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STUDY PROTOCOL

**Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment
Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An
Effectiveness-Implementation Science Study**

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Name and Institution of Principal investigator(s):

Koh Hui Moon, *Department of Pharmacy, Hospital Sungai Buloh, Selangor (Corresponding PI)*

Name and Institution of Co-Investigators:

Dr Benedict Sim Lim Heng, *Department of Medicine, Hospital Sungai Buloh, Selangor (Site PI)*

Dr Annabella Edwin, *TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor*

Abby Ang Shoon Yeun, *MTAC HIV/TB Unit, Department of Pharmacy, Hospital Sungai Buloh*

Dr Izzah Nurhanim Azizan, *TB liaison officer, Public Health Unit, Hospital Sungai Buloh*

Hema Manusri a/p K.Vijayan, *Department of Medicine, University Malaya, Kuala Lumpur*

Dr Nor Arisah Misnan, *Department of Medicine, Hospital Sungai Buloh*

Preethi A/P Raghavan, *MTAC HIV/TB Unit, Department of Pharmacy, Hospital Sungai Buloh*

Farah Syakirah Ahmad, *MTAC HIV/TB Unit, Department of Pharmacy, Hospital Sungai Buloh*

Associate Professor Reena Rajasuriar, *Department of Medicine, University Malaya, Kuala Lumpur*

Professor Asrul Akmal Shafie, *Director of the Institutional Planning & Strategic Centre, University Sains Malaysia, Pulau Pinang*

Associate Professor Lee Yew Kong, *Department of Primary Care, University Malaya, Kuala Lumpur*

Professor Frederick L. Altice, *School of Public Health, Yale University USA (External advisor)*

Name and address of Sponsor:

Hospital Sungai Buloh, Jalan Hospital, 47000 Selangor

University Malaya, 50603 Kuala Lumpur

Study site: Hospital Sungai Buloh, Jalan Hospital, 47000 Selangor

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List of Abbreviations

ADR	Adverse drug reaction
CARE-TB	Comprehensive Digital Adherence and Remote Engagement Strategy
CEA	Cost effectiveness analysis
DALY	Disability-adjusted life years
DAT	Digital adherence technology
DOT	Directly observed therapy
EPIS	Exploration, Preparation, Implementation, Sustainment Framework
FGD	Focus group discussion
HCP	Health care provider
HIV	Human immunodeficiency virus
HRQOL	Health related quality of life
ICER	Incremental cost effectiveness analysis
IRB	Institutional Review Board
KII	Key informant interview
MA	Medical assistant
MOE	Ministry of Education
MOH	Ministry of Health
PI	Principal Investigator
PLHIV	Person living with HIV
PTB	Pulmonary tuberculosis

QALY	Quality-adjusted life years
SAT	Self-administered therapy
SMS	Short messaging service
SOC	Standard of care
TB	Tuberculosis
UM	University Malaya
USM	University Sains Malaysia
VOT	Video-observed therapy
WHO	World Health Organization

Executive Summary

The gold standard for TB treatment requires directly observed therapy (DOT), which means a trained health worker observes the patient swallow each dose of medication every day for 2 months. Despite the practice of DOT in Malaysia, 1 in 20 patients are lost-to-follow-up and non-adherent to treatment. Sub-optimal adherence due to poor treatment acceptability and social desirability promotes TB treatment failure, disease relapse, on-going transmission, drug resistance, and death. Telemedicine offers a flexible and less invasive option to support TB treatment adherence. Despite a high internet (97%) and smartphone (97%) penetration rate, the practical implementation of digital adherence strategies to support and monitor TB treatment remains untested in Malaysia. We propose to design, implement, and measure the effectiveness of a comprehensive, pharmacist-led digital solution for TB treatment support called CARE-TB which combines a package of asynchronous video-observed therapy, digital reminders, telecounselling and e-learning. In addition to delivering health education and counselling, pharmacists will monitor and provide feedback for asynchronous TB VOT. As proficient drug experts, they are ideally positioned to oversee treatment and promptly assist with any complications that may arise. This task-shifting aspect is a key focus of this study. Using the Exploration, Preparation, Implementation and Sustainment (EPIS) framework, we aim 1) To identify patient and provider-level facilitators and barriers to CARE-TB adoption via qualitative evaluation and to design a stakeholder-informed implementation strategy, (2) To implement CARE-TB and assess its effectiveness by evaluating (i) implementation outcomes, (ii) patient health outcomes, and (iii) service outcomes, and (3) To evaluate the cost-effectiveness of CARE-TB compared to standard of care from a societal perspective. This study will use a framework-guided implementation strategy to test the adoption of an innovative digital solution to address a perennial problem in the provision of TB care in Malaysia, while utilizing existing personnel and resources in one of the busiest TB treatment centres in the country. This will help inform the adaptation of similar programs in other TB treatment sites and with more extensive rollout, have the potential to stem TB as an on-going public health threat in Malaysia.

(342 words)

SCHEMA

Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Purpose: Despite a high internet and smartphone penetration rate, the practical real-world implementation of digital adherence strategies to support and monitor TB treatment remains untested in Malaysia. We propose to design, implement, and measure the effectiveness of a comprehensive, pharmacist-led digital solution for TB treatment support called CARE-TB which combines a package of asynchronous video-observed therapy, digital reminders, telecounselling and e-learning to improve adherence to TB treatment.

Design: Multi-methods effectiveness-implementation (Type 2) study

Study population: This study is conducted among TB and TB/HIV-coinfected persons with confirmed pulmonary TB, who are receiving care in Hospital Sungai Buloh. The hospital provides care for approximately 300 TB patients annually. Selected health care providers (HCPs) which includes doctors, pharmacists, nurses, medical assistants, HIV peer support counsellors and hospital administrators involved in the planning and delivery of TB/HIV care will be invited to provide stakeholder feedback during the study. This study will also include feedback from policymakers from the state and federal health departments and community representatives supporting the delivery of TB care services to adults living with or without HIV.

Study size: The study has 3 consecutive phases: (1) *Pre-implementation*: Up to 20 new TB patients, 20 healthcare providers and administrators from TB clinics, 6 policymakers, and 5 community representatives will be recruited to identify determinants to the uptake of CARE-TB strategy through individuals interviews/FGDs. (2) *Implementation*: Utilising feedback from phase 1, a stakeholder-informed digital adherence support programme will be implemented at the site. Up to 80 TB patients will be invited to join the digital adherence programme. Another 80 patients will receive the standard of care and be enrolled as controls. (3) *Post-implementation*: The implementation, sustainability and scale-up of the intervention will be assessed among up to 40 TB patients, 30 healthcare providers and clinic administrators, 4 policy makers and 4 community representatives through interviews and focus group discussions.

Study duration: Study data collection and analysis will be conducted over approximately 27 months

Primary objectives:

- (1) To identify patient and provider-level barriers and facilitators to the uptake of the CARE-TB strategy (VOT, digital reminders, telecounselling and e-learning) and to design a stakeholder-informed implementation strategy to address these barriers,
- (2) To assess the implementation and effectiveness of the CARE-TB strategy by evaluating (i) implementation outcomes, (ii) patient-level outcomes, and (iii) service outcomes, compared to the standard of care, and
- (3) To evaluate the cost-effectiveness of the CARE-TB strategy compared to standard of care from a societal perspective.

Study design overview: The Exploration, Preparation, Implementation, Sustainment (EPIS) framework will be used to guide the design of the overall strategy, implementation process and outcome evaluation. Pre-implementation interviews of patients and providers will assess facilitators and barriers to integrating CARE-TB strategy in TB clinical setting and inform the design for implementation. These interventions will be implemented at the study site for a 12-month period, during and after which the feasibility, acceptability, and sustainability of the interventions, and fidelity to the intervention will be assessed through patient, provider, policymaker, and community representative interviews and discussions. Cost will be assessed throughout preparation and implementation phases of the interventions. Pre- and post-implementation site and participant medical record data will be compared to assess service and patient-level health outcomes, and intervention effectiveness.

1.0 BACKGROUND

1.1 Introduction

Despite being a curable disease, tuberculosis (TB) affects an estimated 10 million people globally and 1.6 million people died from it in year 2021 ¹. Southeast Asia accounted for 45% of global incident cases, and according to WHO staging, Malaysia falls into the category of moderate to high TB burden countries. Estimates of TB incidence in Malaysia increased by 10% from 30000 cases (92/100,000 population) in 2020 to 33000 cases (97/100,000 population) in 2021 ^{2,3}, indicating a significant growing problem. Among all incident cases of TB, 5% are in people living with HIV (PLHIV). Additionally, Malaysia observed a 25% rise in TB deaths in 2021, totalling 2,530 fatalities compared to the 2020 deaths in year 2020.

Malaysia faces a rising burden of TB disease with a treatment failure rate of more than 10%, despite the availability of effective medications which is provided free to all TB patients ⁴. Ensuring high adherence rates to a minimum six-month of standard anti-TB therapy is crucial for TB treatment success; yet 1 in 20 patients were lost to follow-up based on a cohort study of the Malaysian national registry from year 2014 till 2017 ⁴. TB treatment complexity, tolerability issues, and long duration make adherence challenging ⁵. This is further complicated by issues such as mental health disorders and stigma common to both people living with HIV (PLWH) and TB ^{6,7}. Poor adherence promotes TB treatment failure, relapse, transmission, drug resistance, and death, posing a significant public health threat ⁸. The cost of treating an uncomplicated case of TB ranges from USD 727.3 to 916.4 ^{9,10}, but increases significantly, reaching 28 times the initial cost, when multidrug-resistant TB treatment is necessary¹¹.

To overcome issues of adherence, WHO recommends directly-observed-therapy (DOT) whereby treatment is supervised daily in-person by a healthcare provider or lay-person for at least the first two months ¹². Yet, in addition to the fact that DOT is resource-intensive and a potential cause of stigma and disease transmission, DOT was found to have limited benefits and not better than self-administered therapy in terms of adherence, cure, and treatment completion rates ¹³. However, this strategy is the main mode of treatment support utilised by TB programs in Malaysia.

Based on positive experiences across diverse income countries, the World Health Organization has incorporated digital adherence technologies such as digital reminders, video-observed therapy (VOT), and electronic monitoring into its guideline on tuberculosis care and support interventions ¹⁴. While singular interventions like VOT showed mixed results in health outcomes like cure and treatment completion, employing a combination of adherence methods, including but not limited to digital technologies, displayed higher rates of adherence, increased acceptability, and improved cost-effectiveness ^{8,15}. In Malaysia, the effectiveness, practical implementation and cost assessment of digital adherence support and monitoring to optimise adherence to tuberculosis (TB) treatment remains unexplored.

1.2 Literature Reviews

Retention on therapy and medication adherence

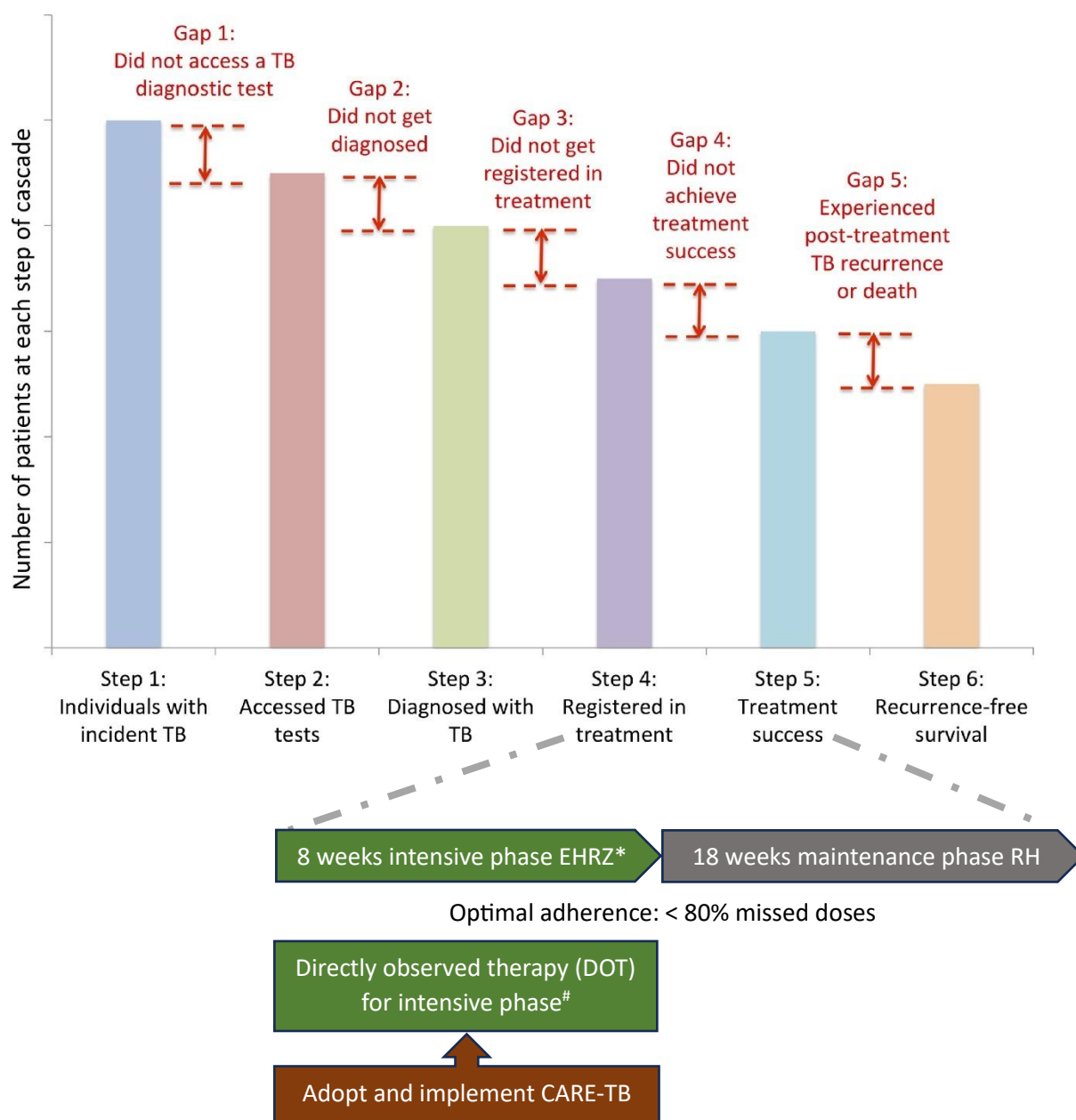


Figure 1: TB Care Cascade for active TB (Source: R. Subbaraman et al., 2019)

**TB medications – Ethambutol(E), Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z); [#]Treatment adherence in most critical in the intensive phase to ensure TB treatment success and reduced transmission risks.*

Closing the gap in the TB care cascade between patients registered for treatment and treatment success has been the central focus of TB control programs worldwide and TB research ¹⁶. This gap refers to unsuccessful TB outcomes including treatment failure, death, and loss to follow-up due to multifaceted factors such as non-adherence, timing of treatment, disease severity, comorbidities, substance or alcohol addiction, psychosocial issues, and malnutrition. TB treatment non-adherence has been associated with death, treatment failure and lower cure rates ¹⁷. Non-adherence is primarily characterized as missing <80 or <90% of the prescribed doses occurring either during the 2-months intensive phase TB treatment with

a four-drug regimen (ethambutol, rifampicin, isoniazid and pyrazinamide) or 4-months maintenance phase treatment with a 2-drug regimen (rifampicin and isoniazid). Higher rates of death and treatment failure were significantly associated with timing of missing doses during the intensive phase as opposed to during the maintenance phase and with HIV co-infections.

Ensuring adherence is a crucial element of the WHO's 'End TB Strategy' ¹⁸. The strategy's first pillar highlights the importance of context-specific supportive treatment supervision to aid patients in consistent medication intake, aiming to facilitate recovery and prevent drug resistance. A context-specific approach means taking a patient-centred approach by understanding the individual patient's needs, values and preferences to tailor treatment adherence interventions such as education, communication, material and psychosocial support, DOT or VOT, while considering the health system capacity and capability. Adherence to treatment can be largely influenced by four broad categories of factors, namely structural, personal, social and health system factors ¹⁹ (Table 1). Given the diversity of possible adherence barriers, strategies that address multiple facets are needed ¹⁸.

Table 1: Factors influencing patient adherence to TB treatment (adapted from: Munro et al.,2017)

Structural	Personal	Social	Health system
Poverty	Motivation	Family and community support	Organization of treatment and care
Gender discrimination	Knowledge	Stigma	Knowledge provision
Costs	Beliefs		Geographical and financial access
	Attitudes		
	Interpretation of illness and wellness		

Systematic reviews found that patients who received a package of combined adherence interventions, including but not limited to digital support, achieved higher rates of treatment success, treatment completion, cure, and adherence, as compared to any single adherence support solutions ^{8, 12}. These combined interventions encompass elements such as patient education, staff training, digital monitors or tracers, psychological support, counselling, and material assistance. WHO recommends that the interventions should be selected based on individual patient needs, provider resources, and implementation conditions. In this study, we will put together a multifaceted digital strategy to be delivered in a manner which can address the structural, personal, social and health system barriers by combining asynchronous video-observed therapy (VOT), telecounselling, medication-taking reminders and online educational package. The evidence supporting each component of this strategy compared to current standard of care is elaborated below;

(a) Digital adherence technologies (DAT) – VOT plus adherence reminders vs directly observed therapy (DOT)

Current TB medication adherence strategies in Malaysia include directly observed therapy (DOT) at clinics or hospitals by healthcare providers, modified DOT by caregivers, and home visits; all of which require the physical contact of the observer/healthcare provider with the patient taking his/her medication in real-time. However, these strategies face challenges related to logistics, cost, time constraints, lack of privacy, disease transmission risk, stigma, and limited-service capacity. These challenges were especially amplified during the COVID-19 pandemic and lockdowns when it became clear that such strategies to optimize adherence were impractical and unsustainable as the typical duration for the intensive phase treatment of TB is two months. A prior Cochrane Review concluded that traditional DOT approaches were no better than self-administered therapy in terms of treatment adherence, and policymakers should contemplate a shift from this approach ¹³.

Video-observed therapy (VOT) together with medication-taking reminders reduce the need for a patient to attend healthcare facilities for direct observation or counselling ¹. Not requiring physical presence at a healthcare facility saves on transportation and work disruption, enhances privacy, and improves accessibility for communication. It also reduces clinic waiting times and lowers the risk of disease transmission, such as COVID-19 and untreated tuberculosis while also reducing stigma. Asynchronous methods like video recordings and scheduled medication-taking reminders demand fewer human resources while enabling medication tracking and digital trace of dosing history. This eliminates the inconvenience of scheduled meetings associated with synchronous VOT.

Patient health and service outcomes

A meta-analysis of 9 studies which compared VOT to directly-observed therapy showed that VOT improved medication adherence (RR=2.79, 95% CI=2.26, 3.45, I²=25%) and proportion of doses (weighted mean difference=0.22, 95% CI=0.06, 0.39, I²=96%) observed despite similar completion rates (RR=1.33, 95% CI=0.73, 2.43, I²=98%) ²⁰. A multicentre, randomized trial showed higher adherence rates with VOT; whereby 70% of patients on VOT successfully completed ≥80% of a 2-month observation compared with only 31% of those on DOT (OR=5.48, 95% CI 3.10 to 9.68) ²¹. On contrary, SMS reminders did not significantly improve adherence ^{15, 22}.

Implementation outcomes

A real-world study assessed the reach and effectiveness of VOT versus DOT under routine implementation in a busy, urban TB program at a health department in California, USA ²³. Individualised decision on DOT modality (VOT, in person DOT or self-report) were made via shared decision making by the program and patient. Out of the 163 TB patients, 94 individuals (58%) opted for VOT as part of their treatment, with 54 of them (57%) exclusively utilizing VOT. VOT led to higher proportions of verified prescribed doses as a measure of adherence, than in-person DOT (68% vs. 54%; P<0.001). Other clinical outcomes were however not measured in this study.

Assessment on programmatic application of video observed therapy for TB in six Eastern Europe and Central Asia countries found clear advantage of asynchronous VOT versus synchronous VOT ²⁴. The key barriers to scaling-up synchronous VOT were scheduling arrangements, workload similar to DOT, as well as lack of effective connectivity in video interactions.

Acceptability and feasibility of these digital tools may vary across different countries and settings, driven mainly by cultural and socioeconomic differences. Thus, data of success from these strategies from individual trials or programmatic evaluation in other countries may not necessarily translate to similar successes in the local Malaysian context. Despite over 95% penetration of smartphone use ²⁵, effective adoption of digital adherence monitoring strategies in supporting TB treatment has not been tested in Malaysia.

(b) TB Counselling - Telecounselling vs face to face counselling

WHO strongly recommends health education and counselling on disease and treatment adherence to all patients on TB treatment ¹². Additionally, during counselling, a healthcare provider (HCP) may be able to identify and address potential barriers to adherence such as poor social support, stigma, illicit drug use, poor nutrition and medication intolerance. Our approach combines an initial in-person pharmacist-led counselling session following the standard care upon treatment initiation, with a subsequent telecounselling session replacing the traditional in-person counselling at the one-month mark. This hybrid strategy may enhance communication effectiveness and personalization between patients and healthcare providers as it has both the advantages of remote and face-to-face engagement. The evidence for pharmacist-led counselling and comparison of its modes of delivery are detailed below.

Patient health and service outcomes

TB counselling in Malaysia is typically performed by either a trained pharmacist or nurse. In Brazil, an effectiveness-implementation study of a pharmacotherapeutic follow-up (PFU) counselling service by pharmacists was performed in 148 primary health care units by 82 pharmacists. Of a total 1076 treatments, 721 were followed up by pharmacists and TB cure rate was significantly higher compared to no PFU service (90.4% vs 73.5%) ²⁶. Pharmacist-led TB counselling which incorporated individualized pharmaceutical care plans showed significant and positive medication adherence impact ^{27, 28}.

Systematic reviews reported positive outcomes in terms of adherence, clinical disease management and patient self-management with pharmacist-led telemedicine in chronic disease management compared to standard care involving in-person and paper-based methods ^{29, 30}. A RCT comparing pharmacist-led to nurse-led telehealth found the former to be superior in improving medication adherence for patients with diabetes and depression ³¹. Two separate studies in Spain showed teleconsultations for pharmaceutical care of HIV outpatients to be acceptable with no detrimental effects on HIV treatment outcomes ^{32, 33}.

Implementation outcomes

A pre- and post-test study on an individualized home-based training and counselling programme via video conference to 50 patients with severe COPD, found good feasibility with

a program completion rate of 74%³⁴. However, execution of pharmaceutical care plans for TB through telemedicine is still a new concept in terms of implementation and regulation in general and evidence of success is still limited.

(c) Patient education - conventional approaches vs e-learning

TB education encompasses knowledge on TB disease, infection control measures, importance of therapy and adherence to therapy, possible adverse effects, dietary habits, and methods to enhance adherence behaviour³⁵. Traditionally, knowledge and information are communicated during counselling by a health-care provider and via printed materials. In the current digital age, a web-based patient and provider education program provides flexibility and accessibility to reliable contents to improve self-efficacy. Utilizing tailored e-learning contents rather than random web searches eliminate unnecessary anxiety, medical mistakes and misinformation due to inaccurate, outdated and erroneous information in health management³⁶. E-learning modules may also be developed in multiple languages and disseminated to patients in their language of preference. This overcomes potential language barriers commonly faced by in multi-ethnic societies like Malaysia where the health care provider may not speak the same language as the patient.

Patient health and service outcomes

A TB health education module delivered via WhatsApp in a local trial resulted in higher adherence and TB treatment success rates versus conventional health education³⁷. In a pre- and post-test study of 146 participants, educational videos significantly increase TB knowledge among low-literacy patients and the community in a remote area of Madagascar³⁸. Similarly, TB video education performed in other countries were successful in improving understanding of TB^{39, 40}.

Implementation outcomes

A qualitative study found video-based health education interventions to promote community care for pregnant women, mothers, and infants in Ethiopia was acceptable and feasible⁴¹. Direct evidence in the context of TB is limited.

Cost-effectiveness of digital adherence technologies (DAT) and telecounselling

With regards to efficiency, there is paucity of evidence regarding the cost-effectiveness of DAT such as VOT in general and this may be a barrier to widespread implementation as there is a general perception that digital solutions are often expensive to rollout and maintain. In terms of direct medical costs and disability-adjusted life years (DALY), a recent modelling study in Hong Kong found VOT to be a cost-effective strategy when compared to self-administered therapy (SAT) (reduced DALYs by 0.4870 and costs by US\$1797)⁴². A prospective randomized controlled trial in China which compared VOT to DOT found significant time- (16.5 min [SD 12.1] vs 44.1 min [SD 3.7]) and cost-savings (¥34.3 [SD 3.8] vs ¥71.6 [SD 49.7]) with high acceptability despite similar treatment outcomes³⁹. While TB treatment is provided free, it imposes a significant economic burden, encompassing out-of-pocket expenses and substantial

productivity losses especially with DOTs ⁴³. The inclusion of cost data in the implementation of this digital package compared to standard of care is vital for informed decision-making by service providers and policy makers to facilitate intervention adoption and sustainability planning. The availability of such data is currently lacking not only in Malaysia but more widely in Southeast Asia.

Complexities of managing TB in people living with HIV (PLWH)

Interacting bidirectionally, HIV accelerates the progression of TB disease and TB hastens the deterioration of immunological functions ⁴⁴. Management of both HIV and TB presents unique challenges to patients, providers, and the health care system. There are complex treatment regimens involved and the need for high rates of treatment adherence for both diseases. Complex regimens mean high pill burden, poor palatability, intolerance, or side effects associated with both HIV and TB medications. Frequent drug-drug interactions necessitate adjustment or a switch in medication. Also, both diseases are highly stigmatized by society in general, presenting a significant psychological and mental stress on patients. In terms of health outcomes, HIV co-infection with low CD4 counts increases the risk of TB IRIS, TB reinfection, and mortality ^{44, 45}. These unique and specific challenges in PLWH thus necessitate a separate assessment of the implementation outcomes of CARE-TB in this study from that of TB-monoinfected patients.

2.0 RESEARCH SIGNIFICANCE

The following are impacts from utilising digital solutions to decentralize TB medication monitoring and education on health outcomes, economic impact/burden of disease, and equity/inequality/marginalization, as well as a statement on quintuple helix:

2.1 Health Outcomes:

Improve treatment adherence and TB outcomes

This patient-centered approach for digital adherence strategy allows for remote monitoring of TB treatment, regular check-ins, medication reminders, e-learning, and virtual counselling sessions that contribute to better adherence and retention to care which is crucial for successful outcomes.

Early detection of complications

Remote monitoring enables early detection of any complications or side effects associated with TB treatment. Healthcare providers can intervene promptly, preventing the escalation of health issues and improving patient outcomes.

Improve quality of life

Digital solutions that enable adherence monitoring and counselling within the homes of patients can potentially improve their overall quality of life by reducing the need to visit a healthcare center. This also reduces risk of stigma and transmission, and improve productivity.

2.2 Economic Impact/Burden of Disease:

Cost savings

Telemedicine can reduce the economic burden on both patients and healthcare systems. Patients save on travel costs and potential lost wages associated with in-person visits. Additionally, healthcare systems can optimize resources by efficiently managing patient loads through remote monitoring and consultations.

Productivity gains

Improved treatment adherence can lead to reduced hospitalizations and complications, resulting in increased productivity for patients who can continue working or contributing to the economy. At the same time, patients save on time and out-of-pocket expenses for frequent clinic visits associated with directly observed therapy.

Decentralise TB care provision

By decentralizing TB medication monitoring, the study envisions a more inclusive group involving pharmacists in addition to nurses and medical assistants to broaden adherence services while utilising existing manpower.

2.3 Equity/Inequality/Marginalization:

Increase access to care

Digital strategies help overcome geographical barriers, providing access to TB care in remote or underserved areas. This is particularly beneficial for populations that face challenges in accessing traditional healthcare facilities due to distance or lack of transportation.

Reduce health disparities

By facilitating regular follow-ups and check-ins, digital adherence strategy can contribute to reducing health disparities. Patients in rural or marginalized communities can receive the same level of care and attention as those in urban areas.

Cost and cost-effectiveness data for resource allocation

Providing policymakers with cost and cost-effectiveness data justifies resource allocation to the digital adherence program, addressing equity in access to healthcare and technology.

2.4 Impact Statement on Quintuple Helix

For **society**, the project will reduce the financial and social burden of TB to the patient and the surrounding community, which often are from the most marginalised segments. The study also provides a unique opportunity for implementation research scientists from **academia** (UM and USM) and real-world implementers (MOH) to work collaboratively to address a growing public health threat through exchange of expertise and capacity building, while taking in the views of the **community**. The framework-guided implementation approach used ensures continued engagement with all stakeholders and detailed documentation of feedback which affords benefits beyond the scientific research outputs of this study. It enables the documentation of **industry-related** issues such as 1) key elements needed for future adoption of digital health solutions in other government health facilities, 2) issues of inequalities in digital access in the community, 3) regulatory barriers and data privacy concerns which impede the scale up of digital health solutions in Malaysia. Finally, the project helps deliver eLearning to patients on the **environmental factors** that may increase their risk of severe TB and help to mitigate environmental risks associated with TB infection.

3.0 HYPOTHESIS AND OBJECTIVES

3.1 Innovation/ Hypothesis /Research Questions

Our innovation is a comprehensive pharmacist-led digital package of patient-centric TB treatment support which includes asynchronous video-observed therapy, digital reminders, telecounselling and e-learning, named the CARE-TB strategy. We hypothesize that implementing the CARE-TB strategy in a manner that addresses identified patient and provider-level barriers and facilitators will lead to an acceptable, feasible, cost-effective, and sustainable program which improves adherence to TB treatment in our local TB care settings. This study aims to address the following questions.

- 1) What are the key patient and provider-level barriers and facilitators influencing the successful implementation and sustainment of the CARE-TB strategy?
- 2) How effective is the CARE-TB strategy in improving TB treatment adherence and patient outcomes compared to standard of care in the targeted local TB care settings?
- 3) How cost-effective is the CARE-TB strategy compared to standard care?

3.2 Objectives

The primary objectives are:

- (1) To identify patient and provider-level barriers and facilitators to the uptake of the CARE-TB strategy (VOT, digital reminders, telecounselling and e-learning) and to design a stakeholder-informed implementation strategy to address these barriers,
- (2) To assess the implementation and effectiveness of the CARE-TB strategy by evaluating (i) implementation outcomes, (ii) patient-level outcomes, and (iii) service outcomes, compared to the standard of care, and
- (3) To evaluate the cost-effectiveness of the CARE-TB strategy compared to standard of care from a societal perspective.

The secondary objectives are:

- (1) To assess implementation, patient-level, and service outcomes of HIV versus non-HIV participants, and
- (2) To evaluate the difference in HRQOL and stigma score between the CARE-TB and standard of care arms.
- (3) To determine predictors (demographics, clinical, social determinants, contextual) of patients who successfully completed VOT.
- (4) To explore stakeholder insights and prioritise key features of participant suitability for VOT using Nominal Group Technique (NGT).

4.0 METHODOLOGY

4.1 Overview of research design:

In this implementation research we will utilize a multi-methods effectiveness-implementation (Type 2) study at one of the largest tertiary centres for TB treatment in Malaysia, involving microbiologically confirmed pulmonary TB adult patients, including those co-infected with HIV. The Exploration, Preparation, Implementation, Sustainment (EPIS) ⁴⁶ framework will be used to guide the implementation process and outcome evaluation. By employing the EPIS framework, we can systematically assess and document each stage of the digital adherence strategy, from the initial exploration of the concept to its implementation sustained over time.

Table 2: Research activities and stakeholders involved in the CARE-TB strategy mapped into EPIS framework

Factors		EPIS Phases			
		Exploration	Preparation	Implementation	Sustainment
Inner context	TB and TB/HIV patients	Barriers and facilitators of pharmacist-led telemedicine model	- Pilot test application - Measure acceptability	- Promote CARE-TB strategy - Train patient - Measure implementation and patient level outcomes	- Adherence and dropout - Maintenance and evaluation
	Pharmacists	- Perception towards CARE-TB strategy - Readiness to provide service	- Convene a telemedicine workgroup - Identify resources and technologies - Train staff - Measure feasibility and acceptability - Revise training module and workflow	- Training programme - Support participation - Measure adoption (%) and fidelity	Fidelity to implementation (adherence, quality of telemedicine delivery, amount delivered, participant responsiveness)
	Peer counsellor				
	Nurses/MA				
	Physicians and hospital administrators	Perception towards CARE-TB strategy		Support and promotion of CARE-TB strategy	
Outer context	Policy-makers from the pharmaceutical services division	Perception and acceptability of CARE-TB strategy	Continuous engagement	Support and promotion of CARE-TB strategy	
	Policy-makers from the state/national TB sector, MOH				
	Community representative				
Bridging factor	MOH-MOE partnership	Establishing working partnership between implementers in MOH with implementation research experts from University Malaya and University Sains Malaysia (MOE) to develop and maintain a detail-oriented framework for CARE-TB Strategy			
	Non-governmental organization (NGOs)	Establishing support from TB NGOs (Malaysian Association for the Prevention of Tuberculosis, MAP-TB) and HIV support group (Kuala Lumpur AIDS Support Services, KLASS) for promotion and community engagement.			

Innovation factor	CARE-TB	Incorporate a pharmacist-led adherence model that combines e-learning, VOT and telecounselling into the TB care cascade	
Cost analysis	Cost-effectiveness analysis using the societal perspective	All direct and indirect costs relevant to society including cost of obtaining care and opportunity costs. Examples: Travel, mobile data (out-of-pocket or direct costs) and productivity losses/time of work (indirect costs)	Indicator of implementation success: fidelity score

(Note: MOH Ministry of Health, MOE Ministry of Education, VOT video observed therapy, MA medical assistants)

Pre-implementation interviews of patients and providers will assess facilitators and barriers to integrating pharmacist-led digital adherence strategy in TB clinical setting and inform the design for implementation. These interventions will be implemented at the study site for a 12-month period, during and after which the feasibility, acceptability, and sustainability of the interventions, and fidelity to the intervention will be assessed through patient, provider, policymaker, and community representative interviews and discussions. Cost will be assessed throughout preparation and implementation phases of the interventions. Pre- and post-implementation site and participant medical record data will be compared to assess service and patient-level health outcomes, and intervention effectiveness (detailed below).

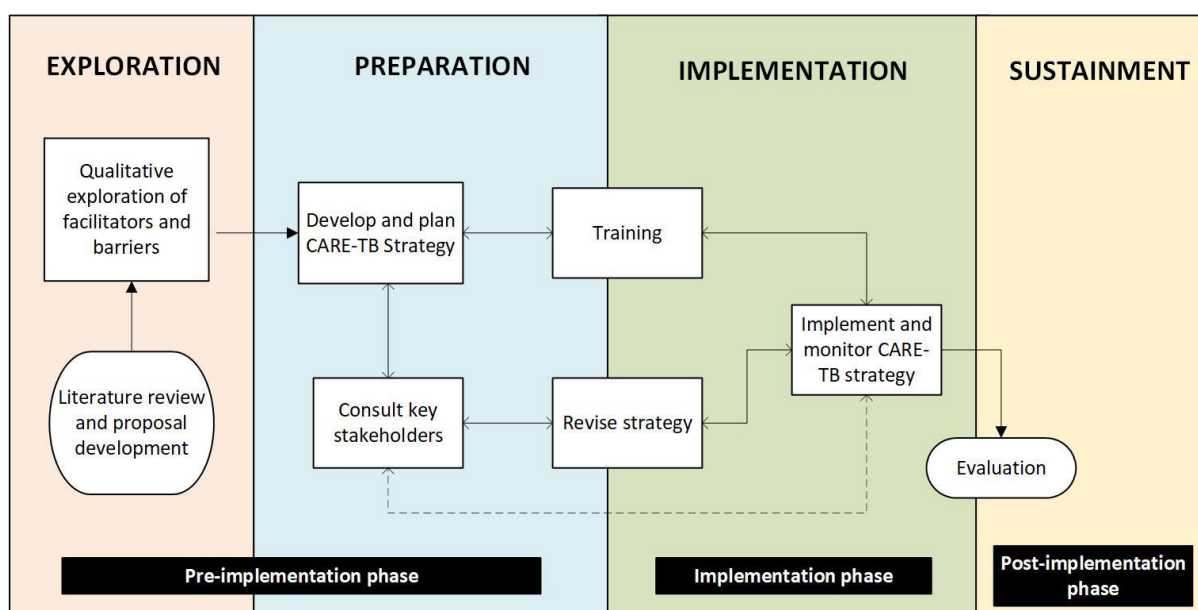


Figure 2: Iterative approach using EPIS framework in the pre-implementation, implementation and post-implementation of the CARE-TB Strategy

The above figure shows mapping of the iterative and dynamic approach used to develop and implement the CARE-TB strategy.

4.2 Study Site: This study will be implemented in one of Malaysia's largest TB treatment tertiary centre, Hospital Sungai Buloh, Selangor.

4.3 Population: This study is conducted among TB and TB/HIV-coinfected persons with confirmed pulmonary TB, who are receiving care in Hospital Sungai Buloh. The hospital provides care for approximately 300 TB patients annually. All diagnosed TB patients are under directly observed treatment in accordance with the National Strategic Plan for TB Control and treatment is provided free of charge. Selected health care providers (HCPs) which includes doctors, pharmacists, nurses, medical assistants, HIV peer support counsellors and hospital administrators involved in the planning and delivery of TB/HIV care will be invited to provide stakeholder feedback during the course of the study. The TB program in Hospital Sungai Buloh has an approximate health care workforce of 20 people. This study will also include policymakers from the state and federal health departments and community representatives supporting the delivery of TB care services to adults living with or without HIV.

4.4 Duration: This study will be implemented in 4 phases over a period of 27 months following ethical IRB approval.

4.5 Aim 1 (Phase 1): To identify patient and provider-level barriers and facilitators to the uptake of a digital adherence strategy (VOT, digital reminders, telecounselling and e-learning) and to design a stakeholder-informed implementation strategy to address these barriers.

4.5.1 Introduction: To ensure successful implementation, it is vital to understand how these promising digital adherence strategies function within specific local contexts. The success of TB/HIV programmes hinges largely on the perception, acceptability, and competency of patients and healthcare providers (HCPs), among other contributing factors (Subbaraman et al., 2018). The rationale for this aim is to identify potential implementation barriers and facilitators, which will inform the design of the strategy and context-specific implementation in Aim 2. We chose a qualitative approach because it allows for in-depth exploration of individual's perspectives, context, and organizational dynamics that will inform the development of a tailored implementation strategy.

4.5.2 Study design: We will employ a qualitative formative evaluation with an exploratory-sequential design, engaging stakeholders such as healthcare providers, TB patients, peer-support counsellors, administrators, and policymakers. Semi-structured key informant interviews (KIIs) and focus group discussions (FGDs) will be conducted to assess patient- and provider-level barriers and facilitators to the integration of medication adherence enhancing digital strategies (VOT, digital reminder, telecounselling, on-demand virtual e-learning databases).

Table 3: Pre-implementation qualitative methodology

Study subjects	Research method	Sampling method	Sample size	Inclusion criteria	Themes to explore
Key population: TB patients (HIV and non-HIV) ≥18 years old	In-depth interviews with TB patients of different age groups (18-34, 35-49, 50-64, ≥65 years old)	Purposive sampling Recruit from TB clinics with patient consent	Number of interviews will depend on when saturation is achieved (Target max = 20)	As in Aim 2 (i. Eligibility and recruitment) below	Barriers and facilitators of pharmacist-led digital adherence strategy
Pharmacists	Key informant interviews	Stratified purposive sampling	5 for each category of providers	Pharmacists involved in TB drug counselling	Perception towards CARE-TB strategy and readiness to provide service
Nurses/MA/ counsellors				Nurses or MA involved in the care of TB patients or DOT programmes	
Physicians				Physicians involved in TB care	
Peer support counsellors	Key informant interviews	Purposive sampling	2	HIV peer support counsellors	Perception towards CARE-TB strategy and readiness to provide service
Clinic administrators	Focus group discussion	Purposive sampling	5	Head of departments and clinic administrators	Perception towards CARE-TB strategy
Policymakers from the pharmaceutical services division	Key informant interviews	Purposive sampling	3	Pharmacists	Perception towards CARE-TB strategy
Policymakers from state/national TB sector, MOH			3	Physicians/ administrators	
Community representatives			5	Society representative/ family member	

4.5.3 Study procedures:

i. Study participants and sampling: We will invite eligible participants directly at TB clinics or by mail which includes an introductory letter explaining the purpose of the study. Participants consist of a cohort of microbiologically confirmed pulmonary TB adult patients, including those co-infected with HIV for interviews. Healthcare providers (HCP) are invited to participate if they serve the role of a pharmacist, community health worker, nurse, clinician, or administrator who are actively involved in the management of TB patients. We will also recruit state and federal TB officers who are actively engaged in supporting the TB control

programme. The axes of diversity of our sampling framework includes age of patient, HCP's role in TB care, level of experience in TB management and type of facility or unit. A maximum variation purposeful sampling strategy will be used to maximise heterogeneity and diversity to select a sample of information rich participants, possessing unique insights crucial to the study's aims (Cohen D, 2006). Study participants and sampling methods are summarised in Table 3. We proposed an approximate sample of 20 TB patients, 20 healthcare providers and administrators from TB clinics, 2 peer counsellors, 6 policymakers, and 5 community representatives but the final sample size will be based upon conceptual saturation, indicating the point at which no new concepts emerged from consecutive interviews (Corbin, 1988).

ii. Development of interview guides: We will develop our interview guides for semi-structured in-depth interviews using the constructs from the Exploration, Preparation, Implementation, Sustainment (EPIS) framework. EPIS consists of four main domains or contexts, namely inner, outer, innovation and bridging factor (Moullin et al., 2019). Within each context are a broad range of constructs: Inner context includes leadership, organizational characteristic, quality and fidelity monitoring/support, organizational staffing and processes, and individual characteristics; Outer context includes leadership, service environment/policies, funding/contracting, inter-organizational environment and networks, patient/client characteristics, and patient/client advocacy; Innovation factor includes innovation fit, innovation developers, and innovation characteristic; Bridging factor includes community academic partnerships and purveyors/intermediaries. Interview guides will be developed in English and translated to Malay language.

iii. Interview conduct: Prior to interviews, we will test the guides with mock discussions with volunteers role-playing as patients or health-care providers. Mock discussions will continue until all questions are verified as clear, concise, and correctly interpreted, and that the questions are organized in a manner that ensures a fluid discussion. Semi-structured interviews and focus group discussion will be conducted by two trained members of the research team. The interviews are performed either in-person or by video calls within 2 weeks of study enrolment and written consent. We will conduct in-person interviews in any available private space within the study site to ensure privacy. Each interview, lasting between 30 to 45 minutes, is conducted in either English or Malay language, depending on the participant's preference, and will be audio recorded. Focus group discussions will be conducted asynchronously using a web-based application (FocusGroupIT). To uphold privacy, patient identifiers will be omitted in all audio recordings of interviews and discussions. During data collection, interviewers maintain detailed records and convene weekly meetings with the study team to analyse interviews and identify emerging themes. Recruitment concludes upon reaching thematic saturation, indicating no further emergence of new themes in the dataset.

iv. Analysis: The NVIVO software will be used to store the transcripts for qualitative data management and thematically analyse translated data. Audio files will be transcribed verbatim, checked for quality, and analysed in their original language to maintain accuracy of data. We will verify transcription and translation quality through random checks on up to 50% of documents for errors, including missing sections, wrong vocabulary, and misunderstanding of meaning and concepts. We will conduct qualitative analysis using the framework approach,

enabling us to focus on predefined areas of interest while also permitting the emergence of new themes from the data. A priori codebook informed by EPIS framework and previous literatures will be reiteratively defined as analyses progress by adding new inductive codes to reflect emergent themes. When finalised upon consensus, the codebook will be applied to all transcripts. Two investigators will independently code transcripts and subsequently collaborate to reach a consensus on the coded content. Following consensus on the coded content, the two coders will independently and then collectively summarize the barriers and facilitators that surfaced in each interview.

v. Outcome: The outcome of this aim is the development of a stakeholder-informed digital adherence strategy to enhance acceptance and seamless integration into the local TB care setting.

4.6 Aim 2 (Phase 2 and 3): To assess the implementation and effectiveness of the CARE-TB strategy by evaluating (i) implementation outcomes, (ii) patient-level outcomes, and (iii) service outcomes, compared to the standard of care.

4.6.1 *Introduction:* This aim evaluates the implementation process and effectiveness of the CARE-TB strategy.

4.6.2 *Study design:* Mixed-methods effectiveness-implementation (Type 2), prospective randomized study comparing CARE-TB strategy to the standard of care.

4.6.3 *Study procedures:* Study procedures are divided into (a) Phase 2: Preparation and training, and (b) Phase 3: Implementation and evaluation. Both phases are overlapping as the processes are iterative and adapted according to rapid-cycle evaluation.

(a) Phase 2: Preparation and training

Based on the outcome of Aim 1, we will design the CARE-TB strategy tailored to the local setting. This strategy will first undergo pilot testing with 20 participants from patient and care-provider groups. The suitability of each component will be assessed through cognitive interviews, where participants will provide feedback while utilising these components. Feedback will be reviewed and used to revise each component. We will select the telecounselling delivery platform (e.g., WhatsApp, Zoom, or Google Meet) based on interviews conducted in the pre-implementation phase, and insights from pilot tests and user feedback. Protocols, costing sheets, training modules, and workflow will be prepared. Training on motivational interviewing techniques will be provided. Provider training can be conducted in-person or via videoconferencing, with assessments to ensure staff competence in executing the CARE-TB strategy. Promotional activities will be organized to boost patient recruitment.

Training modules will be developed to guide patients in using the technology (VOT and teleconferencing), educating them on the optimal conditions for a VOT recording, such as

ensuring a well-lit space, visibility of the face, and having pills and water on hand. Instructions for reporting of adverse effects during the VOT and telemedicine sessions will also be provided.

(b) Phase 3: Implementation and evaluation

i. Eligibility and recruitment: Eligible patients will be screened and recruited from medical wards and TB clinics by trained pharmacists and doctors upon TB diagnosis. Patients discharged from wards or transferred from other facilities are eligible if they are still within the first 3 weeks of the intensive phase. For warded patients, the intervention begins upon discharge. Patient identification and recruitment will adhere strictly to inclusion criteria and are contingent on informed consent.

Below are the inclusion and exclusion criteria for patient selection:

Patient inclusion criteria:

1. Microbiologically confirmed TB
2. 18 years old or older
3. Able to give consent and physically able to participate in the study
4. Own a video-recording device with internet connectivity
5. Within the first 3 weeks of intensive phase TB treatment

Patient exclusion criteria:

1. Complicated TB disease including TB meningitis, TB bone/joint, and disseminated TB with planned treatment duration of 9 to 12 months.
2. Confirmed or suspected drug-resistant (DR)-TB
3. Documented cognitive, motor, or visual disability that will hinder video device use and lack assistance of a caretaker
4. Receiving injectable anti-TB drugs
5. Incarceration or other involuntary detention

ii. Sample size and randomization: The primary endpoint is the proportion of participants achieving ≥80% of scheduled observations during the first 2 months after enrolment. Based on prior data indicating ~70% with VOT versus ~31% with DOT (Story et al., 2019), a two-sided test with $\alpha=0.05$ and 1:1 allocation requires **n=32 per arm** to achieve **90% power** to detect a 39-percentage-point difference in proportions.

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

Sample size estimation for 2-sample proportions:

$N^* = N / 80 (1-R)$, with $R = 0.20$ (20% LTFU). Thus, $32/(1-0.20) = 40$ per arm. The total target sample size is $N = 80$. This sample size is powered for overall treatment effect.

Participants will be randomised 1:1 to intervention or SOC arm using computer-generated blocked randomization sequence implemented in Research Electronic Data Capture (REDCap) platform.

iii. Treatment processes:

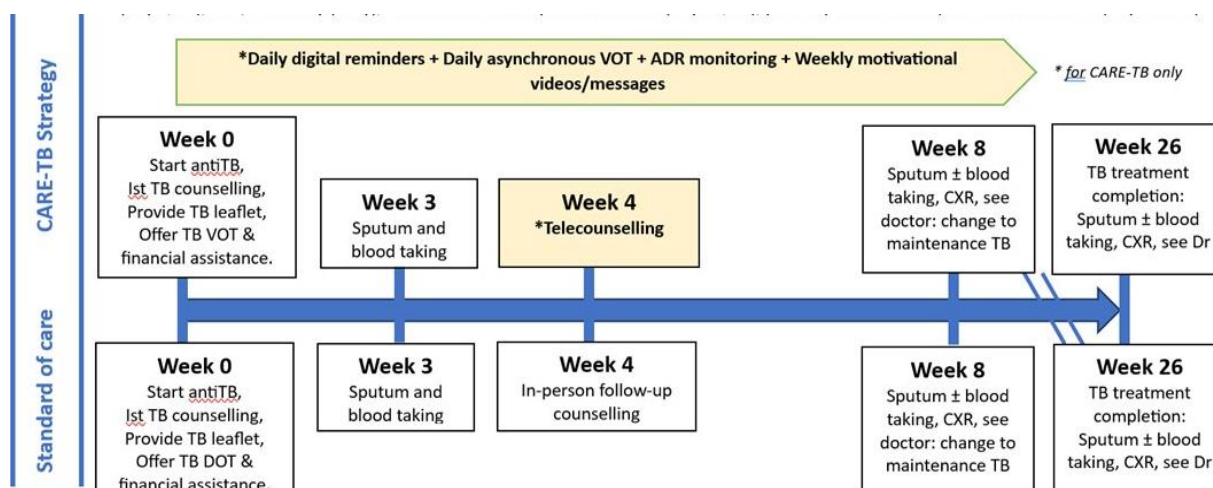


Figure 3: Overview of TB treatment processes

All arms:

All patients will be treated according to the national TB guidelines and receive a 4-drugs standard anti-TB regimen consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide for 8 weeks, followed by isoniazid and rifampicin for 18 weeks (total treatment duration = 26 weeks)⁴⁷. Treatment is provided free of charge. Upon initiation, patient will receive a TB treatment diary, counselling with a pharmacist on disease and treatment education and a standard TB educational pamphlet. Patients will be given appointments to return at 4-, 8- and 26-weeks (end of) treatment for lab and radiological investigations, and clinician visits. Medications are provided at monthly intervals during treatment. All participants will be followed-up until completion of TB treatment (6 months).

Standard of care:

The Malaysian guideline recommends directly observed therapy (DOT) as a standard form of adherence monitoring for the intensive phase of TB treatment (8 weeks) at minimum⁴⁷. Often, patients are subjected to modified DOT where a family member or caretaker observes the intake of medications when the patient is unable to come to the healthcare facility for their daily doses. Each dose is recorded by the observer/caretaker in the TB diary (KKM TBIS 10E). A follow-up in-person counselling with the pharmacist is scheduled post-1month anti-TB treatment for most patients. See figure 3 for a summary of treatment processes.

CARE-TB intervention arm:

Patients who consent to the study will receive a package of digital adherence interventions which include instructions on VOT and e-learning materials. Automated daily reminders via WhatsApp will prompt patients to take their TB medications. For asynchronous VOT, patients

will utilize the 60-second video message feature on WhatsApp to record and send daily real-time videos of pill-taking for the 2-months intensive treatment phase. This real-time video enhances authenticity and end-to-end encryption ensures confidentiality.

Patients will maintain a TB diary (KKM TBIS 10E), while a VOT observer will complete a VOT diary, noting video and audio quality. Weekend doses, typically unobserved in standard DOT will be excluded from analysis. If patients fail to send videos within the same day, they will receive WhatsApp reminders. Failure to send videos for two consecutive days will prompt a phone call to determine reasons for non-adherence, with TB surveillance officers alerted if the patient cannot be reached. VOT will be conducted by a pharmacist. All adverse events reported by patients will be monitored by a pharmacist and referred to a doctor if necessary.

TB counselling will be performed by a trained pharmacist at treatment initiation in the ward or TB outpatient clinic. After 2 weeks of treatment or at least 1-week post-discharge, a telecounselling session will be scheduled to assess treatment progress using motivational interviewing techniques and troubleshoot any VOT issues. Unlike standard care, patients can forgo in-person counselling sessions during their Week 4 blood taking appointment, rendering a shorter hospital visit.

In addition to e-learning materials, patients will receive weekly videos or motivational messages to encourage continued adherence. E-learning material will cover TB disease, medications, adherence, side effects, monitoring, and resources for financial, counselling and community support services.

iv. Criteria for cross over from intervention to standard of care

Patients are switched from the intervention to standard of care arm if they have repeated episodes of non-adherence to VOT or if they chose to do so. Non-adherence is defined as missing three daily doses within a week or missing two daily doses per week for 2 consecutive weeks⁴⁸. Prior to the switch, an attempt to re-establish treatment adherence should be made and if successful, patient can be maintained in the interventional arm.

v. Follow-up and methods for handling missing data and outliers

A TB diary is maintained by either a DOT observer or the patient as part of standard care, while a VOT observer records treatment observations within the VOT administration system. Follow-up continues for 2-months, or until the end of intensive phase, whichever is later. For participants who are loss to follow up, observations will be considered for analyses if they were completed for at least 2 months from time of enrolment. Patients who switch strategies before the end of 2 months from enrolment will be considered a failure for primary outcome (detailed below). Post-switch data will be analysed separately from the main analysis.

vi. Data management and rapid-cycle evaluation

All study staff responsible for data collection will receive training before the study commences. Training will include key methodological issues pertaining the data collection tools, interviews and focus group discussions. Data collection tools will be tested and adjusted where appropriate. Weekly feedback sessions will ensure iterative rapid-cycle evaluations to revise implementation strategy and data collection methods. Rapid-cycle feedback loops are viewed as effective tools for centre-level evaluations, fostering reflexivity and active engagement

among implementation teams by providing timely and constructive information to enhance implementation efforts (Hargreaves, 2014, Balbale et al., 2023). Data collection tools that will be used include semi-structured interviews, time and cost sheets, as well as medical records and DOT/VOT diary review. A set of validated questionnaires will be used to collect patient and provider outcomes data, which includes:

1. AIM-IAM-FIM questionnaire (12-items)⁴⁹
2. EQ-5D-5L Health Related Quality of Life Questionnaire (5-items)⁵⁰
3. Short Form-12 Health Survey, SF-12 (12-items)⁵¹
4. Van Rie TB Stigma Scale (12-items)⁵²

vii: Outcomes: Aim 2 will address the outcomes tabulated in Table 4 below. Study participants will be followed-up until completion of TB treatment at 6 months, loss to follow-up, or death, whichever occurs sooner.

Table 4: Effectiveness outcome and method of measurement in each arm

Type of Outcome	Outcome measure	Method of measurement
Service outcomes (Comparing CARE-TB and SOC arms)	Adherence rate	- Primary outcome (binary): Completed ≥ 80% scheduled observations during the 2 months of following enrolment. - Secondary outcome (continuous): Proportion of doses observed over 2 months (Dose observed divided by total observable doses prescribed)
	Adverse drug reactions (ADR)	Number and type of ADR reported
Patient-level health outcomes (Comparing CARE-TB and SOC arms)	Proportion of TB treatment completion, death, and loss to follow up, hospitalization	Patient records
	TB cure rate	Microbiological TB clearance (sputum smear /TB culture)
	HIV viral load and CD4 cell count	Patient records
	(for HIV/TB co-infected participants)	
	Health related quality of life (HRQOL)	EQ-5D-5L, SF-12
Implementation outcomes (only for CARE-TB strategy)	Acceptability, feasibility, fit	Qualitative interviews, AIM-IAM-FIM questionnaire
	Adoption	Rate of uptake (number of participants who agree to use the CARE TB strategy divided by total number offered)

Fidelity	<i>Patients:</i> rates of drop-out from CARE-TB strategy, adherence to VOT and telecounselling appointments (number of completed sessions divided by number of scheduled sessions) <i>HCPs:</i> rate of ADR referrals, time to identification of ADR, rate of successful telecounselling sessions, observations on timely reminders sent to patients
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(Note: SOC standard of care, ADR adverse drug reaction)

viii. Statistical analysis

Baseline characteristics were summarised by study arm using descriptive statistics. Between-arm differences were assessed using two-sample t-test, Fisher's exact, chi-square, or Wilcoxon rank-sum tests, as appropriate. The primary analysis population was the modified intention-to-treat population, defined as all randomised participants with confirmed TB. Participants with missing adherence data were excluded from the primary adherence analysis. All analyses were conducted in R using two-sided tests with $\alpha=0.05$. See Appendix.

Observed dose adherence outcome

The primary binary outcome ($\geq 80\%$ observed doses) was analysed using modified Poisson regression with robust standard errors to estimate risk ratios and 95% confidence intervals. Crude absolute risk differences were estimated using binomial regression with an identity link. Adjusted risk differences were estimated from predicted probabilities obtained from a regression model including study arm, age, and HIV status. Risk ratios (RR) were reported as the principal relative effect measure, while risk differences (RD) were presented to quantify the corresponding absolute between-arm difference. The secondary outcome – the observed-dose proportion, was analysed using quasibinomial generalised linear models to account for overdispersion. Models were adjusted for selected baseline prognostic variables, including age and HIV status, where applicable. Sensitivity analyses used the same modelling approach.

Safety outcomes: Adverse events (AEs), adverse drug reactions (ADRs), and hospitalisations

Adverse events, adverse drug reactions, and hospitalisations were analysed as participant-level binary outcomes and compared between arms using 2x2 tables, risk differences, risk ratios, Wald 95% confidence intervals, and Fisher's exact tests. Adjusted risk ratios were estimated using modified Poisson regression controlling for age and HIV status. Exploratory models examined the association between ADR occurrence and hospitalisation after adjustment for study arm. Additional exploratory models included study arm and ADR occurrence simultaneously to examine whether the estimated association between study arm and hospitalisation changed after accounting for ADR occurrence. Because ADR occurrence was measured after randomisation and could itself be influenced by the intervention or differential surveillance, these models were interpreted as exploratory pathway analyses

rather than estimates of the causal intervention effect. Participant-level total event counts over 8-week observation period were analysed using Poisson regression with robust standard errors to estimate event count ratios between study arms. Overdispersion was assessed using the residual deviance-to-degrees-of-freedom ratio. Week-level data were analysed using Poisson models with study arm, time, and arm-by-time interaction, with cluster-robust standard errors for repeated observations. Time to AE/ADR detection, ADR type, length of stay, and organ-system distributions were summarised descriptively at the event level. Because participants could contribute more than one event, formal between-arm hypothesis testing was not performed for these event-level summaries. Sensitivity analyses excluding extreme outlying values were conducted for time to detection and length of stay to assess the robustness of findings.

Clinical outcomes: TB treatment success

Treatment success was analysed using 2×2 tables, Fisher's exact tests, risk ratios, and risk differences. Modified Poisson regression with robust standard errors estimated associations between study arm, early adherence, and treatment success. Exploratory mediation-related analyses assessed whether early adherence, defined as ≥80% observed doses during the first 8 weeks, may explain the relationship between CARE-TB and treatment success. Predictors of unfavourable treatment outcomes defined as death, treatment failure, or loss to follow-up, were explored using modified Poisson regression for selected sociodemographic and clinical risk factors, based on published data (Pedersen et al., 2025; Ryuk et al., 2024; Tok et al., 2020).

Stigma outcomes

Total stigma scores were summed and rescaled to 0–50, with higher scores indicating greater stigma, according to the original scoring method (Mann et al., 2009; Peeters & Stiggelbout, 2010; Rie et al., 2008). Participants with missing stigma scores at a given timepoint were excluded from that timepoint analysis. Item-level responses were dichotomised into higher stigma (scores 2-3) versus lower stigma (scores 0-1). Stigma trajectories were analysed using linear mixed-effects models with participant random intercepts and fixed effects for study arm, timepoint, and their interaction. Estimated marginal means described within-arm changes and between-arm differences.

Associations between stigma and 8-week adherence were assessed using baseline stigma and early stigma change (baseline to week 4). Additional analyses examined associations of 8-week adherence with EOT stigma and overall stigma change from baseline to EOT. Stigma change was analysed both continuously and categorically as improved (≤ -5 points), stable (> -5 to $< +5$ points), or worsened ($\geq +5$ points). The 5-point threshold was informed by the approximately 4.3-point minimal clinically important difference previously reported for TB stigma (Dixit et al., 2024; Redwood et al., 2021). Observed-dose proportion was analysed using adjusted linear regression, while achievement of ≥80% observed doses were analysed using adjusted modified Poisson regression. Models adjusted for age, HIV status, and study arm. Effect modification by study arm was tested using interaction terms.

12-Item Short Form Health Survey (SF-12v2)

SF-12 physical (PCS) and mental component scores (MCS) were analysed longitudinally using linear mixed-effects models with participant-level random intercepts and fixed effects for

timepoint, study arm, and their interaction, adjusted for age and sex. Estimated marginal means and contrasts quantified within-arm changes over time and between-arm changes at each timepoint. Complete-case paired analyses were conducted as sensitivity analyses: within-participant changes from baseline to week 8 were assessed using paired t-tests when normality assumptions were met. For PCS, an additional sensitivity excluding an outlier change value assessed the robustness of the paired estimate.

EQ-5D-5L health-related quality of life

EQ-5D-5L descriptive profiles, utility values and EQ VAS scores were analysed at baseline, week 8 and EOT. The proportion of participants reporting any problems within each EQ-5D-5L dimension and the proportion reporting full health (11111) were summarised by timepoint and study arm. Friedman tests were used to assess within-participant changes in dimension scores across the three timepoints among participants with complete responses. Between-arm mean differences in EQ-5D-5L utility and EQ VAS at each timepoint (week 8 and EOT) were assessed using baseline-adjusted analysis of covariance (ANCOVA) model; with week 8 or EOT score as dependent variables, study arm as main exposure, and baseline score as covariate. Repeated-measures linear mixed-effects models (LMM) were used to estimate overall HRQoL trajectories over time and whether trajectories differ by study arm. Models for utility or VAS scores included fixed effects for timepoint, study arm, and time-by-arm interaction, with a random intercept for participant to account for repeated measurements. Estimated marginal means and pairwise contrasts were used to describe within-arm changes and between-arm differences.

The Paretian Classification of Health Change (PCHC) analyses and the related Health Profile Grid (HPG) were presented as exploratory analyses for individual-level health-profile change. PCHC classifies the change in an individual's health state as better (≥ 1 dimension improved and none worsened), worse (≥ 1 dimension worsened and none improved), mixed (≥ 1 dimension improved and worsened), or no change. The HPG visualised individual-level changes between two timepoints. It requires health-profiles for each timepoint to be ordered from best to worst. The HPG function within R statistical software uses a specified value set for ranking profiles with severity ranking between 1 and 3125, where 1 is best and 3125 is worst. For each participant, the health-profile rankings at the two time points are plotted against each other. Points above the 45° line indicate improvement, and the distance above the line reflects the magnitude of improvement. Points below the line indicate deterioration, whereas points on the line indicate no change (Devlin et al., 2010).

Exploratory comparisons of mean utility across sociodemographic and clinical subgroups were conducted using unadjusted one-way ANOVA using available observations at each timepoint, as well as an exploratory longitudinal mixed-effects model where appropriate. QALY analysis method and missing data imputation are described in Chapter 6.

Missing data

Missingness was assessed separately for each outcome and timepoint and summarised by study arm and reason, where available. The administrative data cut-off for this analysis was 31 July 2026. Denominators included participants who were due and eligible for the relevant assessment by this date. Participants who had not yet reached the relevant follow-up

timepoint by the data cut-off were not classified as having missing data and were reported separately. Participants who were due for assessment but were lost to follow-up, transferred without available follow-up data, or did not complete an expected assessment were considered to have missing data for that timepoint. Where a total or scale score could not be calculated because of incomplete item responses, the corresponding outcome was treated as missing.

Deaths were handled according to the nature of the outcome. For TB treatment outcomes, death contributed to treatment non-success according to WHO definitions. Patient-reported outcome assessments after death were not expected and were therefore not treated as ordinary missing data.

For the primary adherence analysis, participants without evaluable observed-dose adherence data were excluded and missing adherence outcomes were not imputed. Deaths occurring before completion of the 8-week observation period were not treated as missing outcomes; these participants remained in the primary analysis and were classified as not achieving the $\geq 80\%$ adherence threshold. Sensitivity analyses assessed robustness of findings using time-at-risk adherence analyses, in which expected doses were counted only up to death, loss to follow-up, transfer, or censoring, as well as using extreme case analyses.

For longitudinal continuous outcomes, including stigma, SF-12v2, and AIM-IAM-FIM scores, mixed-effects models used all available observations under a missing-at-random assumption. Complete-case or paired analyses were conducted as sensitivity analyses where appropriate.

Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) (AIM-IAM-FIM)

Changes from week 2 to week 8 were analysed using linear mixed-effects models with timepoint as a fixed effect and participant as a random intercept. Paired Wilcoxon signed-rank tests were conducted as sensitivity analyses among participants with complete paired responses.

ix. Post-implementation qualitative evaluation through FGDs and KIIs

After the 6-month pilot implementation phase, we will assess the feasibility and acceptability of the intervention among key stakeholders through a series of KIIs and FGDs (Table 5). A maximum variation purposive sampling will be used to obtain a broader perspective from participants of different age groups and genders. Data collection and analysis will follow methods detailed in Aim 1. The triangulation of quantitative and qualitative results will allow validation and thorough understanding of research findings.

Table 5: Post-implementation qualitative interviews

Post-implementation key informant interviews among TB patients stratified by age and gender	Quantity
18-34	5
35-49	5
50-64	5

≥65		5
Post-implementation focus group discussion with health care providers (HCP)	Number of FGDs	Number of participants
Participating pharmacists	1	5
Nurses, counsellors or medical assistants	1	5
Physicians and administrators	1	5

At 12-month extended implementation phase, barriers and facilitators to implementation fidelity, sustainment and scale-up will be assessed through another series of FGDs and KII, using a structured guide to obtain perspectives from patients who received the intervention, HCP who delivered the intervention, and policymakers, and community representatives involved in supporting the delivery of TB service (Table 6).

Table 6: Post-implementation qualitative interviews on implementation, sustainment and scale-up

Implementation, sustainment and scale-up focus groups among TB patients stratified by age and gender	Number of FGDs	Number of participants
18-34	1	5-8
35-49	1	5-8
50-64	1	5-8
≥65	1	5-8

Implementation, sustainment and scale-up key informants	Quantity
Participating pharmacists	5
Nurses, counsellors or medical assistants	5
Physicians and administrators	5
TB service policy-makers	4
Community representatives	4

x. Development of a Stakeholder-Informed Algorithm for VOT Suitability

The study will be conducted in two steps. **Step 1** focuses on identifying predictors—demographic, clinical, social, contextual, and behavioural—that are associated with successful or failed VOT/DOT outcomes. To achieve this, baseline, treatment, adherence, and outcome data will be drawn from Phases 2 and 3 of the CARE-TB study. The following variables will be collected from each participant:

- **Clinical Factors:** Disease severity, co-morbidities
- **Demographic Factors:** Age, gender, race, educational level, employment status
- **Social and Contextual Factors:** Access to technology (availability of smart devices and stable internet), healthcare access (logistics, travel time, and distance), family support, stigma

- **Behavioural Factors:** History of treatment adherence, substance use (e.g., smoking, vaping, alcohol)

A logistic multivariate analysis will be employed to identify key predictors of VOT adherence and eligibility. Variables found significant in univariable analysis ($p < 0.02$) will be entered into a multivariable logistic regression model to refine the algorithm and determine independent predictors of VOT success. In this study, successful VOT is defined as completing $\geq 80\%$ of scheduled video-observed doses within the first two months post-enrolment.

Step 2 will involve structured stakeholder engagement sessions using the Nominal Group Technique (NGT) to contextualize and refine the statistical findings from Step 1. These sessions will bring together a diverse group of stakeholders—including healthcare providers (physicians, nurses, pharmacists), TB program coordinators, community health workers, and participants from the CARE-TB study who have experienced VOT (both successfully and unsuccessfully). Approximately 20–30 participants will be involved. The NGT process will systematically elicit and prioritize key factors for VOT suitability, facilitating consensus through idea generation, pooled ratings, and ranking exercises.

Stakeholder responses will be analysed to identify recurring themes and unique perspectives, grouping them based on relevant factors for VOT eligibility. To ensure a balanced prioritization, stakeholders will rank factors separately by importance (impact on VOT success) and feasibility (ease of implementation), with a weighted scoring approach applied to integrate both criteria. The highest-ranked factors from NGT will then be cross-checked with statistically significant predictors from Phase 1, ensuring that only predictors that meet stakeholder agreement and statistical relevance are incorporated into the algorithm. Finally, the refined model will be evaluated for practical applicability and adjusted based on stakeholder feedback before finalization. By merging statistical evidence with real-world stakeholder perspectives, this phase will ensure the resulting algorithm is both evidence-based and pragmatically grounded.

4.7 Aim 3 (Phase 4): To evaluate the cost-effectiveness of the digital adherence strategy compared to standard of care from a societal perspective.

4.7.1 Introduction: This aim is to inform the efficiency of the CARE-TB implementation strategy as compared to standard of care in terms of cost-effectiveness from a societal perspective.

4.7.2 Study design: Cost-effectiveness study of CARE-TB strategy compared to standard of care

4.7.3 Study procedures:

i. Overview: Population in this study consists of PTB patients recruited for the study and successfully completed their treatment between July 2024 till August 2025.

The costs attributed to VOT and DOT are estimated for the healthcare and patient perspectives. Healthcare costs are estimated using bottom-up, micro costing method. Patient

and caregiver costs are estimated via interviewer-administered questionnaire at initial recruitment and at Week 8 of treatment by a trained pharmacist. Participants who drop-out, defaulted or died during the study period will be excluded.

The cost-effectiveness analysis will be conducted using study data obtained in Aim 2 to inform immediate outcomes and utilize modelling for long-term outcome projections. As study data only extends till end of TB treatment of 6 months, modelling will be employed to extrapolate observed trends from study data, considering relevant factors, and simulating potential occurrence of events such as relapse and development of drug-resistant TB at 12 months.

QALY (utility) weights are derived from participant responses to the EQ-5D at baseline and 6 months. For TB outcomes, average and incremental costs are used. Costs are assessed using MYR at values for 2024. No discounting is required for a time horizon of less than a year, otherwise a 3% annual discount will be considered for both costs and outcomes.

ii. Comparator strategies:

- (a) CARE-TB STRATEGY: video observed therapy (VOT) with telecounselling
- (b) Standard of care (SOC): directly observed therapy (DOT) with in-person counselling

iii. Cost analyses

Prospective Directly Observed Therapy and Video Observed Therapy Logs

For clinic DOT and VOT, the healthcare providers (nurse/medical assistant/pharmacist) will complete time-motion logs for 3-5 days of DOT sessions on randomly chosen weekdays over a sampling period of 16 weeks (Table 7). Likewise, family members who serve as DOT providers will be required to complete DOT logs. For each DOT/VOT session, the following are recorded:

- Patient characteristic: days on treatment, type of monitoring (DOT by HCP or family, VOT)
- Start and end time for DOT session
 - o Start time: DOT – patient entered DOT room/ space; VOT – staff start logging on to observe a dose
 - o End time: DOT – patient leave DOT room/space; VOT – when staff logs off after viewing the dose
- Missed or rescheduled sessions
- Reported medications side effects
- Travel time and distance (for clinic-based DOT)

DOT/VOT sessions will be identified using generic staff and patient codes. We will use corresponding salary scale by occupational category from the Public Services Commission of Malaysia⁵³ to estimate salary cost and added 30% for fringe benefits. The salaries will be converted into salary per minute (MYR/min) with assumptions of 8-hour workday and 20 working days per month.

Counselling logs

The standard care protocol includes an in-person counselling session with the pharmacist after the first month of intensive phase treatment. In contrast, the CARE-TB arm incorporates a telecounselling session within 2 to 3 weeks of treatment initiation. Each of these sessions will be time-motion logged. In-person counselling time starts when the patient enters the counselling room and ends when the patient exits the room. For telecounselling, the time begins when both patient and provider logs onto the application and ends when they log off (Table 7).

Table 7: Time tasked for each activity

COST CENTRE	ACTIVITY		
Patient's home or TB clinic	Activity: DOT		
	No	Start	End
	1	Patient prepares the medication, a glass of water and TB diary on the table	Patient completes preparation
	2	Carer enters the same space as the patient	Patient gets ready to take the medication
	3	Patient places the pill into mouth while being observed by carer	Patient swallows the pill with water
	4	Repeat Step 2 as necessary until all pills are taken	
	5	Carer checks that all doses are taken for the day	Carer holds TB diary
	6	Carer date and sign TB diary	Carer finishes record
TB clinic	Activity: Follow-up counselling at clinic		
	Specific activity: Registration		
	No	Start	End
	1	Staff holds appointment card	Staff calls number, patient goes to the counter
	2	Staff looks for patient's file	Staff stamps date on BHT, receives payment, gives number to patient
	3	Staff records registration in eHIS (computerised record)	Staff finishes record
	4	Staff sends file to blood taking/counselling room	Staff comes back to counter
	Specific activity: Blood taking		
	No	Start	End
	1	Staff holds appointment card	Staff calls number, patient goes to the room
	2	Patient enters blood taking room	Staff verifies patient identity
	3	Staff starts blood taking process	Staff completes blood taking
	4	Staff safely stores labelled products	Patient exits the room
	Specific activity: Counselling		

	No	Start	End
	1	Pharmacist holds appointment card	Pharmacist calls number, patient goes to the room
	2	Patient enters counselling room	Pharmacist verifies patient identity
	3	Pharmacist starts counselling process	Pharmacist completes counselling
	4	Pharmacist records session in eHIS	Patient exits the room
Patient's home	Activity: Video observed therapy (VOT)		
	No	Start	End
	1	Patient prepares the medication, a glass of water and phone on the table	Patient completes preparation
	2	Patient turns on WhatsApp application	Patient gets ready to record
	3	Patient turns on video message recording, ensuring that his/her face can be seen	Patient places phone on table to record
	4	Patient places the pill into mouth while being recorded	Patient swallows the pill with water
	5	Repeat Step 4 as necessary until all pills are taken	
	6	Patient ends recording	Patient sends the video message to healthcare provider
Patient's home	Activity: Telecounselling		
	No	Start	End
	1	Pharmacist checks appointment list	Pharmacist gets ready to call
	2	Pharmacist video calls patient	Patient picks up the video call
	3	Pharmacist begins telecounselling session	Pharmacist ends call session and records in eHIS

Healthcare cost

Healthcare cost includes implementation start-up costs like training and materials. All fixed and variable costs associated with healthcare provider perspectives on DOT/VOT and counselling are detailed below (Table 8).

Table 8: Summary of healthcare costs data

Type of cost	Costing method	Source of data
Start-up training costs for VOT	Time spent training x corresponding salary	Training log;

		Public Services Commission of Malaysia (salary)
Fixed cost		
Data charges	Time used for each activity x data charges per minute (RM/min)	Time-motion logs; Provider expenditure reports
Phones	Actual expenditure	Provider expenditure reports
Headsets	Actual expenditure	Provider expenditure reports
Training materials	Actual expenditure	Provider expenditure reports
Variable cost		
Staff time for each activity (DOT, VOT, telecounselling)	Average hourly wages x mean time spent for each activity	Time-motion logs; Public Services Commission of Malaysia (salary)
Patient training by staff	Average hourly wages x mean time spent for each activity	Time-motion logs; Public Services Commission of Malaysia (salary)

We did not include computers that are used for daily operational tasks onsite in the cost analysis. As TB programs operate TB clinics regardless of DOT or counselling type, we did not include overhead and drug costs associated with maintaining a TB clinic.

Patient and caregiver cost

We will collect information on age, ethnicity, health status, country of birth, education, occupation, monthly income, distance travelled to the TB clinic, travel time and cost, and time spent waiting at the clinic. For patients on clinic DOT, we estimate time spent in the clinic by using the DOT time reported by staff. The questionnaires encompass queries related to VOT, including time dedicated to software learning, hardware used (e.g., phones or tablets), and technical issues encountered in recent sessions. Patient needs for childcare during visits to the TB clinic and the frequency of patient-staff communication via phone, text, or email to coordinate DOT visits were gathered.

The valuation of time spent on DOT and travel, we use patient's self-reported income but if this is unreported, we will match their self-reported occupation with data from the Malaysian Bureau of Labour Statistics. We will prorate the cost of patients' personal phones used for VOT,

in proportion to the time the patient spent on VOT. We assume the same useful life and price of smartphones following average market value for all patients. The value of dependent care is estimated by using productivity loss due to time spent for DOT and accompanying patient at clinic.

Table 9: Summary of patient and caregiver cost data

Type of cost	Costing method	Source of data
Start-up training costs for VOT	Time spent training x corresponding salary	Time-motion logs; Interviews with patient
Fixed cost		
Data charges	Time used for each activity x data charges per minute (RM/min)	Interviews with patient
Phones	Cost per unit time x time spent for VOT	
Variable cost		
DOT/VOT time cost	Time spent x corresponding hourly salary	Interviews with patient
Counselling time cost (to include waiting time for clinic-based in-person counselling)	Time spent x corresponding hourly salary	
Travel time, round trip	Time spent x corresponding hourly salary	
Travel out-of-pocket	Actual expenditure	
Coordination time	Time spent x corresponding hourly salary	
Dependent time cost	Time spent x corresponding hourly salary	
Childcare needs during clinic visits	Time spent x hourly childcare cost	

Societal cost

For each type of activity (DOT, VOT and counselling), we add up the provider and patient costs to estimate societal costs.

Quality-Adjusted Life Years (QALY)

Health related quality of life (HRQOL) will be measured using EQ-5D which will then be converted to health state utility value using the Malaysian tariff ⁵⁰. Participants will complete the EQ-5D questionnaire at baseline and at 6 months. The QALY gained for each intervention arm will be calculated by adjusting the accrued utility value by the time spent alive.

Calculation of cost-effectiveness and incremental cost effectiveness analysis (ICER):

First, the proportion of patients who completed each treatment arm is multiplied by the cost of managing a patient up till treatment completion. Incremental cost per case cured and incremental cost per death averted are calculated using the difference in the cost of implementation strategies divided by the difference in cure rate or death rate. Incremental

cost per QALY gained is incremental cost of achieving on additional QALY with the CARE-TB strategy vs standard of care strategy. Incremental cost per adherence rate equals to the difference in implementation cost divided by the difference in adherence rate, in other words, the cost necessary to gain one additional adherent patient.

Tuberculosis model:

The cost effectiveness of the implementation strategies will be evaluated in a decision tree model for projected long-term outcomes. The model consists of TB treatment for 6 months. Standard treatment outcome definitions from the WHO will be used (Table 10). For each intervention, a patient can follow one of four possible pathways (treatment success, died, failed treatment, or loss to follow-up/transferred out) (Figure 4). Beyond 6 months up to 1 year, cost-effectiveness modelling will be done for potential occurrence of drug resistance and recurrent cases. Model input will use prospective implementation study data, published literature (systematic reviews, RCTs), Malaysian TB sector databases.

Analysis of the decision tree model is executed based on few assumptions. Firstly, TB adherence strategies follow a standard guideline for in-person DOT and VOT. Secondly, all procedures for DOT and VOT were assumed to be standardized with no significant variation in the number of personnel, consumables, devices and time consumed for each method. Hence there should be no difference in cost incurred although observations are performed in different settings. Thirdly, TB treatment cost is assumed to be the same for both strategies.

Table 10: Definition of treatment outcomes for TB patients (excluding rifampicin-resistant, RR-TB or multidrug-resistant, MDR-TB)

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure <i>but</i> with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of <i>cured</i> and <i>treatment completed</i>

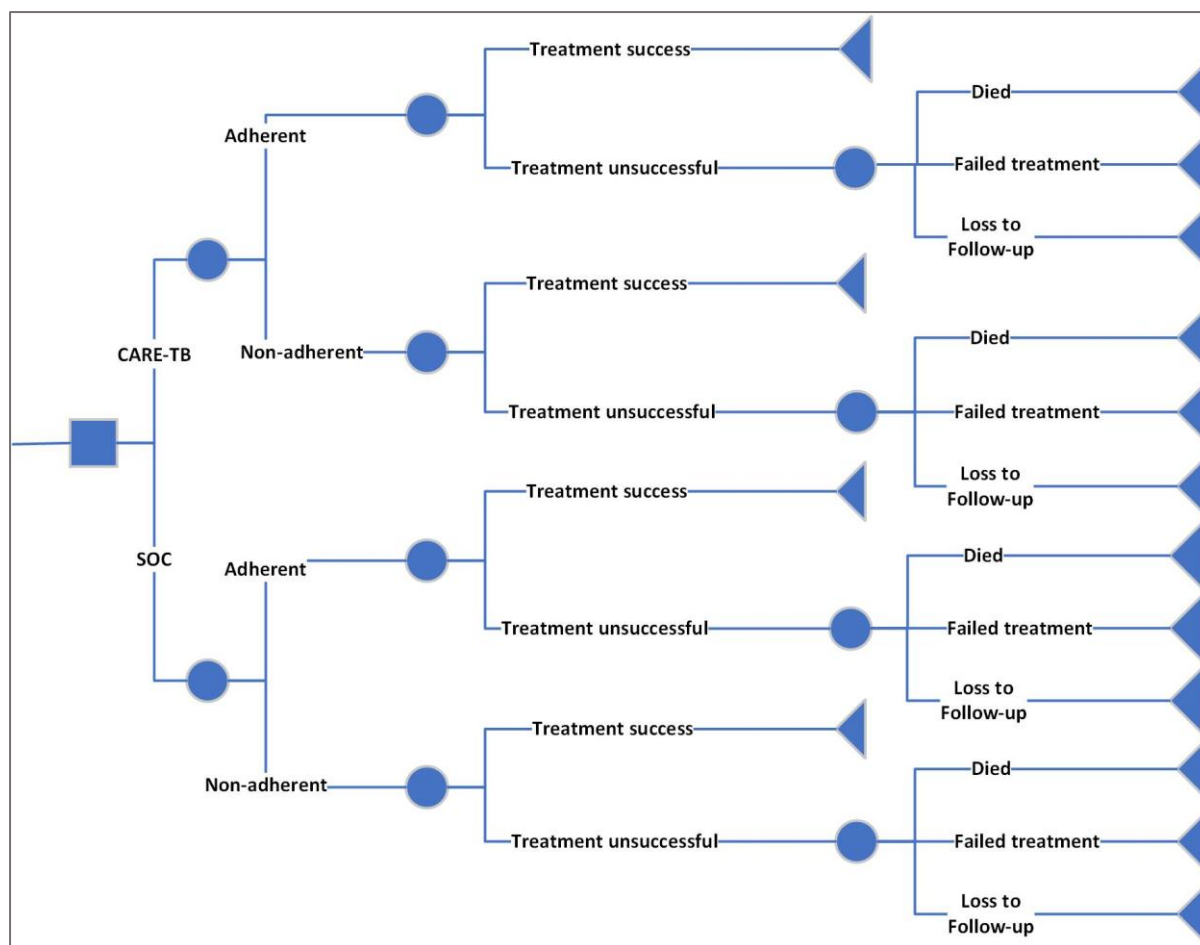


Figure 4: Representative decision tree for TB model

iv. Outcome measures

(a) Short-term, study-based outcomes (6 months): Cost per patient cured, Cost per treatment completion, Cost per death averted, Cost per QALY gained, Cost per adherence rate, and ICER for each outcomes

(b) Long-term, modelling outcomes (12 and 24 months): Cost per recurrent case, Cost per drug resistant case

v. Sensitivity analyses

Probabilistic sensitivity analysis using bootstrap will be performed on costs or effects about which there is some uncertainty. Sensitivity analysis will be conducted for model robustness that includes indirect cost saved (reduced transmission), varying discount rates/ adherence levels/ time-cost and using healthcare only perspective. Subgroup analyses will be employed to reduce the effect of heterogeneity on cost effectiveness (e.g. stratified analysis between HIV and non-HIV patients, young and elderly adults).

vi. Statistical analyses

The economic analysis will be conducted by intention to treat. Cost, QALY and resource use data will be summarised and analysed using RStudio software (4.3.1).

5.0 ETHICAL CONCERNS

5.1 Human subjects

This research will adhere to local ethical standards for research in human subjects. It will be conducted in accordance with all applicable regulatory requirements, and in accordance with good clinical practice (GCP).

5.1.1 Institutional Review Board

The study protocol and associated documents including informed consent documents, as well as any subsequent modifications of these, will be reviewed and approved by the designated IRB with respect to scientific content and compliance with applicable research and human subject's regulations. The local institutional review board (IRB)/ethics committees (EC) responsible for oversight of this study is the National Medical Research Register, National Institutes of Health, Ministry of Health Malaysia, Shah Alam.

5.1.2 Confidentiality and Security of Source Documents and Study Data

To address patient data and video privacy concerns, investigators will use end-to-end encrypted video messaging application, comply with data protection regulations, and conduct regular security audits. Videos submitted by patients will be deleted from the research phone one week after receipt, following documentation and quality assurance procedures. Only authorized personnel will have access to patient information. The research phone and its data will be password-protected and stored securely under lock and key.

Patient names and other information that can be used to identify participants will be kept private and confidential at study sites. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. Site Principal Investigators would be responsible for data protection and storage. Participants will not be personally identified in published results or in presentations. If a breach of confidentiality or private identifiable data is inadvertently disclosed, the study PI, site PI, and IRB will be immediately informed. An investigation into the breach will be conducted and appropriate measures to minimize impact and prevent recurrence will be undertaken.

All data obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. In the dissemination or presentation of research findings, the identities of respondents will not be disclosed unless explicit consent is obtained. Study data will be archived for a duration of 3 years following the conclusion of the study for analytical purposes, with the assurance that respondent identities will remain undisclosed throughout this period. Data will be destroyed after the above-mentioned period.

Subjects will be given access to their personal information and study findings via email.

5.1.3 Risks and Risk Minimization

The research risks and risk assessment plan for this project are detailed below.

Description of risk (Low/Medium/High)	Proposed risk-mitigation measures
---------------------------------------	-----------------------------------

Patient data privacy and safety concerns. (medium)	Use end-to-end encryption video messaging application, comply with data protection regulations, and conduct regular security audits. Ensure that only authorized personnel have access to patient information. Keep research phone and data secure under lock and key.
Low user recruitment rate. (high)	Run promotional activities and ease recruitment procedures by diverting recruitment documentations to research assistants. Devise a backup plan to recruit participants from other sites.
Insufficient manpower for implementation. (medium)	Reduce the number of implementation activities or packaged components, eliminating ones that are least effective and acceptable.
Patients or healthcare providers may resist or struggle to adapt to the new technology, leading to low usage rates. (low)	Involve end-users in design phase, provide comprehensive training and user-friendly instructions. Employ iterative rapid-cycle evaluations to revise implementation strategy.
Inaccurate or unreliable data may be collected, leading to incorrect assessments of patient outcomes e.g. adherence. (medium)	Ensure data accuracy through training, rigorous testing, validation, and continuous monitoring.

5.1.4 Benefits to Participants

Study participants are continuously linked to a healthcare provider through a messaging platform for the entire duration of intensive phase TB treatment allowing for direct and prompt diagnosis of any complications that may arise from the treatment. Participants on both arms are linked to sources of financial aid (e.g., Selangor TB Prihatin fund) upon consent. Indirect benefit includes improved counselling workflow and engagement to address stigma and other barriers to medication adherence.

5.1.5 Costs and Compensation

There is no cost for joining this study. All patient and community participants will receive financial compensation of up to approximately RM 100, as compensation for time taken to participate in each KIIs and FGDs. Health care providers, administrators and policymakers will not be compensated for time taken to participate in KIIs or FGDs.

5.1.6 Informed Consent

Each participant will receive a Participant Information Sheet, and signed consent will be obtained for participation in the study, interviews, and Focus Group Discussions (FGDs) (see Annexes 1a to 7a). The site Principal Investigator and site study staff will be responsible to obtain informed consent and make clear that declining participation will not compromise the quality of care received. Informed consent forms will describe the purpose of the study, study procedures, the scope of data to be collected, and any risks and benefits to participation. The

consent form will be in the appropriate language for the participant and will remain in each study participant's study file. A copy of their signed consent will be offered to all participants.

5.1.7 Participation and Withdrawal from Study

Participants may withdraw from the study at any time without affecting the medical care they receive. A Study Termination / Treatment Completion Form should be completed upon withdrawal. For qualitative data, if consent is withdrawn after participation has begun, data collection will cease, and any previously gathered data will be destroyed and excluded from analysis. However, in the randomized study, data collected prior to withdrawal will be retained to maintain the study's integrity and validity. All data will be handled confidentially, following ethical guidelines and data protection regulations.

5.1.8 Report of Violations and Deviations

Any deviation from the study protocol will be reported to the study and site principal investigator. Any deviations from the study protocol deemed serious by the site principal investigator will be promptly reported to the local IRB and study sponsor, including their details and measures taken to address them.

5.2 Assessment of Medication Side Effects

Participants will be asked to report any possible medication side or adverse effects during VOT sessions or clinic visits, in accordance with local procedures. Symptoms will be graded and reported in the "Adverse Drug Event" form. Adverse events reporting due to TB treatment will be done as per usual practice, using the local standard reporting protocol via pharmacy to the National Pharmaceutical Regulatory Agency.

5.3 Termination Rules for Study Participation

Study investigators can withdraw a participant from the study if they no longer meet the eligibility criteria and the reason for withdrawal will be documented on the Study Termination / Treatment Completion Form as late exclusion. The following are non-mutually exclusive late exclusion criteria:

- i. Diagnosis changes to multidrug resistant TB, pre-XDR, or XDR TB.
- ii. Clinician rules out TB
- iii. Unexpected incarceration
- iv. Serious adverse event

5.4 Study Discontinuation

The study may be stopped at any time by the sponsor or local IRB as part of their duties to ensure that research participants are protected. Reasons for terminating the study may include, but are not limited to the following:

- Data recording is inaccurate or incomplete at the site
- The site does not adhere to the approved protocol or applicable regulatory guidelines in conducting the study

5.5 Conflict of Interest

None of the investigators have known conflicts of interest to report in relation to the study.

6.0 PUBLICATION AND DISSEMINATION OF RESEARCH FINDINGS

Upon receiving approval from the Director General (DG) of Health, the study results will be disseminated through academic abstracts or manuscripts submitted to relevant conferences or peer-reviewed journals. Data from this study may also be presented to regional, national or local stakeholders with interest in the study and its assessed issues. Data used in related publications or presentations will be deidentified.

7.0 STUDY GANTT CHART AND MILESTONES

Gantt chart/ workplan

Year	2023	2024				2025				2026
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Literature review and protocol development	x									
IRB protocol submission & approval; other study preparations	x	x								
Facilitators & barriers data collection & analysis (FGDs; KIIs)			x	x						
Write-up and publish qualitative study					x					
Develop and test implementation strategy; site staff training (iterative)					x	x	x	x		
Implementation phase (12-months)						x	x	x	x	
Cost data collection						x	x	x	x	
Feasibility and acceptability data collection & analysis (FGDs; KIIs)							x	x		
Post-implementation site cost record review & analysis								x	x	
Sustainment and scale-up data collection & analysis (FGDs; KIIs)								x	x	
Cost effectiveness analysis									x	
Abstract and manuscript development (multi-methods effectiveness-implementation and cost-effectiveness)										x

Milestones

Description	Date	Cumulative Project Completion Percentage (%)
Literature review and protocol development	02/10/2023	5%
IRB protocol submission & approval; other study preparations	01/01/2024	10%
Proposal defense and recruitment for interviews	20/06/2024	11%
Facilitators & barriers data collection & analysis (FGDs; KIIs)	15/09/2024	20%
Write-up and publish qualitative study	30/12/2024	25%

Develop and test implementation strategy; site staff training (iterative)	01/01/2025	30%
Implementation phase and cost data collection	15/03/2025	35%
Feasibility and acceptability data collection & analysis (FGDs; KIIs)	15/09/2025	45%
Post-implementation site cost record review & analysis	01/01/2026	55%
Sustainment and scale-up data collection & analysis (FGDs; KIIs)	01/04/2026	60%
Cost effectiveness analysis	30/07/2026	65%
Thesis submission, abstract and manuscript development	30/11/2026	85%
Publish 2 papers (mixed-methods effectiveness-implementation and cost-effectiveness)	01/05/2027	95%
Thesis defense and final submission	15/06/2027	100%

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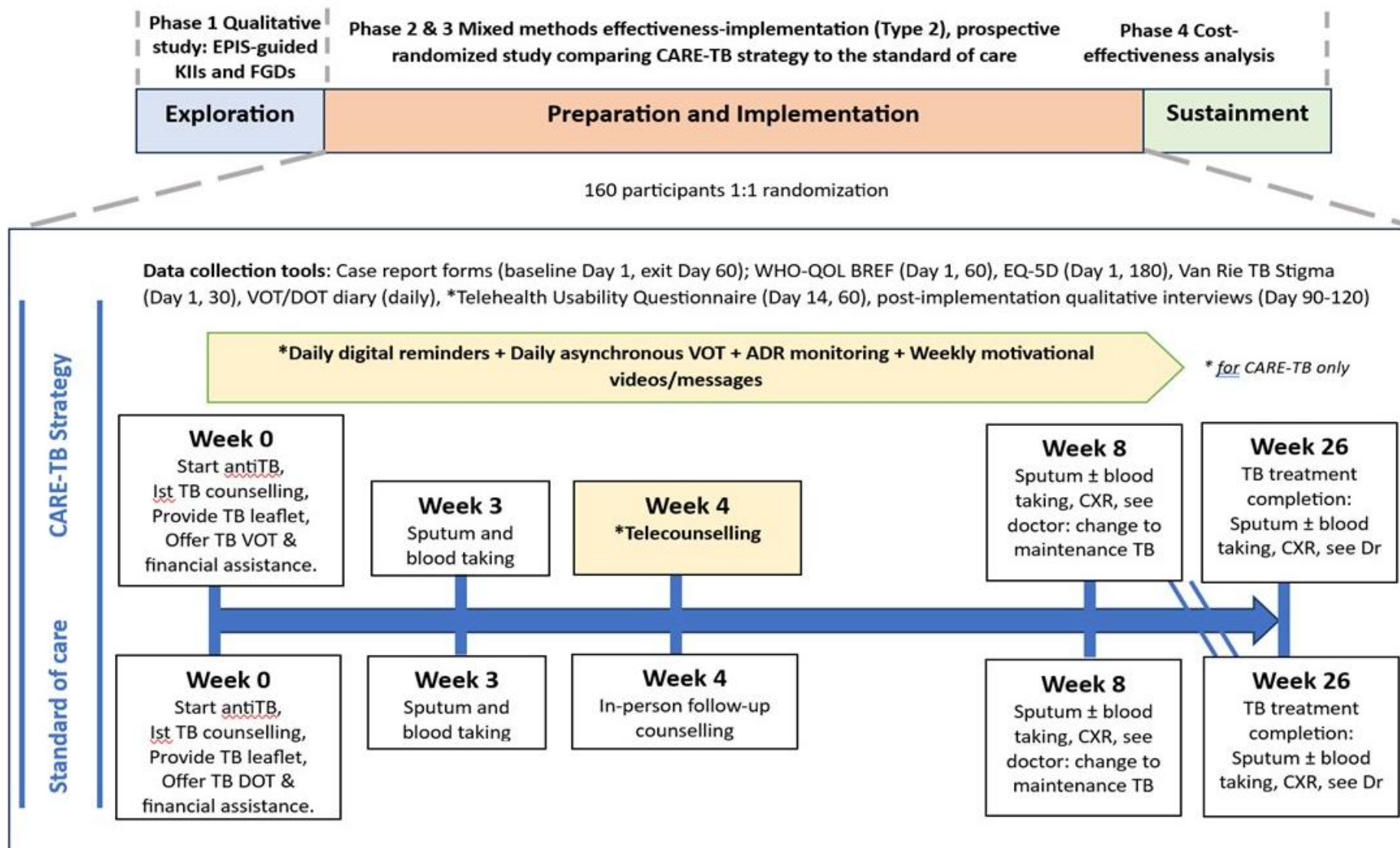
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Annex A Study Flowchart



Annex B Practice Guidelines for VOT

Practice Guidelines on Asynchronous Video-Observed Therapy (CARE-TB Study) for Healthcare Providers

Directly Observed Therapy (DOT) serves as a tool to enhance adherence and ensure positive treatment outcomes for individuals with active tuberculosis (TB). Video Observed Therapy (VOT) presents a potentially more convenient and client-centered method of delivering medication for some clients.

It is important to note that the guidelines provided herein are for informational purposes only. These guidelines cover eligibility and VOT processes for consideration, and the information should not be considered as legal or medical advice to be relied upon.

Eligibility Criteria

A healthcare provider should assess the specific circumstances of each case to determine the suitability of the client for Video Observed Therapy (VOT). The following criteria are provided as points to consider when evaluating if a client can be considered for VOT in the CARE-TB study.

Patient inclusion criteria:

1. Microbiologically confirmed pulmonary TB (smear- or culture-positive PTB)
2. 18 years old or older
3. Able to give consent and physically able to participate in the study
4. Own a video-recording device with internet connectivity
5. Within the first 3 weeks of intensive phase TB treatment

Patient exclusion criteria:

1. Complicated TB disease including TB meningitis, TB bone/joint, and disseminated TB with planned treatment duration of 9 to 12 months.
2. Confirmed or suspected drug-resistant (DR)-TB
3. Documented cognitive, motor, or visual disability that will hinder video device use and lack assistance of a caretaker
4. Receiving injectable anti-TB drugs
5. Incarceration or other involuntary detention

Reasons to discontinue Video Directly Observed Therapy (VOT) and revert to in-person or modified Directly Observed Therapy (DOT) include:

1. Changes in the client's eligibility status.
2. Client expresses a preference to return to in-person or modified DOT.
3. Inability to maintain confidentiality in VOT settings (e.g., housing or technology issues).
4. Client consistently misses VOT defined as missing three daily doses within a week or missing two daily doses per week for 2 consecutive weeks
5. Client defaults on other aspects of adherence (e.g., missing medical appointments, not returning calls).

(Note: VOT can resume if the issues leading to its discontinuation are resolved, and there is mutual agreement between the healthcare provider and the client.)

VOT Process

Initiation of VOT

At the start of TB treatment, all of the following must be completed before initiating VOT:

1. Staff assess for VOT inclusion and exclusion criteria for eligibility.
2. Staff discuss the option of VOT with the client.
3. Client agrees to participate in VOT and signs a consent form to participate in VOT that includes:
 - a. Adherence requirements/expectations for VOT
 - b. Possible confidentiality concerns
 - c. Steps required by client for VOT (follow instruction brochure)
 - d. Client responsibilities in case of technical failure and unable to send video: WhatsApp text or call to inform on the same day or next day.
4. Client saves the corresponding VOT phone number on his/her phone under “Klinik TB VOT”.
5. Client and staff agree on a regular frequency (for WhatsApp video message).
6. Staff review the procedure for completion of VOT.

VOT Staff Responsibilities

VOT providers are responsible for the following:

1. Provide client with instructions and training on how to use the VOT application(s)/equipment. Retrain client as required.
2. Document each encounter in the VOT diary.
3. Provide client with information about who to call with questions or in an emergency.
4. Reestablish VOT by sending reminders based on protocol.
5. Refer for further follow-up if necessary e.g. occurrence of adverse drug reactions

Protocol for WhatsApp video message asynchronous VOT

1. Client prepares the tablets and a glass/bottle of water on a table.
2. Client turns on WhatsApp.
3. Client activates WhatsApp video message.
4. Client identifies themselves and remains in the camera view for the duration of the video recording.
5. Client shows each pill separately, places the pills in their mouth one-by-one after identification and swallows the pills with water.
6. Client opens mouth after ingesting pills to show the staff that the pills were swallowed.
7. Clients presses on the “send button” to stop recording and send the video to the healthcare provider.
8. Staff review the store-and-forward videos and complete required documentation in a timely manner.

Ensuring Client Confidentiality

Staff completing VOT must conform to all applicable legal provisions and study protocol regarding the protection of patient information.

Patient Asynchronous Video Observed Therapy (VOT) Agreement Form

Date: ____ (D)/ ____ (M)/ ____ (Y)

I, _____, understand that I have been diagnosed with tuberculosis (TB) and have been prescribed medication by a physician to treat this disease. If my disease goes untreated, there may be serious consequences:

- My illness will become more severe and last longer
- I may spread TB to others
- I may develop and spread drug-resistant TB
- I may die from TB

During my treatment, observation will be performed remotely through WhatsApp video messages. I agree to record and send video messages of my intake of TB medications to my healthcare provider once a day for 2 months. My healthcare provider will watch me take my medications everyday.

To complete my treatment and protect my family and friends, I will:

1. Come to the clinic to give sputum and blood specimens when required.
2. Keep all appointments for medical evaluation and X-rays.
3. Participate in VOT as agreed upon with my healthcare provider. For any reasons that I am unable to send the videos, I will notify my healthcare provider immediately.

I understand that I may switch back to standard directly observed therapy (DOT) at any time during the treatment.

I have read this agreement and understand the following (tick each box):

- ☐ My adherence to this treatment regimen is very important.
- ☐ I am responsible for the three tasks mentioned above.
- ☐ If I failed to complete treatment, legal action may be taken to ensure that I complete treatment (under the Prevention and Control of Infectious Diseases Act 1988).

Patient Signature: _____ Date: ____ (D)/ ____ (M)/ ____ (Y)

Provider Signature: _____ Date: ____ (D)/ ____ (M)/ ____ (Y)

Annex C TB Counselling Checklist

Tuberculosis Counselling Checklist				
1. TUBERCULOSIS				
Yes/No	Brief introduction			
2. MEDICATION				
Yes/No	TB medication			
Yes/No	Length of treatment			
Yes/No	Administration			
Yes/No	Possible side effects and its management			
3. DRUG INTERACTION				
Yes/No	Drug - Drug interaction (eg, antacid, methadone etc)			
Yes/No	Ethanol / Nutrition / Herb interactions			
4. ADHERENCE				
Yes/No	TB book			
Yes/No	Emphasize follow ups			
Yes/No	What is DOTS			
Yes/No	Is DOTS possible?			
	If yes, done by:	☐ Healthcare worker	☐ Family/caregiver	☐ Prison/detention centre
5. POTENTIAL BARRIERS TO ADHERENCE				
Yes/No	Unable to identify			
Yes/No	Difficult to swallow pills			
Yes/No	Self-administer (No DOTS)			
Yes/No	Active illicit drug user			
Yes/No	Logistic/transport issues			
Yes/No	Poor social support			
Yes/No	Others, please state: _____			
6. SEEK MEDICAL ASSISTANCE IF:				
Yes/No	Nausea or vomiting			
Yes/No	Jaundice - yellowish skin or eyes, dark urine (orange / red urine is a normal side effect and is not harmful)			
Yes/No	Unexplained fever or tiredness			
Yes/No	Tingling or numbness of hands or feet, or joint pains			
Yes/No	Skin rash, itching skin or bruising			
Yes/No	Visual changes or change in red - green colour vision			
BODY WEIGHT (kg):				
CURRENT TB REGIME:				
INTENSIVE PHASE START DATE:				
MAINTENANCE PHASE START DATE:				
REMARKS:				

Annex D Pre-implementation Qualitative

1a Pre-implementation Patient Information Sheet and Informed Consent

Version 3.0, 26 March 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10

people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve your ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) to improve patient-centered TB care in Malaysia should be implemented and sustained. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

Up to 20 TB patients who are or were on TB treatment, 20 healthcare providers and administrators from TB clinics, 6 policymakers, and 5 community representatives will be interviewed to learn their opinions and perspectives on challenges and barriers to integrating digital adherence services into TB care.

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

We are interested in your thoughts and experiences with the digital adherence programme, which includes whether you find it practical, easy to use, and what you think are potential barriers or facilitators to scaling up the program. The interview will take about an hour, and it will be recorded with your permission to help us understand your answers better. We will also ask for some basic information like your age, gender, job, income, education, marital status, and where you live to help us analyse the results.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. Answering questions related to stigma in tuberculosis may make you feel uncomfortable. You can choose not to answer those questions, and it won't cause any problems. Talking about your thoughts and experiences might be emotional. If you ever feel like the interview is becoming too much for you, please let us know, and we will stop the interview right away.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM100 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future. If you withdraw your consent after you begin participating in this study, your data will no longer be collected. Data that was collected prior to your withdrawal will also be destroyed and will not be used in the data analysis later.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner, and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;
9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

.....

Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at
_____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

If the patient is illiterate, a witness must be present during the consent process. After the patient gives consent to participate in the study by placing a mark in the place of his/her signature (e.g., with an X, thumb print, or other mark), the witness will write the name of the patient and the date in the above lines, then sign and date in the below lines.

Signature of Witness, for non-literate participant: _____

Witness's Name (print): _____ Date: _____

IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____

IC number: _____

1b Pre-implementation EPIS guided semi-structured interview questions for patient (non-users)

The aim of this interview is to explore TB patients' experiences with current TB DOT and counselling practice, and to explore their views on the CARE-TB strategy (VOT, telecounselling, and Elearning)

Building rapport: How have you been coping with your TB disease? Can you share your experience with the treatment so far?

EPIS Constructs

Questions	Prompts	EPIS Framework
1. TB medications need to be taken daily for 6 months. What is it like to take TB tablets every day?	From a scale of 1 to 10, how important is it for you to take medications everyday? From a scale of 1 to 10, how confident are you that you can take them everyday? How do you remember to take your medications daily? How would you prefer to receive daily reminders from the hospital, if they were to provide them? (Probe methods and frequency)	OUTER CONTEXT Patient characteristics
2. Who is observing your TB medication intake daily?	If none: What do you think of this current method of an observer monitoring your intake in-person every day? How does it influence you to take your medications? What do you think of the ease of use/cost/time/loss of productivity?	OUTER CONTEXT Patient characteristics
3. Does having knowledge about TB affect your compliance to treatment (sticking with treatment)?	If yes, how? If no, why? How do you get information or knowledge on your TB disease and treatment? How will this impact your ability to complete treatment?	OUTER CONTEXT Patient characteristics
4. What are your thoughts on having weekly educational videos or messages sent through WhatsApp (to share information about TB disease and treatment)?	Are there other ways we can help you get the TB information you need?	INNOVATION FACTOR Innovation characteristic

5. How do you feel about people knowing you have TB?	Who have you disclosed your status to? What are your concerns? On a scale of 1 to 10, how concerned are you about transmitting TB to others?	OUTER CONTEXT Patient characteristics
6. One alternative to being observed by health workers or family is taking video observed therapy. Have you heard of video observed therapy (VOT)?	If yes, - where have they heard about it? What do they think it is? <i>/ If no- share video (steps in recording and how we use and store the recordings).</i> What are your thoughts about the idea of recording yourself taking medications daily? Will having additional support from friends and family make a difference? Do you have any concerns or worries about being able to use it? (daily routine fit, privacy) What might be some of the advantages of this method (compared to the current method)? Can you elaborate? Are you comfortable with sharing your video recordings with your healthcare provider? Why? Are you concerned about the privacy and confidentiality issues with regards to stored videos or information that are shared with your health care provider? Why or why not? Do you think there is extra cost involved? E.g data or new phone Who would you prefer to view your recordings?	INNOVATION FACTOR Innovation fit / innovation characteristic OUTER CONTEXT Patient characteristics
7. Did you get counselled on TB and medications when you started treatment?	If yes, how was it? If no, what are your thoughts on the value of counselling for your treatment? Who counselled you? Who do you think are the best people to provide counselling on TB treatment or drugs?	INNOVATION FACTOR Innovation fit
8. How do you feel about getting counselling via a videocall (using WhatsApp or Zoom)?	Do you have any concerns?	INNOVATION FACTOR Innovation characteristic

	What potential benefits do you see in video-call compared to in-person counselling at the TB clinic? Can you elaborate?	
9. Are there something else you think should be included in this package which can help you through your treatment process?	Weekly reports of adherence? Links for financial assistance? Do you need financial aid for TB treatment? Do you need assistance to apply for financial aid from the social welfare department, if you are eligible?	INNOVATION FACTOR Innovation characteristic

Conclusion: Thank you for sharing your insights. Is there something else you would like to discuss or add before we conclude our interview?

2a Pre-implementation Information Sheet and Informed Consent for Community Representatives and Peer Counsellors

Version 3.0, 26 March 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10 people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve your ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) to improve patient-centered TB care in Malaysia should be implemented and sustained. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

Up to 20 TB patients who are or were on TB treatment, 20 healthcare providers and administrators from TB clinics, 6 policymakers, and 5 community representatives will be interviewed to learn their opinions and perspectives on challenges and barriers to integrating digital adherence services into TB care.

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

We are interested in your thoughts and experiences with the digital adherence programme, which includes whether you find it practical, easy to use, and what you think are potential barriers or facilitators to scaling up the program. The interview will take about an hour, and it will be recorded with your permission to help us understand your answers better. We will also ask for some basic information like your age, gender, job, income, education, marital status, and where you live to help us analyse the results.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. Answering questions related to stigma in tuberculosis may make you feel uncomfortable. You can choose not to answer those questions, and it won't cause any problems. Talking about your thoughts and experiences might be emotional. If you ever feel like the interview is becoming too much for you, please let us know, and we will stop the interview right away.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM100 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. Data that was collected prior to your withdrawal will also be destroyed and will not be used in the data analysis later.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner, and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;

9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

.....

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at
_____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____ IC number: _____

2b Pre-implementation EPIS guided semi-structured interview questions for community or peer volunteer.

The aim of this interview is to explore community or peer counsellors' experiences with current TB practices, and to explore their views on the CARE-TB strategy (VOT, telecounselling, and Elearning)

Building rapport:

1. What is your role in TB/HIV care and support within this facility and beyond?
2. How long have you been a community health worker and how long have you worked with TB/HIV?

EPIS Constructs

Questions	Prompts	EPIS Framework
1. TB medications need to be taken daily for 6 months. How important is it to take TB tablets everyday?	In your opinion, what is the best way to remember to take medications daily? Will getting daily reminders be helpful? Why? In what form would you like to get these reminders (probe: what do you think about reminders being sent through WhatsApp?)	INNER FACTOR Individual characteristic
2. Can knowledge on TB help with a persons TB recovery/treatment adherence? Can you explain how so?	How or where do you get information or knowledge disease and treatment?	INNER FACTOR Individual characteristic
3. What is your opinion on having weekly educational videos or messages sent through WhatsApp to patients, to share information about TB disease and treatment?	Do you think it is acceptable and useful for patients? Why or why not? How do you feel about the convenience of sharing information through WhatsApp? Would you suggest another method to share information?	INNOVATION FACTOR Innovation characteristic
4. How comfortable are you with talking to or being in the same space with a person who has TB?	On a scale of 1 – 10 (least > most comfortable), how comfortable are you? What are your concerns? Will be afraid of getting the disease?	INNER FACTOR Individual characteristic

5. What do you think about having patients take <1-min video messages of themselves ingesting TB medication (VOT) and sending them over WhatsApp to their healthcare provider daily?	Do you believe that patients can perform VOT, at least for a period of 2 months? What are your concerns? - <i>complexity/usability, cost, confidentiality/privacy of data</i> Do you think a lay person or community volunteer can take on the role of verifying every dose taken via videos sent by TB patients, document the doses, and relay reported side effects (if any) to the doctor or pharmacist? How do you think VOT can be integrated into your current workflow? (<i>probe on workload, time</i>)	INNER FACTOR Individual characteristic INNOVATION FACTOR Innovation characteristic INNER FACTOR Organization characteristic INNOVATION FACTOR Innovation fit
6. What are your thoughts on receiving counselling on TB disease and treatment through video calls?	Any concerns? Any comments about the engagement that occurs during video call sessions? How can we improve engagement? Who do you think should deliver the counselling?	INNER FACTOR Individual characteristic INNOVATION FACTOR Innovation characteristic INNER FACTOR Organization characteristic
7. Proposed digital package contains: a. VOT: send daily reminders, keep track of your medication intake & allow reporting of medication-taking problems, b. telecounselling: motivational counselling and education on TB disease/ treatment, c. e-learning: online educational materials (videos, infographics)	Which components do you think will be most helpful to improve adherence? Why? Is there any component you will omit? Why? Which components would you be most comfortable assisting with? Is there something you would suggest adding on?	INNOVATION FACTOR Innovation characteristic

What do you think of the bundling of this digital adherence package?		
8. What kind of training do you think you will need to carry out the monitoring work?	Focus of training? How frequent? What is the preferred format of training? (<i>manual, workshop, TB web portal with online evaluation</i>)	INNER FACTOR Organization staffing processes
9. If you encounter an adverse drug reaction reported by patient, what will you do?	Who do you prefer to report to? (<i>doctor or pharmacist</i>) What is your preferred method of reporting? (<i>verbally in person or call, messaging service, document in paper/system</i>)	INNER FACTOR Individual characteristic

Conclusion: Thank you for sharing your insights. Is there something else you would like to discuss or add before we conclude our interview?

3a Pre-implementation Information Sheet and Informed Consent for Healthcare Providers, Administrators, and Policymakers

Version 3.0, 26 March 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10 people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve your ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) to improve patient-centered TB care in Malaysia should be implemented and sustained. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

Up to 20 TB patients who are or were on TB treatment, 20 healthcare providers and administrators from TB clinics, 6 policymakers, and 5 community representatives will be interviewed to learn their opinions and perspectives on challenges and barriers to integrating digital adherence services into TB care.

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

We are interested in your thoughts and experiences with the digital adherence programme, which includes whether you find it practical, easy to use, and what you think are potential barriers or facilitators to scaling up the program. The interview will take about an hour, and it will be recorded with your permission to help us understand your answers better. We will also ask for some basic information like your age, gender, job, income, education, marital status, and where you live to help us analyse the results.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. If you ever feel like the interview is becoming too much for you, please let us know, and we will stop the interview right away.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM50 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. Data that was collected prior to your withdrawal will also be destroyed and will not be used in the data analysis later.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner, and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;

9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

.....

Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at
_____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____ IC number: _____

3b Pre-implementation EPIS guided semi-structured interview questions for pharmacist/nurse/doctor provider.

The aim of this interview is to explore a health care provider's experience with current TB DOT and counselling practice, and to explore their views on the CARE-TB strategy (VOT, telecounselling, and Elearning)

Building rapport:

1. What is your role in TB care and support within this facility and beyond?
2. How long have you been a (pharmacist/nurse/clinician) and how long have you worked with TB?

EPIS Constructs

Questions	Prompts	EPIS Framework
1. Medication adherence is important for TB treatment success. What do you think of continuous monitoring (DOT) vs allowing patients to manage their own medication adherence?	Why do you say so?	INNER FACTOR Individual characteristic
2. How do you feel about the current DOT program?	What are the advantage and disadvantages? Effective? Cost? Convenience? Shortfall?	INNER FACTOR Individual characteristic
3. Have you heard of digital solutions such as VOT as part of TB treatment adherence support?	Do you know of any clinics running VOT (synchronous or asynchronous)? How effective has it been? What factors do you believe contribute to the differences between VOT and DOT? (pros and cons)	INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic
4. What do you think about having patients take <1-min video messages of themselves ingesting TB medication (VOT) and sending them over WhatsApp to their healthcare provider daily as an alternative to the current DOTS program?	Do you believe that patients can perform VOT, at least for a period of 2 months? What are your concerns? - <i>complexity/usability, cost, confidentiality/privacy of data</i> Which care provider do you think is best suited to monitor VOT (trace videos sent daily, send reminders, refers/addresses ADR reported)?	INNER FACTOR Individual characteristic INNOVATION FACTOR Innovation characteristic INNER FACTOR Organization characteristic

	- <i>pharmacist/nurses/MA/ community counsellor</i> What do you think of a pharmacist or a counsellor taking on this role? (<i>probe on workload, time</i>) How do you think VOT can be integrated into the workflow in the TB clinic? What resources do we need to execute this? Where can we get this from? Would you suggest an alternative platform for VOT?	INNOVATION FACTOR Innovation fit INNER FACTOR Organization characteristic INNOVATION FACTOR Innovation characteristic
5. What is your perception about TB counselling via teleconferencing method?	Any concerns? What are the potential advantages or disadvantages compared to face to face? How can we improve engagement? Who should deliver the counselling?	INNER FACTOR Individual characteristic INNOVATION FACTOR Innovation characteristic INNER FACTOR Organization characteristic
6. What is your opinion on having weekly educational videos or messages sent through WhatsApp to patients, to share information about TB disease and treatment?	Do you think it is acceptable and useful for patients? Why or why not? Do you think it is feasible to implement? Would you suggest other method(s) to share information?	INNOVATION FACTOR Innovation characteristic INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic
7. Proposed digital package contains: a. VOT: send daily reminders, keep track of your medication intake & allow reporting of medication-taking problems,	Which components will be most helpful to improve adherence? Why? Is there any component you will omit? Why?	INNOVATION FACTOR Innovation characteristic

b. telecounselling: counselling and education on TB disease/ treatment using motivational interviewing technique, c. e-learning: online educational materials (videos, infographics) What do you think of the bundling of this digital adherence package?	What would be the challenge or barrier to implementing this? Is there something you would suggest adding on? (<i>nutritional evaluation, linkage to social/financial support etc.</i>)	
8. Who do you think should be included as leaders or champions to drive the implementation in this facility or beyond?	How can they influence uptake (of the intervention)?	INNER FACTOR Leadership
9. Do you think the program should be open to all or only specific groups of patients? Why? (<i>TB disease type, sociodemographic background</i>)	How and when will you talk to patients, making it easy for them to accept the intervention?	INNOVATION FACTOR Innovation fit
10. How do you suggest training be carried out to support the implementation?	Focus of training? Who should be trained? How frequent? What is the preferred format of training? (<i>manual, workshop, TB web portal with online evaluation</i>)	INNER FACTOR Organization staffing processes
11. How should the feedback and reports on the implementation outcomes be communicated to the relevant stakeholders (e.g. among multidisciplinary practitioners, hospital TB programme manager, administrators)?	What form of reporting? (<i>on paper/excel</i>) What patient safety and efficacy data would be important to monitor? (<i>uptake, adherence, ADR, cost</i>) How often should reporting and feedback occur? What reporting channels to use? (<i>WhatsApp or email groups</i>)	INNER FACTOR Quality and fidelity monitoring/ support

Conclusion: Thank you for sharing your insights. Is there something else you would like to discuss or add before we conclude our interview?

3c Pre-implementation EPIS guided key informant interview guide for policymakers in the Selangor state and National TB Control Programme.

The aim of this interview is to explore a health policymaker's experiences with current TB DOT and counselling practice, and to explore their views on the CARE-TB strategy (VOT, telecounselling, and Elearning)

Building rapport:

1. What is your role in TB care and support?
2. How long have you been a (pharmacist/nurse/clinician) and how long have you worked with TB?

EPIS Constructs

Questions	Prompts	EPIS Framework
1. Do you view enhancing medication adherence as a priority to improve TB outcomes?	How does adherence to TB medication translates into TB outcomes? What are the current top priorities for the management of TB in the state/country?	OUTER SETTING Service environment/policies
2. What are the methods currently employed in government clinics and hospitals to improve adherence to TB treatment?	DOT/VDOT - How has it been going? How can they be improved? VOT: What are the <i>platforms</i> used? Acceptability and feasibility? <i>Health outcomes</i> vs DOT/SAT e.g completion rate? Reported <i>barriers</i> ? Reported <i>enablers</i> ? <i>Improvement</i> efforts done? What is the <i>coverage</i> and would you want to see it scaled up?	INNOVATION FACTOR Innovation characteristic
3. What are the regulatory facilitators and barriers to authorise and institutionalize video observed therapy in the country?	National Strategic Plan or State TB Programme; TB Treatment Guidelines and protocols; Standard operation procedures (including informed consent procedures); M&E framework; User manuals for patients and care providers; Terms of use and privacy policy	OUTER SETTING Service environment/policies
4. Is there an established working group for VOT within the TB sector?	Who are the champions? What work has been done?	OUTER SETTING Leadership

5. For health clinics that use VOT, how are the roles of staff determined?	Who are the direct (<i>nurse, MA, pharmacist, Dr</i>) and indirect personnel (<i>programme management, M&E staff, ICT staff</i>)? What factors determine who perform or run the VOT service? (human resource and workload) Can the roles change depending on the institution?	INNER FACTOR Organization characteristic
6. How have training been done for all personnel?	Is there a training guide and logbook? Mode of training? Frequency of training? How are the feedback on the training? Are there any additional training aspects not covered in the current modules?	INNER FACTOR Organization staffing processes
7. Is there systematic feedback on maintenance and evaluation of the programme?	Monitor data verification/consistency, patient/provider feedback How has the feedback been communicated? How often?	INNER FACTOR Quality and fidelity monitoring/support
8. How do you view the funding landscape or financial support for the implementation of digital adherence solutions for TB in Malaysia?	Special budget allocation? Distribution of tools? (e.g. mobile devices)	OUTER FACTOR Funding
9. Proposed digital package contains: • daily asynchronous VOT via WhatsApp: send daily reminders, keep track of medication intake & allow reporting of medication-taking problems, (with task-shifting to pharmacist or community health workers) • telecounselling: motivational counselling and education on TB disease/ treatment, (by pharmacist) • e-learning: online educational materials (videos, infographics)	What do you think of the bundling of this digital adherence package? What are your concerns? - <i>complexity/usability, cost, confidentiality/privacy of data</i> What do you think about task shifting the role of VOT from MA/nurses to pharmacists?	INNOVATION FACTOR Innovation characteristic INNOVATION FACTOR Innovation characteristic INNER FACTOR Organization characteristic

10. Do you think that adherence support via digital technologies like VOT and e-learning can be sustained and expanded in the state/national level?	Can you tell me more on how to sustain and expand these services?	INNER FACTOR Quality and fidelity monitoring/support

Conclusion: Thank you for sharing your insights. Is there something else you would like to discuss or add before we conclude our interview?

3d Pre-implementation EPIS guided focus group discussion for administrators of the organization (head of medical dept, pharmacy and nursing)

The aim of this interview is to explore a healthcare opinion leader's experiences with current TB DOT and counselling practice, and to explore their views on the CARE-TB strategy (VOT, telecounselling, and E-learning)

Building rapport:

1. What is your role in TB care and support?
2. How long have you been in the role as an administrator, in current and previous facility?

EPIS Constructs

Questions	Prompts	EPIS Framework
1. Medication adherence is important for TB treatment success. What do you think about continuous monitoring with DOT vs allowing patients to manage their own medication adherence?	Why do you say so? What is the evidence? Do you view enhancing medication adherence as a priority to improve TB outcomes?	INNER SETTING Organization characteristic
2. How do you feel about the current DOT program?	What are the advantage and disadvantages? Effective? Cost? Convenience? Shortfall?	INNER FACTOR Individual characteristic
3. Have you heard of digital solutions such as VOT as part of TB treatment adherence support?	If yes, how has it been?	INNOVATION FACTOR Innovation fit
4. What do you think about having patients take <1-min video messages of themselves ingesting TB medication (VOT) and sending them over WhatsApp to their healthcare provider daily, at least for a period of 2 months?	What are your concerns? - <i>complexity/usability, cost, confidentiality/privacy of data</i> Which care provider do you think is best suited to monitor VOT (trace videos sent daily, send reminders, refers/addresses ADR reported)? - <i>pharmacist/nurses/MA/ community counsellor</i> What do you think of a pharmacist taking on this role? (<i>probe on workload, time</i>) How do you think VOT can be integrated into the workflow? Do you think we can execute this program by redistributing workload/existing	INNER FACTOR Individual characteristic INNER FACTOR Individual characteristic INNER FACTOR Organization characteristic INNOVATION FACTOR

	tasks without needing too much additional resources? What resources do we need to execute this? Where can we get this from? Would you suggest an alternative platform for VOT?	Innovation fit INNER FACTOR Organization characteristic INNOVATION FACTOR Innovation characteristic
5. What is your perception about TB counselling via teleconferencing method?	Any concerns? What are the potential advantages or disadvantages compared to face to face? How can we improve engagement? Who should deliver the counselling?	INNER FACTOR Individual characteristic INNOVATION FACTOR Innovation characteristic INNER FACTOR Organization characteristic
6. What is your opinion on having weekly educational videos or messages sent through WhatsApp to patients, to share information about TB disease and treatment?	Do you think it is acceptable and useful for patients? Why or why not? Do you think it is feasible to implement? Would you suggest other method(s) to share information?	INNOVATION FACTOR Innovation characteristic INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic
7. Proposed digital package contains: a. VOT: send daily reminders, keep track of your medication intake & allow reporting of medication-taking problems,	Which components will be most helpful to address adherence? Why? Is there any component you will omit? Why? What would be the challenge to implementing this?	INNOVATION FACTOR Innovation characteristic

b. telecounselling: counselling and education on TB disease/ treatment using motivational interviewing technique, c. e-learning: online educational materials(videos, infographics) What do you think of the bundling of this digital adherence package?		
8. Who are currently the key people at your department/unit who have been important to support patient adherence in TB?	If so, what do they do that helps? How could those people be supported?	INNER FACTOR Leadership
9. In your opinion, what kinds of organizational changes are needed to provide digital adherence support and telecounselling?	Changes in scope of practice? Changes in formal policies? Changes in information systems or records? Will you please describe the process that will be needed to make these changes?	INNER FACTOR Organization characteristic
10. How do you suggest training be carried out to support the implementation?	Focus of training? How frequent? What is the preferred format of training? (<i>manual, workshop, TB web portal with online evaluation</i>)	INNER FACTOR Organization staffing processes
11. Do you think that the digital adherence support can be sustained in your hospital and expanded to state/national level?	Can you tell me more on how to sustain and expand these services?	INNER FACTOR Quality and fidelity monitoring/ support

Conclusion: Thank you for sharing your insights. Is there something else you would like to discuss or add before we conclude our interview?

Add on Do you think the program should be open to all or only specific groups of patients? Why? (*TB disease type, sociodemographic background*) : How and when will you talk to patients, making it easy for them to accept the intervention?

Annex E Post-Implementation Qualitative

4a Post-implementation Patient Information Sheet and Informed Consent

Version 4.0, 10 October 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10 people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve a TB patient's ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) to improve patient-centered TB care in Malaysia should be implemented and sustained. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

Up to 40 TB patients, 30 healthcare providers, 4 policy makers and 4 community representatives will be interviewed to learn their opinions on challenges and barriers to using and implementing the digital adherence strategy through interviews and focus group discussions.

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

We are interested in your thoughts and experiences with the digital adherence programme, which includes whether you find it practical, easy to use, and if the service is worth continuing and scaling up. The interview will take about an hour, and it will be recorded with your permission to help us understand your answers better. We will also ask for some basic information like your age, gender, job, income, education, marital status, and where you live to help us analyse the results.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. Answering questions related to stigma in tuberculosis may make you feel uncomfortable. You can choose not to answer those questions, and it won't cause any problems. Talking about your thoughts and experiences might be emotional. If you ever feel like the interview is becoming too much for you, please let us know, and we will stop the interview right away.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM80 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. Data that was collected prior to your withdrawal will also be destroyed and will not be used in the data analysis later.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner, and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;

9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

.....

Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at
_____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

If the patient is illiterate, a witness must be present during the consent process. After the patient gives consent to participate in the study by placing a mark in the place of his/her signature (e.g., with an X, thumb print, or other mark), the witness will write the name of the patient and the date in the above lines, then sign and date in the below lines.

Signature of Witness, for non-literate participant: _____

Witness's Name (print): _____ Date: _____

IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____

IC number: _____

4b Post-implementation EPIS guided key informant interview guide for patients.

Interview information

Study ID	
Date of screening	(dd-mm-yyyy)
Date of interview	(dd-mm-yyyy)
Time of IDI Initiation	(00:00)
Time of IDI Completion	(00:00)
Location of IDI	☐ ID/TB Outpatient Clinic ☐ Virtual Platform ☐ Others (Please specify: _____)
Name of Interviewer	
Language of Interview	☐ English ☐ Malay
All participants consented to be audio-recorded	☐ Yes ☐ No
Consent form for IDI signed by interviewer	☐ Yes

Participant sociodemographic information

Age	
Gender	
Ethnicity	☐ Chinese ☐ Malay ☐ Indian ☐ Others (Please specify: _____)
Highest Education Level	
Occupation	
Relationship Status	☐ Single ☐ Partnered (Male / Female) ☐ Married ☐ Widowed ☐ Divorced
Monthly household income	☐ < RM 4850 (B40) ☐ 4,850 - 10,959 (M40) ☐ ≥ 10960 (T20)
Number of people living in the same household	___ Adults (18+ years) ___ Children (6-17 years) ___ Small children (less than 6 years)

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KII Interviewer's Script

Interviewer: Good morning / afternoon / evening. Thank you for taking the time to participate in this study. My name is _____ (interviewer's name) and I am working alongside Dr. ... The purpose of this study is to explore factors that can facilitate or hinder the integration of digital adherence services, namely asynchronous video observed therapy, digital reminders, telecounselling and e-learning materials for tuberculosis (TB), in Hospital Sungai Buloh.

We are meeting with service providers from the TB/ID clinic and the pharmacy department – including medical doctors, nurses, pharmacists, medical assistants, counsellors, clinic administrators as well as people living with TB to better understand what might or might not work in this intervention. We have invited you because you have participated in the digital adherence programme for TB treatment in Hospital Sungai Buloh. We hope to gain valuable insights from your perspective to enhance the implementation of our intervention.

There are no wrong answers. Please feel free to openly share your thoughts and comments. We are just as interested in the negative comments as well as the positive comments, and at times the negative comments are the most helpful.

This interview will last from 45 – 60 minutes. Your participation in today's interview is entirely voluntary, and you may choose to stop participating at any time. There is no penalty or reasons needed for withdrawing from this interview. Rest assured that your care in Hospital Sungai Buloh will not be compromised.

We will be audio recording this session because we do not want to miss any of your comments. People often say very helpful things in these interviews and we are unable to write fast enough to get them all down. This audio recording will be transcribed onto paper, combined with other interviews and then analysed to understand the common topics across the interviews as well as the differences. The audio files will be kept on a secure computer network and only the research team will have access to it. Please note that I have not started the audio recording yet.

Do you have any questions about what you are being asked to do today?

(pause to wait for any questions)

Is it okay if we begin recording now? *(Recording begins)*

KII Interview Guide

Questions	Prompts	EPIS Framework
1. What are your overall impressions of VOT?	How has it gone? What has worked well? What has not worked well? (Within the past month), how often have you forgotten to take your medications? Why?	INNOVATION FACTOR Innovation characteristic OUTER CONTEXT Patient characteristics OUTER CONTEXT Patient characteristics

	(Within the past month), how often did you forget to send videos to your healthcare provider? Why? Can you describe any difficulty you experienced when sending video messages to your healthcare provider everyday? How does it fit into your daily routine? Does it trouble you? What is your suggestion to make it easier for you to use the service? Did you need any help or support from your family or friends to use these digital solutions? Please elaborate. What do you think about the daily reminders sent to you through WhatsApp, on supporting your treatment? What are your thoughts on the privacy and confidentiality issues pertaining VOT? <i>(Are you concern about the videos sent to your healthcare provider? Did you have to find a private space to take the video to prevent others from knowing? How did you feel about it?)</i> Were there any additional costs that you need to bear to use VOT?	INNOVATION FACTOR Innovation characteristic INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic OUTER CONTEXT Patient characteristics INNOVATION FACTOR Innovation characteristic OUTER CONTEXT Patient characteristics INNOVATION FACTOR Innovation characteristic
2. Do you think the training and information provided were sufficient for you to effectively use VOT?	What would you suggest improving? - materials/information - frequency, time - mode of training	INNOVATION FACTOR Innovation developers
3. Were the counselling sessions helpful?	How so? Were you satisfied with the counselling given? - <i>professionalism, knowledge, address stigma and other concerns</i>	INNOVATION FACTOR Innovation characteristic OUTER CONTEXT Patient characteristics

	Which method do you prefer – in-person or telecounselling, or no preference? Why?	
4. What are your thoughts on the educational materials shared throughout the programme?	How helpful was it? What other information would you like to have? Do you wish for less/more information? Why? Would you suggest another way to share information?	OUTER CONTEXT Patient characteristics
5. What are your thoughts on the level and quality of care given by your health care providers during your participation in this TB programme?	On a scale of 1-10, how satisfied were you with the service? Are there any suggestions to improve the service?	INNOVATION FACTOR Innovation developers
6. How satisfied were you with the overall experience?	In your opinion, what is the most helpful feature of the program? Why? What are the main benefits? <i>E.g. easy access, time saved, meet healthcare needs, can easily communicate with HCP, effective communication</i> What are the key disadvantages? <i>E.g. effort needed to take and send video, privacy concerns</i> Will you recommend this programme to someone else?	INNOVATION FACTOR Innovation characteristic

5a Post-implementation Information Sheet and Informed Consent for Healthcare Providers, Administrators, and Policymakers

Version 3.0, 26 March 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10 people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve a TB patients ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) to improve patient-centered TB care in Malaysia should be implemented and sustained. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

Up to 40 TB patients, 30 healthcare providers, 4 policy makers and 4 community representatives will be interviewed to learn their opinions on challenges and barriers to using and implementing the digital adherence strategy through interviews and focus group discussions.

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

We are interested in your thoughts and experiences with the digital adherence programme, which includes whether you find it practical, easy to use, and if the service is worth continuing and scaling up. The interview will take about an hour, and it will be recorded with your permission to help us understand your answers better. We will also ask for some basic information like your age, gender, job, income, education, marital status, and where you live to help us analyse the results.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. If you ever feel like the interview is becoming too much for you, please let us know, and we will stop the interview right away.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM50 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. Data that was collected prior to your withdrawal will also be destroyed and will not be used in the data analysis later.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner, and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;
9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at
_____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____ IC number: _____

5b Post-implementation EPIS guided focus group discussions with health care providers.

Focus Group Discussion (FGD) Information Sheet

Focus Group Session	
Date of Focus Group Discussion	(dd-mm-yyyy)
Time of FGD Initiation	(00:00)
Time of FGD Completion	(00:00)
Location of FGD	☐ XX meeting room ☐ Virtual Platform ☐ Others (Please specify: _____)
Name of Facilitators	1. 2.
Language of Interview	☐ English ☐ Malay
All participants consented to be audio-recorded	☐ Yes ☐ No
Consent form for FGD signed by facilitator	☐ Yes

Participant Information:

No.	Nickname	Specialty Clinic (ID or TB)	Years working in the specialty clinic	Role in specialty clinic (SN, MA, PH, DR, CA)
1.	Participant A			
2.	Participant B			
3.	Participant C			
4.	Participant D			
1.	Participant E			
6.	Participant F			

* Staff Nurse (SN), Medical Assistant (MA), Pharmacist (PH), Doctor (DR), Clinic Administrator (CA)

Facilitator's Script

F1: Lead facilitator

F2: Supporting facilitator

F1: Good morning / afternoon / evening and welcome to our session. Thank you for taking the time to join us today. My name is _____ (F1's name), and assisting me is _____ (F2s name). We are working alongside Dr.. The purpose of this study is to explore factors that can facilitate or impede the integration of digital adherence services, namely asynchronous video observed therapy, digital reminders, telecounselling and e-learning materials for tuberculosis (TB), in Hospital Sungai Buloh.

We are meeting with service providers from the infectious diseases and the pharmacy department – including medical doctors, nurses, pharmacists, medical assistants, counsellors, clinic administrators as well as people living with TB to better understand what might or might not work in this intervention. We have invited you due to your involvement in Hospital Sungai Buloh's administrative system. We hope to gain valuable insights from your perspective to enhance the implementation of our intervention.

We encourage you to openly share your thoughts and suggestions. Diverse viewpoints are welcomed, and there are no right or wrong answers. Your input may differ from that of others in the group, and that's perfectly fine. We equally value constructive criticism, as it can be particularly informative in refining our approach. Your feedback, both positive and negative, is invaluable to us in our efforts to improve this initiative.

This discussion will last from 1 to 1.5 hours. It is our duty to ensure that the group starts on time and ends on time. Therefore, we should remain focused on the topics that we are going to discuss today and might not be able to discuss other interesting topics during this session, as we promise to have this group discussion completed by _____ (end time).

Kindly remember that your participation in today's focus group discussion is entirely voluntary, and you may choose to stop participating at any time. There will be no adverse consequences or penalties should you opt to withdraw, and you are not obliged to provide a justification for your decision.

While every effort will be made to uphold the confidentiality of the information shared, please be aware that the nature of focus group discussions makes it challenging to guarantee complete confidentiality. We kindly request all participants to respect the privacy of their fellow participants and refrain from disclosing the contents of the discussion to others.

Each of you has been assigned an alphabet, which is written on the paper in front of you (or listed in the chat box if you're in a virtual setting). We will use these alphabets to refer to you during our discussion, and we encourage participants to do the same when addressing each other.

We'll be recording this session to ensure that we capture all your valuable comments. Often, insightful points are made in these discussions, and we want to make sure we don't miss any of them due to the limitations of notetaking. These audio recordings will later be transcribed, combined with other interviews from various focus group discussions, and analyzed to identify common themes and differences. Rest assured, the audio files will be securely stored on a protected computer network, and only the research team will have access to them. Please note that we haven't started recording yet.

Do you have any questions about today's session?

(pause to wait for any questions)

Is it okay if we begin recording now? (recording begins)

Please tell us a little about the work you do in Hospital Sungai Buloh.

(Participants introduce themselves and their roles)

FGD Interview Guide

Questions	Prompts	EPIS Framework
Related to the intervention		
1. What are your overall impressions of the digital adherence programme? (Discuss individual components) • VOT • Telecounselling • e-learning	How has it gone? What has worked well? What has not worked well? What do you think about the complexity or ease of use for these solutions? <i>(duration, scope, intricacy and number of steps involved)</i> What improvements do you suggest? Are there components that should not be altered? Which ones? How well do you think this digital solution meet the needs of your patients? In what ways do you think it serves their needs? How does this compare with what we were doing previously? <i>(DOT/SAT; in-person counselling)</i>	INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic INNOVATION FACTOR Innovation characteristic INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic
2. How well prepared are you to screen, refer and facilitate patients for this digital adherence programme?	What are your concerns? How was the overall reception of patients towards the programme? How well do these digital solutions integrate into your healthcare practice or daily routines? What changes do you suggest making to the proposed strategy to make it a better fit for your setting? How motivated do you and your colleagues feel about the work that you're doing? What would help motivate you further?	INNER FACTOR Individual characteristic OUTER FACTOR Patient characteristic INNER FACTOR Organization characteristic INNER FACTOR Individual characteristic

3. What were the gaps in your training?	Is the training sufficient? - What kind of materials or information need to be added? - Timely? - Frequency? - Mode of training satisfactory?	INNER FACTOR Organization staffing processes
Related to the organization		
4. What are your comments on the availability of resources and support to effectively implement this programme?	Were resources sufficient? (<i>space, personnel, inventory</i>) What was the level of support from leaders? What are the other forms of support needed? Were there any personal costs to you that weren't covered by your organization?	INNER FACTOR Organization characteristic & leadership INNOVATION FACTOR Innovation characteristic
5. How was the collaboration and communication amongst you and other healthcare providers in running this programme?	How effective was it? How can it be improved?	INNER FACTOR Organization characteristic
6. Are there key individuals in your organization who have been and will be important to keep this digital adherence programme running long-term?	If so, what do they do that helps? How could those people be supported?	INNER FACTOR Leadership
7. What kinds of organizational changes are needed to effectively run and maintain this programme?	Changes in standard operating procedures? Changes in formal policies? Changes in records? Will you please describe the process that will be needed to make these changes?	INNER FACTOR Organization characteristic
8. How was the feedback and reports on the implementation communicated to the relevant stakeholders (e.g. among multidisciplinary practitioners, hospital TB	What form of reporting was used? (<i>on paper/excel</i>) What were the specific reports? (<i>uptake, adherence, ADR, cost</i>) How often did reporting and feedback occur?	INNER FACTOR Quality and fidelity monitoring/ support

programme manager, administrators)?	What are the preferred reporting channels? (<i>WhatsApp or email groups</i>)	
9. Do you think this programme can be sustained in your hospital and scaled-up to a state or national level?	What are the facilitators and barriers to sustainment and scale-up?	INNER FACTOR Quality and fidelity monitoring/ support

6a Post-implementation Information Sheet and Informed Consent for Community Representatives and Peer Counsellors

Version 4.0, 10 October 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10 people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve a TB patient's ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) to improve patient-centered TB care in Malaysia should be implemented and sustained. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

Up to 40 TB patients, 30 healthcare providers, 4 policy makers and 4 community representatives will be interviewed to learn their opinions on challenges and barriers to using and implementing the digital adherence strategy through interviews and focus group discussions.

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

We are interested in your thoughts and experiences with the digital adherence programme, which includes whether you find it practical, easy to use, and if the service is worth continuing and scaling up. The interview will take about an hour, and it will be recorded with your permission to help us understand your answers better. We will also ask for some basic information like your age, gender, job, income, education, marital status, and where you live to help us analyse the results.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. Answering questions related to stigma in tuberculosis may make you feel uncomfortable. You can choose not to answer those questions, and it won't cause any problems. Talking about your thoughts and experiences might be emotional. If you ever feel like the interview is becoming too much for you, please let us know, and we will stop the interview right away.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM80 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. Data that was collected prior to your withdrawal will also be destroyed and will not be used in the data analysis later.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner, and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;

9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

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Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at
_____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____ IC number: _____

6b Implementation, sustainment and scale-up key informant interview guide for healthcare workers, administrators, policy makers or community representatives

Building rapport:

1. What was your role in the CARE-TB programme?
2. How long have you been a (pharmacist/nurse/clinician) and how long have you worked with TB?

EPIS Constructs

Questions	Prompts	EPIS Framework
Related to the intervention		
1. What are your overall impressions of the digital adherence programme? (Discuss individual components) • VOT • Telecounselling • e-learning	Related to the intervention: How has it gone? What has worked well? What has not worked well? What should be altered? What are your suggestions?	INNOVATION FACTOR Innovation fit INNOVATION FACTOR Innovation characteristic
2. How do you plan to continue training providers in screening, referral, and facilitation for digital adherence programme?	Time and frequency of training? Mode of delivery? Who will deliver training? Training manual?	INNER FACTOR Organization staffing processes
Related to the organization		
3. What are your comments on the availability of resources and support to effectively implement this programme?	Were resources sufficient? (<i>space, personnel, inventory</i>) What was the level of support from leaders? What are the other forms of support needed?	INNER FACTOR Organization characteristic & leadership
4. Are there key individuals in your organization who have been and will be important to keep this digital adherence programme running long-term?	If so, what do they do that helps? How could those people be supported?	INNER FACTOR Leadership
5. What kinds of organizational changes are needed to effectively run and maintain this programme?	Changes in standard operating procedures? Changes in formal policies? Changes in records? Will you please describe the process that will be needed to make these changes?	INNER FACTOR Quality and fidelity monitoring/ support

6. Are there any drivers that may influence your decision to continue implementing this digital adherence programme in your setting?	- Guidelines/ policies/ national performance measures / incentives - Organizational priorities	OUTER FACTOR Service environment / policies INNER FACTOR Organization characteristic
7. How will you assess progress towards implementation and intervention goals?	What will you measure? What are the goals? How will feedback be obtained from staff and patients? Feedback reports – content, mode, form, frequency, from whom, to whom? How will you communicate with key stakeholders what is working and other findings?	INNER FACTOR Quality and fidelity monitoring/ support
8. Is your organization committed long-term?	Could that shift? Has anything changed? Do you think this programme can be sustained and scaled-up to other TB clinics? What will facilitate sustainment and scale-up? What are the barriers? Will resources or cost be an issue to scale up and expansion of these services? Is there anything else that's important for us to know about how to sustain or expand these digital adherence services?	INNER FACTOR Quality and fidelity monitoring/ support

Conclusion: Thank you for sharing your insights. Is there something else you would like to discuss or add before we conclude our interview?

Annex F Implementation Data Collection

7a (i) Implementation Phase Participants Information Sheet and Informed Consent – CARE-TB Group

Version 4.0, 10 October 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

You are invited to participate in this implementation study of a pharmacist-led digital adherence support model for tuberculosis in Hospital Sungai Buloh. Before you decide whether to be part of this study, please read this document carefully. It explains why we are doing this study and gives you all the details about it. If you have any questions or concerns, feel free to talk to the health care providers involved in the study at the clinic or hospital. They will answer your questions and talk through any concerns you have. You can also take your time to talk to your family or people you trust about whether you should join the study. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

Introduction

Tuberculosis (TB) is a curable disease but still affects around 10 million people globally, with over a million deaths every year. In a state like Selangor, which has a high number of TB cases, 1 in 10 people didn't complete their TB treatment in 2021-2022. TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve your ability to take medications everyday. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Study objective

This study aims to determine how a pharmacist-led medication adherence-enhancing telemedicine strategy (CARE-TB) should be implemented and sustained in a tertiary hospital setting. This study will be conducted in Hospital Sungai Buloh, the main treatment centre for infectious disease in Malaysia.

Study procedures

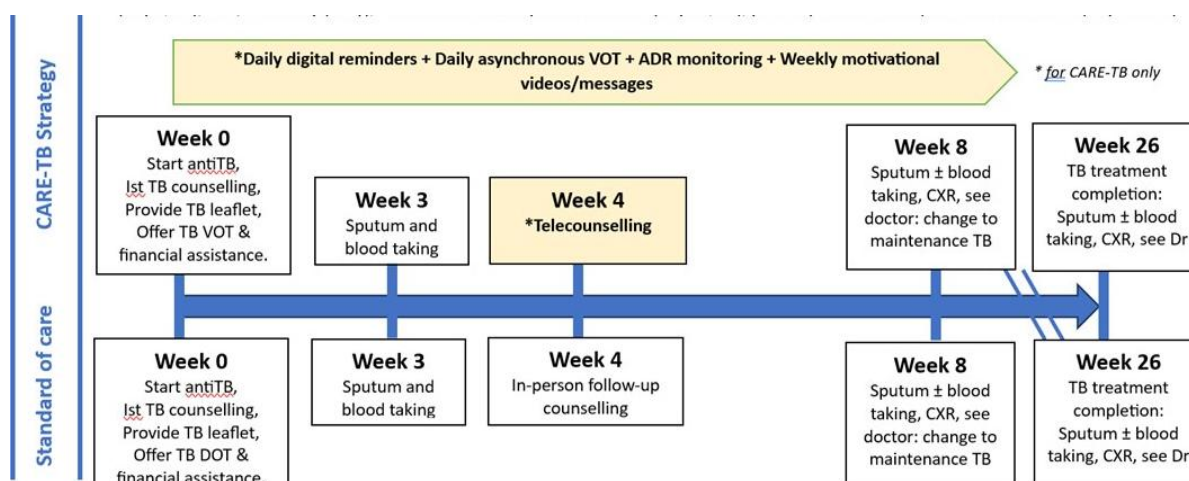


Figure 1: Study flowchart for standard of care and CARE-TB participants

Up to 80 TB patients will be invited to join the digital adherence programme. Another 80 patients will receive the standard of care and be enrolled as controls. Refer study flowchart above (Figure 1).

The research team will talk to you about the study and answer any questions you might have. If you are eligible and interested to join, you will need to sign a consent form.

At the start of TB treatment, you will receive counselling on TB disease and treatment from a pharmacist, after which you will be invited to join the study. Upon consent, you will be randomly assigned (like a flip of a coin) to join the standard of care or the CARE-TB arm.

The Malaysian guideline recommends directly observed therapy (DOT) as a standard form of adherence monitoring for the intensive phase of TB treatment (8 weeks) at minimum.

For standard of care DOT, a family member or caretaker observes the intake of medications when a patient is unable to come to the healthcare facility for their daily doses. Each dose is recorded by the

observer/caretaker in the TB diary. A follow-up in-person counselling with the pharmacist at the TB clinic is scheduled post-1month anti-TB treatment.

The CARE-TB arm will include a package of interventions to improve your medication taking via video-observed therapy, automated reminders, telecounselling and e-learning materials, as detailed below:

Video observed therapy (VOT) and automated medication reminders

You will receive instructions on VOT from your healthcare provider. Automated reminders will be sent to you via WhatsApp in the morning daily to remind you to take your TB medications. You will be required to record a ≤60-sec WhatsApp video messages of yourself taking your pills and send them to your healthcare provider daily for the duration of 2-months intensive phase treatment.

Immediately after sending the video, please sign and date the dose taken in your TB diary. As the video message is recorded and sent in real-time, it offers a sense of immediacy compared to a pre-recorded video saved for later transmission. Your healthcare provider can view and record the actual time at which the video is taken, which significantly enhances its authenticity. These video messages are end-to-end encrypted, ensuring complete confidentiality to both sender and recipient, not even the administrators of WhatsApp, can access them.

If your healthcare provider did not receive a video within the same day (during work hours), you will be reminded via WhatsApp message to take the dose and to send the recording if you have not done so. If you have taken the dose but forgot to record, kindly inform your healthcare provider via WhatsApp messaging. If you fail to send the videos for 2 consecutive days, a phone call will be made to you to ascertain reasons of not complying to medications or VOT.

Telecounselling

After 2 weeks of treatment or at least 1 week post discharge, a telecounselling session will be scheduled with you to assess treatment progress and to troubleshoot any issues with VOT. As opposed to the standard care, patients will not need to attend in-person counselling sessions during their blood taking appointment at Week 4, allowing a shorter hospital visit.

E-learning

Upon consent at initial visit, you will be given a link to TB e-learning materials. Then, you will receive weekly short videos or motivational messages via WhatsApp to encourage continued treatment adherence. The e-learning material will include aspects of education on TB disease, medications, adherence, side effects and monitoring; resources for financial and counselling support services; as well as relevant contact numbers of healthcare providers and community support groups.

The study staff will (a) collect your medical and laboratory data, available from your medical records, (b) collect information on your socioeconomic status such as job, income, education, marital status, where you live and health related expenditures, (c) ask you to complete a quality of life assessment at the start and at the end of treatment, (d) ask you questions about possible negative views on tuberculosis at the start of treatment and at day 30 of treatment, and (e) ask you questions about the your experience in using VOT and telecounselling if you are a CARE-TB participant. You will not be asked to come to clinic for any extra clinic visits. The assessments will be performed during your initial or subsequent clinic visits, or via online forms.

(a) Medical and laboratory data

The study team will access your medical records and collect information usually used to assess your TB infection and health as part of your routine care, for example adherence to your TB medicines, TB outcomes and concurrent illness. Your name, medical record number, health insurance number, and/or identification number will all be removed from the information. The data will then be sent via a secure file sharing program to the study's data management team for the study analysis.

(b) Socioeconomic status

To assess the cost-effectiveness and viability of the employed method for implementation, we require information regarding your employment, income, education, marital status, residence, and health-related expenses related to tuberculosis.

(c) Quality of life assessment

You will be asked to complete two questionnaires at the start of treatment, asking about your quality of life during the past 30 days: (1) EQ-5D-5L, a 5-question assessment which takes about 5-mins to complete. (2) SF-12, a 12 questions assessment which takes about 2-5 mins to complete. You will be asked to complete both today, and again in the next 2 months (EQ-5D-5L and SF-12) and at the end of 6 months TB treatment (EQ-5D-5L).

(d) TB stigma assessment

You will be asked to fill in a 12-questions assessment on TB stigma at the start of TB treatment and again after 1 month, as we would like to your views and feelings about having TB. This information will allow us to come together to find a solution to tackle stigma and provide better service to improve TB care.

(e) AIM-IAM-FIM Questionnaire (for CARE-TB participants only)

A 12-item questionnaire will be used to assess your opinion and experience on the usability of VOT and telecounselling during your telecounselling visit with your pharmacist. A follow-up session will be conducted at the conclusion of the 2-month VOT period to assess if there are any changes in your opinions regarding the usability of the VOT solution.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. Answering questions related to stigma in tuberculosis may make you feel uncomfortable. You can choose not to answer those questions, and it won't cause any problems, or you can talk to your healthcare provider about it.

To address patient data and video privacy concerns, investigators will use end-to-end encrypted video messaging application, comply with data protection regulations, and conduct regular security audits. Videos submitted by patients will be deleted from the research phone one week after receipt, following documentation and quality assurance procedures. Only authorized personnel will have access to patient information. The research phone and its data will be password-protected and stored securely under lock and key.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers. Residents of Selangor can opt to receive TB financial aid from the Selangor government, with study staff providing assistance in the application process.

Can I refuse to take part in the study?

Yes, you can

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM100 as compensation for time taken to participate in this interview.

Taking part in the study and leaving the study

Taking part in this study is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. However, any data collected prior to your withdrawal will still be used for research purposes. This is to ensure the integrity of the study and its findings. Your data will be handled confidentially and in accordance with ethical guidelines and data protection regulations.

Confidentiality

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future. To ensure patient data and video privacy, researchers will use encrypted video messaging, comply with data protection regulations, and conduct security audits. Patient-submitted videos will be deleted one week after receipt, with access restricted to authorized personnel. The research phone and its data will be password-protected and securely stored.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;

6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;
9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

.....

Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at _____ (address)

have read the attached information sheet for research participants version 1.0 dated 20 Sept 2023, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

If the patient is illiterate, a witness must be present during the consent process. After the patient gives consent to participate in the study by placing a mark in the place of his/her signature (e.g., with an X, thumb print, or other mark), the witness will write the name of the patient and the date in the above lines, then sign and date in the below lines.

Signature of Witness, for non-literate participant: _____

Witness's Name (print): _____ Date: _____

IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____

IC number: _____

7a (ii) Implementation Phase Participants Information Sheet and Informed Consent- Standard of Care (SOC) Group

Version 3.0, 26 March 2024

Information Sheet

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Study sponsor: Hospital Sungai Buloh

Site Principal Investigator

Name-Surname: Koh Hui Moon

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0126323240

Site Co-investigator(s)

1. Name: Dr Benedict Sim Lim Heng

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454333

2. Name: Abby Ang Shoon Yeun

Address: Hospital Sungai Buloh, Jalan Hospital, Selangor, 47000, Selangor

Phone number: 0361454126

3. Name: Dr Annabella Edwin

Address: TB/Leprosy Unit, Jabatan Kesihatan Negeri Selangor, No 1 Wisma Sunway, Jalan Tengku Ampuan Zabedah C 9/C, Seksyen 9, 40100 Shah Alam, Selangor, Malaysia

Phone number: 0351237333

Dear participants,

We'd like to invite you to take part in our research study on a pharmacist-led digital adherence support model for tuberculosis (TB) in Hospital Sungai Buloh. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us. If you agree to take part in this study, you will be asked to sign the consent form for this study and a copy will be offered to you to keep.

What is the purpose of the study?

TB treatment is difficult because it needs you to take medications for long periods and can have side effects, and many people face emotional stress and stigma. Not following the treatment plan properly can lead to TB treatment failing, the disease re-occurring, spreading the disease to others, or becoming drug-resistant, which is a big health risk.

The researchers leading this study want to investigate the use of a digital method to improve your ability and motivation to take medications every day. It is hoped that this could help TB patients cope better with their medications and disease to improve their health outcomes while saving cost.

Why have I been invited?

You have been invited to join the study because you have been diagnosed with lung tuberculosis (TB). Up to 160 participants with lung TB will be invited. 80 participants will join the digital method (CARE-TB) group while another 80 participants will receive the standard of care.

What will happen to me if I decide to take part?

At the start of TB treatment, you will receive counselling on TB disease and treatment from a pharmacist, after which you will be invited to join the study. If you agree, you will be randomly assigned (like a flip of a coin) to join the standard of care or the CARE-TB arm.

The Malaysian guideline recommends directly observed therapy (DOT) as a standard form of adherence monitoring for the intensive phase of TB treatment (8 weeks) at minimum.

For standard of care DOT, a family member or caretaker observes the intake of medications when a patient is unable to come to the healthcare facility for their daily doses. Each dose is recorded by the observer/caretaker in the TB diary. A follow-up in-person counselling with the pharmacist at the TB clinic is scheduled post-1month anti-TB treatment.

The CARE-TB arm will include a package of interventions to improve your medication taking via video-observed therapy, automated reminders, telecounselling and e-learning materials, as detailed below:

The study staff will (a) collect your medical and laboratory data, available from your medical records, (b) collect information on your socioeconomic status such as job, income, education, marital status, where you live and health related expenditures, (c) ask you to complete a quality of life assessment at the start and at the end of treatment, and (d) ask you questions about possible negative views on tuberculosis at the start of treatment and at day 30 of treatment. You will not be asked to come to clinic for any extra clinic visits. The assessments will be performed during your initial or subsequent clinic visits, or via online forms.

(a) Medical and laboratory data

The study team will access your medical records and collect information usually used to assess your TB infection and health as part of your routine care, for example adherence to your TB medicines, TB outcomes and concurrent illness. Your name, medical record number, health insurance number, and/or identification number will all be removed from the information. The data will then be sent via a secure file sharing program to the study's data management team for the study analysis.

(b) Socioeconomic status

To assess the cost-effectiveness and viability of the employed method for implementation, we require information regarding your employment, income, education, marital status, residence, and health-related expenses related to tuberculosis through a questionnaire.

(c) Quality of life assessment

You will be asked to complete two questionnaires at the start of treatment, asking about your quality of life during the past 30 days: (1) EQ-5D-5L, a 5-question assessment which takes about 5-mins to complete. (2) SF-12, a 12 questions assessment which takes about 2-5 mins to complete. You will be

asked to complete both today, and again in the next 2 months (EQ-5D-5L and SF-12) and at the end of 6 months TB treatment (EQ-5D-5L).

(d) TB stigma assessment

You will be asked to fill in a 12-questions assessment on TB stigma at the start of TB treatment and again after 1 month, as we would like to your views and feelings about having TB. This information will allow us to come together to find a solution to tackle stigma and provide better service to improve TB care.

What are the possible risks for participating in this study?

Minimal risks include possible breaches of individual confidentiality. However, we have taken steps to minimize this risk by de-identification and secure storage of your data. Answering questions related to stigma in tuberculosis may make you feel uncomfortable. You can choose not to answer those questions, and it won't cause any problems, or you can talk to your healthcare provider about it.

What are possible benefits from participating in this study?

The information you provide will help inform improved TB medication adherence management and monitoring in TB clinic which could have subsequent benefits to patients and healthcare providers. Residents of Selangor can opt to receive TB financial aid from the Selangor government, with study staff providing assistance in the application process.

Do I have to take part?

No. Your participation is entirely voluntary. You can withdraw from this study at any time for any reason and this will not affect the care you receive in any ministry of health clinics now or in the future.

If you withdraw your consent after you begin participating in this study, your data will no longer be collected. However, any data collected prior to your withdrawal will still be used for research purposes. This is to ensure the integrity of the study and its findings. Your data will be handled confidentially and in accordance with ethical guidelines and data protection regulations.

What are the costs to you for participating in this study?

There is no cost for joining this study.

Will you receive any payment as part of participating in this study?

You will receive RM100 as compensation for time taken to participate in the study.

Will my taking part in the study be kept confidential?

Maintaining confidentiality for your participation in the study is important to your doctor and the study researchers. Your personal information will be kept in a private and confidential manner and will not be disclosed to the public. Your name and address will not be used in any reports, public communications, or publications. All local electronic databases used to enter study data will be secured with password-protected access systems. No patient and healthcare provider names will be entered into the site study electronic database and data will be anonymized by assigning unique codes to each participant. The code list will be kept in accordance with local IRB requirements. If you cancel your consent after you begin participating in this study, your personal information will no longer be collected. However, the information that was already collected may be used to evaluate the research results in the future. To ensure patient data and video privacy, researchers will use encrypted video

messaging, comply with data protection regulations, and conduct security audits. Patient-submitted videos will be deleted one week after receipt, with access restricted to authorized personnel. The research phone and its data will be password-protected and securely stored.

What are your rights as a study participant?

As a study participant, you will have the following rights.

1. you will be informed of the objectives of this study and how the researchers plan to conduct the study procedures;
2. you will receive explanations about the research procedures that will be used in this study;
3. you will receive explanations about the possible risks and discomforts of joining in this study;
4. you will receive explanations about the possible benefits from participating in this study;
5. you will have the opportunity to ask questions about the study or study procedures;
6. you will be told that by consenting to participate in this study, you can still withdraw from this study at any time for any reason, without it making any difference to the care you receive now or in the future;
7. you will have the opportunity to make a free decision whether or not you will participate in the study without influence, threat or deception by the study team, clinic staff, or other investigators associated with the study.
8. you will receive a copy of the signed and dated consent form;
9. you will be able to hear about the study findings. After the study is completed, the researcher will send you a summary of the findings via email - this will not include any personal information about individual study patients.

If you have any questions about your participation in this study, you can contact:

Mdm Koh Hui Moon
Telephone number: 0126323240
Email: kohhuimoon@moh.gov.my

Any complaints in relation to the research can be addressed to the

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251

Thank you very much for your cooperation.

.....

Consent

Research Project Title: Comprehensive Digital Adherence and Remote Engagement to Optimise Treatment Adherence for Tuberculosis Patients (CARE-TB Study) in Selangor, Malaysia: An Effectiveness-Implementation Science Study

Date of consent: Day _____ Month _____ Year _____

I, _____ (name), residing at _____ (address)

have read the attached information sheet for research participants version 3.0 dated 26 March 2024, and voluntarily consent to participate in this study. I have received a copy of the signed and dated consent form along with the information sheet for research participants. Before signing this consent form, I confirm that the study staff have explained in detail the objectives of the study, the duration of the study, the study procedures, the risks that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options if I choose not to participate. I have had enough time and opportunity to ask all my questions until I clearly understood the study and the potential risks and benefits of my participation. The study staffs have clearly answered my questions to my satisfaction.

I have the right to withdraw from this study at any time for any reason without it effecting my position now or in the future at the clinic.

The study team assures me that my personal information will be kept confidential and will be disclosed only with my permission or if required by law. My records may be reviewed by representatives from the study sponsors, the Institutional Review Boards responsible to ensure my rights as a study participant are protected, the study team, and study monitors to confirm the correctness of the information. By giving consent, I agree to have my medical history reviewed for this purpose and for the purposes of the research study.

The study team assures me that if I withdraw from the study, no additional information will be collected but data already analyzed cannot be withdrawn. And if I want to have any or all study documents collected destroyed, I can request this in writing and the study team will ensure that my request is carried out.

I understand that I have the right to review or modify my personal information and I can cancel the agreement to have my personal information used by contacting the study team.

I am aware that the information in this study, including my medical information, will go through several processes such as putting the information into study forms and a computer database, checking that the information matches with my medical records, analyzing the results of the study, and reporting the results. I understand that the information will not contain my name and will be used only for scientific purposes and for my medical care.

I have read the above sentences and clearly understand them. I willingly agree to my participation in this study and have signed this consent form to confirm this.

Signature of participant: _____ Date: _____

Participant's Name (print): _____ IC number: _____

If the patient is illiterate, a witness must be present during the consent process. After the patient gives consent to participate in the study by placing a mark in the place of his/her signature (e.g., with an X, thumb print, or other mark), the witness will write the name of the patient and the date in the above lines, then sign and date in the below lines.

Signature of Witness, for non-literate participant: _____

Witness's Name (print): _____ Date: _____

IC number: _____

I have explained in detail the objectives of the study, the study procedures, the dangers or symptoms that may arise from participating in the study, the benefits that may arise from participating in the study, and other treatment and care options to the participant's named above. I confirm that the participant clearly understands the study and has willingly signed this consent form.

Signature of Investigator: _____ Date: _____

Investigator's Name (print): _____

IC number: _____

7b Baseline Data Collection Form for Study Patients

Site ID:

Study ID:

Sociodemographic status and risk factors

1. Age
2. Sex
 - 1=Male; 2=Female; 3=Other; 99=Unknown
3. Pregnant (Y/N)
4. Weight (kg), height (cm), BMI
5. Nationality
 - 1=Malaysian; 2=Indonesia; 3=Philippines; 4=Myanmar; 5=Nepal; 6=Bangladesh; 7=India; 8=China; 9=Others, specify
6. Ethnicity
 - 1= Malay; 2=Chinese; 3=Indian; 4=Caucasian; 5=Filipino; 6=Thai; 7=Indonesian; 8=Japanese; 9=Vietnamese; 10=Khmer; 11=Korean; 98=Other, specify
7. Marital status
 - 1=Never married; 2=Married/de facto¹; 3=Separated; 4=Widowed; 99=Not available
8. Main Occupation, specify
9. Other jobs, specify
10. Healthcare provider? (Y/N)
 - Institution where you work: 1=hospital; 2=clinic (community/private/military)
11. Living conditions
 - 1=House; 2=prison; 3=correctional institution; 4=nursing home; 5=dormitory; 6=worker quarter; 98=Others, specify
12. Highest level of Education
 - 1=No formal education; 2=Primary school; 3=High school; 4=College/vocational training; 5=University; 99=Not available
13. Monthly total household income²
 - 1=no fixed income; 2= <2500; 3= 2500 to <5000; 4= 5000-9999; 5= >10k; 99=not available
14. TB risk factor
 - 1=Tb contact; 2=prisoner; 3=nursing home dweller; 4=people who use drugs; 5=malnutrition; 6=HIV/AIDS; 7=Chronic kidney disease; 8=smoker; 9=CCRC customer; 10=rheumatoid arthritis on anti-TNF; 11=chronic alcohol intake; 12=cancer; 13=refugee; 98=others, specify

Current TB diagnosis and treatment

1. Anatomy of TB and diagnosis:
 - 1=PTB; 2=PTB & Extrapulmonary TB; 3= Extrapulmonary TB only
2. State full diagnosis:
3. Main symptoms (select all that applies):
 - 1=Cough > 2 weeks; 2=cough with sputum; 3=bloody cough; 4=loss of weight; 5=fever; 6=night sweat; 7=loss of appetite; 98=others, specify
4. TB case category:
 - 1=New; 2=recurrent; 3=case post treatment interruption; 4=case post treatment failure
5. Initial CXR:
 - 1=not done; 2=no lesion; 3=minimal; 4=moderate; 5=advanced
6. Bacteriology:

- i. Sputum direct smear, date
 - 1=no afb sent; 2=sent but no results yet; 3=scanty; 4=1+; 5=2+; 6=3+
- ii. Culture, specimen type
 - 1=positive; 2=negative; 3=contaminated
- iii. Gene Xpert, state specimen type
 - 1=not detected; 2=detected; 3=rifampicin resistant
7. TB treatment
 - 1=Yes, start date; 2=no medication started
 - Drug list with dosage regimen
 - Drug susceptibility testing (Mtb isolates only): 1=reported; 2=not ordered
8. If reported, collection date of isolate tested:
9. Drug susceptibility results:
 - 1=sensitive; 2=resistant; 3=indeterminate; 4=not done

Comorbid status

1. HIV status:
 - 1=positive; 2=negative; 3=refused; 4=indeterminate; 5=results not shared; 6=not offered, state why
2. If positive, is patient on antiviral medications?
 - 1=Yes, specify; 2=no
3. HIV VL baseline:
4. CD4 count baseline:
5. State concurrent health conditions:
 - 1=DM; 2=heart disease; 3=liver disease; 4=chronic renal failure; 5=malabsorption syndrome; 6=underlying steroid treatment; 7=smoking; 8=alcohol addiction; 9=drug/substance addiction; 10=HIV/AIDS; 11=history of gastrectomy; 12=cancer; 98=others, specify
6. State concurrent medications:

¹Married/de facto includes a marriage or long-term partnership with or without a marriage certificate (e.g. common law marriage)

²Household income definition: Total income from all people living in a particular household or place of residence. Income refers not only to the salaries and benefits received but includes every form of income, e.g., salaries and wages, retirement income, near cash government transfers like food stamps, investment gains, dividends and other income.

7c Patient and family resource use

Patient and family resource use (SOC participants)

Site ID:

Patient ID:

Productivity losses

Monthly household income: RM _____

DOT Carer relationship with patient:

	Patient	Carer
Individual monthly salary	RM	RM
Time spent for daily DOT (mins)	mins	mins
Total time spent for a counselling session with pharmacist at TB clinic (including waiting time)	mins	mins
Total time spent (days) absent from work for TB treatment and monitoring in a month	days	days
Childcare cost during TB clinic visit (hourly cost)	RM	RM

Travelling and transport cost

Home address:

Distance travelled from home to hospital: _____(km) one way; _____(km) return trip.

Time taken to travel from home to hospital: _____(mins) one way; _____(mins) return trip.

Transport and cost to hospital		Walking		Bicycle
		Motorcycle		Car
		Public transport (bus, train)	RM /one-way trip RM / return trip	
		Taxi/ GRAB/ UBER	RM /one-way trip RM / return trip	
		Others, specify:	RM /one-way trip RM / return trip	
Accommodation cost for appointment or review			RM	

Patient and family resource use (CARE-TB participants)

Site ID:

Patient ID:

Productivity losses

Monthly household income: RM _____

Handphone data charges per month: RM _____

Cost of handphone: RM _____

	Patient	Carer
Individual monthly salary	RM	RM
Time spent for daily VOT (mins)	mins	mins
Total time spent for TB telecounselling session with pharmacist	mins	mins
Coordination time (to schedule session) with pharmacist	mins	mins
Total time spent (days) absent from work for TB treatment and monitoring in a month	days	days
Childcare cost during TB clinic visit (hourly cost)	RM	RM

Travelling and transport cost

Home address:

Distance travelled from home to hospital: _____(km)

Transport and cost to hospital (tick where applicable; fill in out-of-pocket cost where applicable)		Walking		Bicycle
		Motorcycle		Car
		Public transport (bus, train)	RM	/one-way trip
			RM	/ return trip
		Taxi/ GRAB/ UBER	RM	/one-way trip
			RM	/ return trip
		Others, specify:	RM	/one-way trip
			RM	/ return trip
Accommodation cost for appointment or review			RM	

7d Study Termination / Treatment Completion Form

Participant ID:

Date of study close out: [dd/mm/yy]

Reason for study close out or termination (Tick where applicable):

- ☐ Treatment completion
 - ☐ Date of final treatment dose: [dd/mm/yy]
- ☐ Withdrawal
 - ☐ Withdrawal initiation:
 - Participant initiated
 - Investigator initiated
 - ☐ Reason for withdrawal:
 - Participant no longer meets eligibility criteria (including diagnosis change)
 - Serious adverse event
 - Non-adherence to study protocol
 - Loss to follow-up
 - Unexpected incarceration
 - Failed treatment
 - Others, specify _____
- ☐ Death