analyses. To be cautious and account for an estimated 20% attrition, the recruitment target was increased to 46.

Data Analysis/Interpretation: All analyses will be based on intention-to-treat. Statistical analyses will be performed using IBM SPSS, version 20 (Chicago, IL). Independent-sample *t*-tests will be conducted for continuous outcomes and 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 less than 0.05 will be set to detect a statistically significant difference for all analyses. I will compare group baseline characteristics including: age, gender, education, travel time to center, take other medication on a regular basis, and baseline TB knowledge. For qualitative data, the transcripts will be entered into Nvivo to organize and iteratively code using thematic and descriptive qualitative methods.

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