STUDY PROTOCOL

Effectiveness of Mobile Application to Improve Adherence to Tuberculosis Treatment: A Study Protocol

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ABSTRACT

Introduction: Tuberculosis (TB) is a leading cause of death due to a single infectious agent. The disease is treatable by a minimum of six months of anti-TB drugs. However, prolonged duration of treatment using directly observed therapy (DOT) causes significant inconvenience to patients and is ineffective in improving treatment outcomes. Therefore, incorporating the Health Belief Model into the development of digital technology could help change behaviour and improve adherence. This study aimed to determine the effectiveness of mobile applications in improving TB medication adherence. **Methods:** This study proposed to conduct a randomized trial among TB patients in the Kota Kinabalu, Penampang, and Putatan districts of Sabah, Malaysia. The eligible sample will be randomly assigned to the mobile application DOT arm and standard DOT arm. The primary outcome is the adherence level calculated by the percentage of medication observed divided by the intended dose taken in two months, with 80% and more successfully observed treatment considered highly adherent. The secondary outcomes are health-related quality of life, satisfaction, and monthly household income. Multiple logistic regression and repeated measures ANCOVA will be used to determine the effectiveness of interventions to achieve primary and secondary outcomes. **Discussion:** The findings from this study could hopefully provide insight into rethinking TB care delivery to achieve better TB treatment outcomes. **Trial Registration:** This study protocol has been approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-21-01949-73X) and registered with ClinicalTrials.gov (NCT05259254).
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Keywords: Tuberculosis, Medication adherence, Digital adherence technology, Health belief model, Direct observed therapy

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Globally, TB is among the top ten causes of death and a leading cause of death due to a single infectious agent (1). The World Health Organization (WHO) estimated that ten million people fell ill due to TB infection in 2019, causing death to 1.2 million people(1,2). TB infection is treatable using a standard medication for at least six months, which can pose significant challenges to TB patients. A previous study estimated that treatment loss mainly occurs at the point of treatment completion, with only 53% of overall TB cases being able to complete treatment (3). Failure to complete anti-TB therapy can lead to drug-resistant TB, complications and death (4,5).

Hence, adherence to TB therapy is critical for TB treatment success. However, non-adherence remains a significant problem. Non-adherence could be attributed to several factors, including psychosocial (e.g., forgetfulness, psychological distress, alcohol, and cigarettes use) (6–8), individual (e.g., comorbidity, poor knowledge, misperception) (7,9), therapy-related (e.g., side-effect) (10,11), and health system (e.g., poor patient-provider interaction, logistic issue, and inflexible schedule) (10).

In Malaysia, treatment default contributes to a substantial proportion of unsuccessful TB treatment outcomes. A retrospective cohort study in Malaysia from 2014 to 2017 reported that 5.3% of the overall cohort was lost to follow-up (12). Meanwhile, in Sabah, a Malaysian state, the unsuccessful treatment outcome rate is 17%, where 2% (n=663) from the overall cohort was reported

to be lost to follow-up (13). Even though the percentage appears to be low, TB deaths have been increasing trend, from 9.9% (2012 cohort) to 10.2% (2014 to 2017 cohort) (12,14). The increased trend of TB mortality warrants further efforts to mitigate these issues, including emphasizing TB treatment adherence.

Since the 1990s, WHO has recommended directly observed therapy (DOT) to ensure TB medication adherence. The DOT aims to ensure patients complete their entire TB treatment course and monitor for any side effects or complications. DOT is usually operationalized in either: (1) Health facility-based DOT: patients visiting a health facility to take their medication under the healthcare worker's direct supervision, and (2) Community-based DOT: patients receiving medication from a trained volunteer who visits their home or workplace to observe medication intake. However, despite DOT's importance, it causes inconvenience, is considered intrusive, causes stigma, and leads to additional costs (15,16). Furthermore, previous studies reported that DOT by various providers has not substantially improved treatment success than self-administered therapy (16–18).

A mobile application called "PatuhTB" has been developed through collaboration with experts from the Faculty of Computing and Informatics, Universiti Malaysia Sabah. The mobile application contents were qualitatively obtained among the TB experts using the nominal group technique (NGT). Through the NGT, the experts have identified four essential features which align with the health belief model (HBM): (1) health education, (2) a reminder system, (3) a feedback system, and (4) video observed therapy (VOT).

The health education section contains basic knowledge about TB, its medications, the benefits of medication adherence, and the severe impact of not adhering to treatment. This section applied three HBM constructs: (1) perceived susceptibility of the likelihood to be affected by the impact of medication non-adherence, (2) perceived seriousness of an illness that is arising from treatment non-adherence, and (3) perceived benefits that the recommended health behavior is effective to prevent the impact of non-adherence to treatment. The reminder system lets patients set up mobile applications for medication intake notifications. This section serves as a cue for action (another HBM construct), providing a stimulus to trigger recommended behavior. The VOT allows patients to submit pre-recorded video clips of medication ingestion through the mobile application. In addition, a feedback panel was also included to enable the patients to report any problems related to the medication or any technical issues. This section signifies another HBM construct: the perceived barrier to anti-TB medication adherence.

Digital adherence technology (DAT) has been introduced to improve TB medication adherence, with diverse levels of effectiveness (19–21). According to the Department of Statistics Malaysia's survey, smartphone access and internet connectivity were substantially increased (22). Even though affordability, low digital literacy level, and perceived lack of relevance might serve as a barrier, the gap in mobile phone usage has decreased from 24% to 10% worldwide, mainly contributed by increased affordability and internet access (22). Malaysia's high mobile phone usage and internet connectivity provide an opportunity to improve TB patient care. However, the DAT developers may have overlooked the need for a behavioral change model in their planning. This oversight resulted in the technology being inefficient in altering behavior and justifying its cost (23). Thus, incorporating the behavioral change model into the development of DAT could provide the best medication adherence outcomes. Studying the DAT's effectiveness in the local population could provide knowledge to develop strategies to improve TB treatment success. Furthermore, to our best knowledge, no RCT was published in Malaysian settings to identify the effectiveness of DAT in improving TB medication adherence.

Besides medication adherence, measuring health-related quality of life (HR-QOL), patient satisfaction, and patient income is crucial. Measuring HR-QOL can provide information on how the DAT affects the patient's physical, psychological, and social well-being. This information can help healthcare providers better understand patients' needs and develop targeted interventions. Patient satisfaction is crucial for TB treatment success, which the use of DAT can influence. It provides information on whether the patient feels supported and engaged in their treatment, which helps identify improvement areas. Finally, measuring a patient's income is to understand the potential financial implications of the interventions. The researchers aimed to determine if the use of DAT can help alleviate the financial burden associated with TB treatment. This research can provide insights into the economic impact of interventions and inform policymakers and healthcare providers about strategies to support patients with limited financial resources, ultimately improving treatment outcomes.

This study aims to determine whether the mobile application DOT enhances adherence to anti-TB medications compared to standard DOT. Another study objective is to determine whether the mobile application DOT can improve the patient's health-related quality of life (HR-QOL), satisfaction, and income compared to the standard DOT.

MATERIALS AND METHODS

Study design and location

This study will adopt a randomized, open-label,

controlled trial. The study will be conducted in three public health clinics providing TB patients care: Kota Kinabalu, Penampang, and Putatan District of Sabah. These facilities were purposively selected due to their relatively highest number of TB cases than other health facilities in the district, based on information from Sabah State Health Department, up to the 12th epidemiology week year 2021. The districts' selection is because these locations were mainly located in urban areas with relatively good internet connectivity, and the patients were perceived to have good digital literacy and mobile phone usage.

Duration of observation

This study planned to observe the participants for two months from the date of randomization. Currently, there is no specific duration to monitor the medication to be adequately powered to detect a significant difference between the treatment and control groups while minimizing the risk of bias due to external factors (24). Based on previous RCTs, VOT was significantly improving medication adherence measured at two weeks (25), one month (19), and two months (21). Therefore, the researcher has chosen the two months as treatment observation duration as it might be reasonable to believe that our mobile application can change behavior within this duration.

Study population

The study population is all TB patients receiving standard anti-TB treatment in the study location regardless of anatomical classification and treatment phases. Inclusion criteria including those with age 18 years old and above and receiving standard anti-TB therapy according to Malaysian guidelines. Figure 1 shows the list of exclusion criteria. Meanwhile, the withdrawal criteria are the patient's willingness to withdraw from participating in the study.

Sample size

The sample size was calculated using G*Power software version 3.1.9.6 for differences between two independent proportions. Given the proportion of successful primary outcomes is 75% (in the treatment group) and 60% (in control groups) (21), with type 1 error set at 0.05 and 80% power to find 15% differences in the proportion of successful primary outcome, the estimated sample size required is 120 per treatment arm. After the allowance of 20% drop out, the sample size required is 150 per arm.

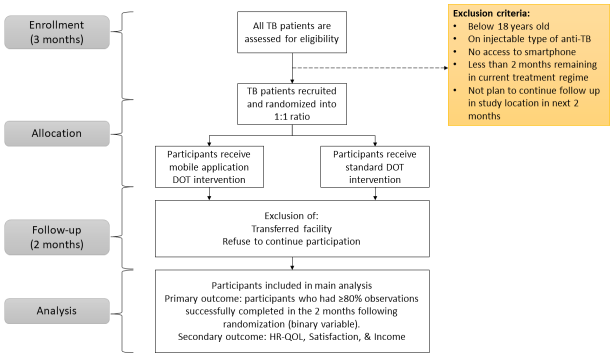

Figure 1: Study Participants' Enrolment and Randomization

Randomization

All eligible participants will be randomized to either mobile application DOT or standard DOT. The randomization will be performed using a web-based program (26), where a random allocation sequence will be generated using a computer-generated randomized list. Subsequently, an opaque envelope will be sequentially numbered and sealed for allocation concealment. The research team will recruit the potential TB patients identified as eligible study participants. Blinding is not done because of the nature of the intervention.

Sampling method

Proportionate stratified sampling was used to determine the sampling population for each clinic. The population strata proportions were determined by the number of TB cases registered in each study location. Using the data from the TB surveillance system (MyTB), up to the 12th epidemiology week of 2021, the proportion of TB cases registered in Klinik Kesihatan (KK) Luyang was 49.3%, followed by KK Penampang (35.3%), and KK Putatan (15.3%). Therefore, the number of TB patients that should be recruited from KK Luyang was 148, KK Penampang (106), and KK Putatan (46).

Study procedure

Eligible study participants will be randomized to two intervention groups: standard DOT and mobile application DOT. Figure 1 shows the summary of the study procedure.

a. **Standard DOT:** Patients diagnosed with TB will be provided with anti-TB therapy as an outpatient if they are not in a life-threatening condition. The patient will receive medication monitored closely through DOT by healthcare staff or family members. Observation of medication consumption will be conducted daily. The DOT observers will sign the DOT diary provided to the patient to verify that the patient has consumed the drug. An observer will complete the DOT observation record until the end of the study period.

b. **Mobile application DOT:** TB patients will be asked to download and install the mobile application. Researchers will teach patients how to use the mobile application and record and send videos of every dose of medication ingested daily. Participants will be trained to take medicines from the blister pack, say the drug's name, the number of pills, and the size and colour of the medication ingested. Participants must also show their mouth is empty by opening and sticking out their tongue. The participant must record and send a self-recorded video of daily medication consumption. The researcher will subsequently view the video through a

password-protected website. The observer will complete the observation of medication intake until the end of the study period.

Data collection instrument
The data will be collected at the baseline, at two months following randomization, and DOT documentation throughout the study duration:

a. Baseline information: This data will be collected during the enrolment of participants in the study. Data that will be collected as follow:
i. Sociodemographic: This information will be collected through interviews or medical records.
ii. Behavioural: This information on alcohol intake, cigarette smoking status, and drug abuse history will be collected through interview.
iii. Clinical information: This information will be assessed from the patient's clinical record. The data collected includes the type of TB diagnosis (pulmonary or extrapulmonary, sputum smear-positive or negative), comorbidity, and TB clinical risk factors.

b. Data collected both at baseline and two months following randomization:
i. Health-related quality of life (HR-QOL): HR-QOL will be assessed using a standardized EUROQOL EQ5D-3L instrument. The questionnaire was validated and available in Malay and English language. The translated version was verified and certified by EuroQoL Group Translation Committee. The questionnaire consists of two pages; the EQ5D descriptive system and the EQ5D visual analogue scale (EQ-VAS). The EQ5D descriptive system comprises five dimensions that evaluate the different aspects of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three severity levels: no problem, mild to moderate, and severe. The respondents will be asked to indicate their health status by checking the box against the most appropriate answer for each dimension. The EQ-VAS assesses the respondent's self-rated health in a vertical visual analogue scale, with two endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine.'
ii. Satisfaction: Participants will be assessed using the Short-Form Patient Satisfaction Questionnaire (PSQ-18), initially developed by Marshall and Hays (27). This questionnaire was widely used to evaluate health service satisfaction in clinical settings. PSQ-18 consists of eighteen items with seven dimensions: general satisfaction, technical quality, interpersonal manner, communication, financial aspect, time spent with a healthcare provider, and accessibility and convenience. A five-point Likert scale will be used to score the eighteen items. One is reflecting on "strongly agree," two (agreed), three (neutral), four (disagreed), and five reflected "strongly disagree." A higher score reflects greater satisfaction with medical care. After item scoring, items within the same subscale were averaged to create the seven subs-scaled scores.
iii. Patient's household income: Participants will be asked to estimate how much monthly income they obtained in previous months due to their employment in Ringgit Malaysia (RM).

c. Data collected continuously during the study period:
Doses of medication ingested by the patient at both treatment and control arms. The number of drugs taken is observed through a video uploaded using a mobile application in the intervention arm or DOT taken in the control arms. The data will be obtained for the calculation of treatment adherence.

Outcome measures
The outcome of this study can be divided into primary outcomes and secondary outcomes:

Primary outcome: successfully completing 80% or more of the treatment observations scheduled in the two months following randomization (binary outcome variable). This primary outcome measure assesses the level of adherence to anti-TB treatment. The decision to use 80% as a cut-off point is based on previous literature, which concluded that adequate adherence was defined by the threshold of 76% to 80% of the intended dose taken (28). According to the Malaysian national tuberculosis guideline, if medication interruption is less than 20% during maintenance, the treatment might be stopped, provided the sputum AFB smear is negative. Thus, an 80% cut-off point is selected as a proxy measure to determine medication adherence. 80% and more is considered high adherence and less than 80% is regarded as low adherence to medication. Treatment observations occurring when the patient is admitted to a hospital or prison are considered successfully observed in both intervention arms.

Secondary outcome:
i. HR-QOL: participants will be compared in both trial arms regarding their time trade-off utility score and visual analogue scale. The time trade-off is quality-adjusted life years using specific weight (Malaysia-specific weightings), which represents the health state of patients, ranging from 0 (state equivalent to death) to 1 (full health state). Meanwhile, for the visual analogue scale, the health state will range from 0 (worst health state participants can imagine) to 1 (best health state participants can imagine) (continuous variable).
ii. Patient satisfaction: the outcome measure will be a continuous variable. A higher score will reflect better satisfaction with the health service provided.
iii. Income: the outcome measure will be a continuous variable. The outcome variable will be how much income the participants obtained from their employment (in Ringgit Malaysia). The measurement is based on subjective approximation by the participants.

Details of the study procedure

Strategy to achieve an adequate number of participants: The investigator aimed to collaborate with the Sabah State Health Department and respective Area Health Office to recruit sufficient participants.

Criteria to discontinue and strategy to address non-adherence to intervention: Definition of non-adherent to medication: missing three daily doses within one week or two doses per week in two consecutive weeks (29).

Suppose a participant in the intervention arm meets the definition of non-adherence to medication. In that case, the observer will attempt to re-engage the participants through a face-to-face meeting to identify causes of non-adherence and to provide re-training. Suppose the participants agreed to be re-training but have subsequent episodes of non-adherence. In that case, the participants will be referred to healthcare staff to determine the preferred mode of continuing to support adherence for the remainder of their care. The participants will also be reassessed whether their non-adherence is due to the mobile application technical issue. If they do and the problem is persisted, the participants will be switched to standard DOT.

Participants that remain non-adherent to observation after re-training will be regarded as intervention failure for the intervention group or DOT failure for the control group for the primary outcome. Furthermore, participants meeting the criteria of non-adherence also be referred to a health inspector for the subsequent management of non-adherence as stipulated in the Prevention and Control of Infectious Disease Act 1988 under Malaysian law.

All study participants are allowed to withdraw anytime during the study period. Suppose the participant is still keen to withdraw after the counseling, the treating doctor will be informed, and the patient will be switched to standard DOT.

Following the study participants' withdrawal, new participants will be recruited, using a similar method for participant randomization to ensure uniformity of study participants' selection.

Strategies to improve adherence to intervention: Training will be provided. The participants will be ascertained whether they understand how to use the mobile applications and submit video clips of them taking medication. The participants will also receive a pamphlet about basic mobile application information. Additional training also will be provided if the participants fail to submit satisfactory video clips.

Participant's timeline:
Study participants' timeline is shown in Figure 2.

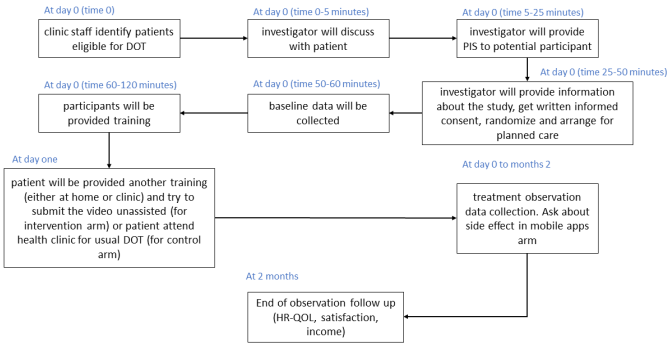

Figure 2: Study Participants' Timeline

Patient care cost: Malaysian health services provide TB treatment free of charge. Therefore, the patient incurs no anticipated additional cost following the TB diagnosis. TB patients randomized to the mobile application can use the application with no extra charges. However, if the study participants wish to get treatment from a private general practitioner, the expenses are the sole responsibility of the respective patient. The participants in this study are not expected to receive any reward.

Data analysis

The data will be analysed using International Business Machine Statistical Program for Social Sciences (IBM SPSS) version 27. Initially, the data will be explored and cleaned to ensure no missing data. A histogram and Shapiro-Wilk test will assess the numerical variables for normal distribution. The variables will be described in mean and standard deviation for normally distributed data or median and interquartile range for not-normally distributed data. The categorical variables will be presented as numbers and percentages. The baseline characteristics of participants will be compared to ensure that the participants have balanced randomization. Statistical analysis will be conducted accordingly, with the alpha value (type 1 error) set at 0.05. The p-value obtained below the alpha value will be considered statistically significant. The logistic regression analysis will be used to analyse the primary outcome while adjusting for potential confounders. Meanwhile, a repeated measures analysis of covariance (RM-ANCOVA) will be used to compare the trial groups' secondary outcome measures (HR-QOL, satisfaction, and income). The main and sensitivity analysis approach will be used in data analysis to handle missing data. For the main analysis, those in the mobile application group will be classified as successfully completed if all the medications were observed or if the video uploaded by participants was received but could not be read. This is because there will be anticipated technical issues, and the participants have no control over the technical issues. The researcher decided to accept the video received but unable to read as 'observed medication intake' as we want to consider the behavioural changes effect from the use of different intervention, while excluding the

technical issue impact. Meanwhile, sensitivity analysis is only considered for uploaded and videos that can be read as successfully completed.

Data Management Plan

All participating patients will be assigned a unique identification (ID) number. The ID number will be associated with other information and entered into computer software. The link between participants' personal information and unique ID number will be kept separately in a compact disc (CD) secured using password protection. All the paper-collected data will be stored in locked file cabinets, only accessible by the principal investigator.

Subsequently, regarding access, sharing, and re-use, the principal investigator is the main responsible party for managing the data. Upon publication, the data is not expected to be publicly accessible. However, if the data is required to be accessible for publication, prior MREC permission will be obtained. Furthermore, the investigator must ensure that the personal information will be de-identified from the data before publication. The timeframe of the data accessibility will be reviewed accordingly.

Ethical Approval

Researchers will adhere to the principles of the Declaration of Helsinki. The potential participants will be informed regarding the research and the risk and benefits of the study before their recruitment. They will be provided a patient information sheet and consent form to be signed if they agree to participate. The participants are assured that they can withdraw from participating in the research anytime during the study. This study protocol has been approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-21-01949-73X) and registered with ClinicalTrials.gov (NCT05259254).

Quality control measures

Attrition bias: there is a possibility of participants dropping out of the study. Therefore, the investigator wants to ensure they are capable and fully motivated to receive treatment before recruitment. For those selected for the mobile application DOT, a training and information pamphlet will be given to ensure they are knowledgeable and can refer to the information in the leaflet if they forget. Attempting to call the patient will be done if they miss one day of observation. Furthermore, sensitivity analysis and multiple imputations during data analysis will be used to infer missing data.

Social interaction: there is a possibility that participants knew they were not getting the intervention that they wished, thus performing poorly in their trial arm. Therefore, patients will be reminded not to disclose their treatment to others during recruitment.

Timeline

Recruitment of participants is still ongoing and is expected to end by June 2023. The data analysis will commence by July 2023, and the study article write-up will be completed by August 2023.

DISCUSSION

Implementation of DAT might provide a good strategy for improving TB medication adherence. Before the initiation of the study, a mobile application was developed, which took the behavioural change theory into the development process. The developed mobile application provides additional value to enhance behavioural changes by adding extensive features. Other types of digital adherence technology, including electronic pillboxes, biometric technology, and wireless-enabled medication packaging, might have advantages in medication adherence (30). However, those interventions can be costly and may not be accessible to all patients.

In comparison, a mobile application with comprehensive features can provide medication reminders, VOT, feedback systems, and health education all in one place, simplifying patient treatment. Moreover, its usage is free of charge. However, there are also potential disadvantages, such as the need for patients to have access to a smartphone and the potential for technical difficulties. Thus, implementing the RCT as proposed will provide substantial insight into the effectiveness of the mobile application on TB medication adherence, health-related quality of life, patient satisfaction, and income.

This study is not without limitations. It is difficult to blind the patients, researchers, or healthcare providers to the interventions. This study also doesn't investigate variations in sputum smear conversion rate, treatment completion, loss to follow-up, treatment relapse, or drug resistance development. However, it is reasonable to assume that greater treatment adherence might improve all these outcomes. Moreover, this study cannot ascertain whether the observed medication in the mobile application group accurately shows the patient taking the drug on the same day. Therefore, the researcher assumed the medication was taken on the same day by referring to the video submission date.

CONCLUSION

Poor adherence to TB medications is still a significant concern. The expansion of DOT using mobile applications incorporating the behavioural change model into their product is expected to help improve medication adherence. The proposed research is essential to explore the effects of the intervention and can be used to enhance DOTs implementation in local settings.

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