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Study Protocol

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Effectiveness of gamified real-time video-observed therapy for adherence in drug-susceptible tuberculosis: Non-inferiority randomized trial protocol

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ABSTRACT

Tuberculosis (TB) treatment adherence remains challenging despite directly observed treatment, short-course (DOTS). This study will evaluate gamified real-time video-observed therapy (GRVOTS), a smartphone-based adherence intervention, against standard DOTS care among adults with newly diagnosed drug-susceptible pulmonary tuberculosis in Malaysia. In this two-arm, parallel-group, open-label, non-inferiority randomized controlled trial, 70 participants will be allocated 1:1 to GRVOTS or standard DOTS care for six months. A non-inferiority design was selected to determine whether GRVOTS can maintain medication adherence while offering a more flexible treatment-support option rather than universally replacing standard DOTS care. The protocol follows the standard protocol items: recommendations for interventional trials 2025 statement. The primary outcome is medication adherence rate (%), with a prespecified non-inferiority margin of -15 percentage points. Secondary outcomes include medication-adherence behavior, sputum acid-fast bacilli conversion, TB treatment outcomes and intrinsic motivation. Trial registration: Thai clinical trials registry (TCTR20260411006).

Keywords: tuberculosis, pulmonary, medication adherence, mobile applications, directly observed therapy, randomized controlled trial

INTRODUCTION

Tuberculosis (TB) remains a major global public health challenge despite being preventable and curable. In 2024, an estimated 10.7 million people developed TB worldwide and approximately 1.23 million died from the disease, making TB the leading cause of death from a single infectious agent globally [1]. The burden remains disproportionately concentrated in the World Health Organization (WHO) South-East Asia, Western Pacific and African regions, which together account for most incident TB cases [1]. The continuing global burden of TB is also reflected in sustainable development goal (SDG) 3.3, which calls for ending the epidemics of AIDS, TB, malaria and neglected tropical diseases by 2030. Progress in TB control under this target is monitored through SDG indicator 3.3.2, defined as TB incidence per 100,000 population [2].

Within this global commitment, Malaysia continues to experience a substantial TB burden despite sustained national control efforts. In 2025, 26,745 new TB cases were recorded nationally, corresponding to an incidence of 78.13 per 100,000 population [3]. Selangor recorded 5,481 new cases, with an incidence of 74.00 per 100,000 population, while Kuala Lumpur recorded 1,959 cases, corresponding to 89.25 per 100,000 population [3]. The continuing burden in these highly urbanized areas, including the Klang Valley, reinforces the importance of improving treatment completion and preventing treatment interruption as part of national TB control efforts.

Treatment of drug-susceptible pulmonary tuberculosis (DS-PTB) requires the regular administration of multiple anti-TB medications over several months, with treatment generally extending for at least six months [4, 5]. In Malaysia, the standard treatment regimen for DS-PTB is six months, although longer treatment may be required in selected clinical circumstances [6]. Medication adherence, defined as the extent to which medications are taken as prescribed, is essential for successful treatment and effective disease control [7, 8]. Non-adherence may result in treatment interruption, loss to follow-up, treatment failure, disease recurrence, prolonged infectiousness, development of drug-resistant TB, increased mortality and greater healthcare expenditure [8-12].

Malaysia adopted the directly observed treatment, short-course (DOTS) strategy under the national tuberculosis control program in 1994 [13]. Direct observation has traditionally been

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used within TB treatment support to promote adherence by supervising medication intake during treatment. However, conventional in-person treatment observation may require repeated attendance at healthcare facilities or other designated locations and can impose transportation costs, loss of income, disruption of employment and daily activities, concerns regarding privacy and stigma, and additional demands on healthcare personnel [14-16]. Consequently, although direct observation provides a mechanism for monitoring medication-taking, its implementation may itself contribute to treatment burden for both patients and healthcare services.

Importantly, medication adherence may remain suboptimal despite DOTS because adherence is influenced by multiple interacting patient-, treatment-, socioeconomic- and health-system-related determinants [17]. Malaysian studies have identified financial difficulties, work commitments, transportation and logistical barriers, inadequate treatment knowledge, adverse drug reactions, stigma and healthcare-related challenges as contributors to treatment interruption and loss to follow-up [18, 19]. Adverse drug effects may reduce willingness to continue medication, while indirect costs and competing employment, family and daily responsibilities may make sustained treatment adherence increasingly difficult over a prolonged treatment period [14, 15, 18, 19]. These findings indicate that direct observation alone may not address the full range of determinants influencing medication adherence and support the need for more flexible and patient-centered approaches to treatment support.

Digital adherence technologies (DATs) have consequently emerged as potential tools for supporting TB treatment, including short-message services, electronic medication monitors, mobile applications and video-supported treatment. Video-observed therapy (VOT or VDOT) enables healthcare providers to assess medication-taking remotely and may reduce the need for repeated face-to-face observation [20, 21]. Evidence from randomized and observational studies indicates that VOT can achieve medication adherence comparable with conventional directly observed treatment, while systematic reviews have reported favorable patient acceptability, reduced healthcare-provider observation time and potential reductions in patient and health-service costs [22-24]. Patients' acceptance and preference for VOT have been associated particularly with convenience, privacy, flexibility, empowerment, and savings in travel time and treatment-related costs [25].

Nevertheless, the potential advantages of DATs should not be interpreted as justification for their universal replacement of conventional treatment support. WHO guidance on TB care places treatment support within a people-centered model of care and emphasizes that treatment-support interventions should be selected according to individual patient needs, acceptability, preferences, available resources and implementation conditions [26]. Video-supported treatment may replace in-person treatment support when the necessary communication technology is available and the intervention can be appropriately organized and operated by healthcare providers and patients [26]. Digital approaches should therefore function as tools within patient-centered TB care rather than as uniform replacements for other forms of treatment support.

The implementation and potential effectiveness of DATs are shaped by the setting in which they are deployed. Digital literacy, language, smartphone access, Internet connectivity, technological complexity, privacy, healthcare-provider capacity and system reliability may influence the ability of patients and healthcare services to adopt and sustain digital treatment support [27]. A recent scoping review found that mobile-phone access among people with TB varied substantially across settings (50%-100%), and that technology-related barriers excluded 2%-31% from DAT access, highlighting potential threats to digital equity and the generalizability of program findings [28].

Furthermore, economic evaluations indicate that VOT can lower societal costs relative to conventional healthcare-provider DOT, in part by reducing patient travel and time costs; however, these estimates arise from particular service configurations and settings and may not be transferred directly to other programs [29]. Recent pragmatic trials of other DAT modalities have also shown that digital interventions do not necessarily improve TB treatment outcomes across different settings, further indicating that their effects are technology- and context-dependent [30, 31].

Beyond treatment monitoring, sustained medication adherence may also be influenced by behavioral and motivational processes that affect engagement throughout a prolonged treatment course [17]. Gamification has emerged as a strategy for promoting engagement with digital health interventions by incorporating features such as progress feedback, goals, achievement mechanisms and rewards [32, 33]. Although encouraging evidence has been reported in other areas of healthcare, evidence regarding the application of gamification specifically to TB medication adherence remains limited. Combining motivational and gamification components with video-observed treatment may therefore provide an additional approach to supporting sustained engagement during TB treatment, but its effectiveness requires rigorous evaluation.

Gamified real-time video-observed therapy (GRVOTS) was developed as a mobile health application integrating video-observed treatment with gamification and motivational features to support medication adherence among patients receiving TB treatment. The application was developed using behavioral, motivational, gamification and technology-design frameworks, and its gamification and motivational components demonstrated excellent content validity, with a mean agreement score of 97.95% (standard deviation [SD] = 2.51%) [13]. A subsequent single-arm intervention study reported a mean medication adherence of 90.87%, which was 10.87 percentage points higher than the prespecified 80% reference adherence level (95% confidence interval [CI]: 7.29-14.46; $p < 0.001$) [34]. Although these findings provide encouraging preliminary evidence regarding GRVOTS, the study did not include a concurrent standard-care comparator and therefore could not establish its comparative effectiveness relative to standard DOTS care.

Consequently, an important evidence gap remains regarding whether GRVOTS can maintain medication adherence relative to standard DOTS care under routine TB treatment conditions. This uncertainty is important because the potential flexibility and operational advantages associated with digital treatment support should be considered alongside its ability to maintain medication adherence relative to established standard care. Robust randomized comparative evidence is therefore required before the potential role of GRVOTS as an alternative patient-centered treatment-support

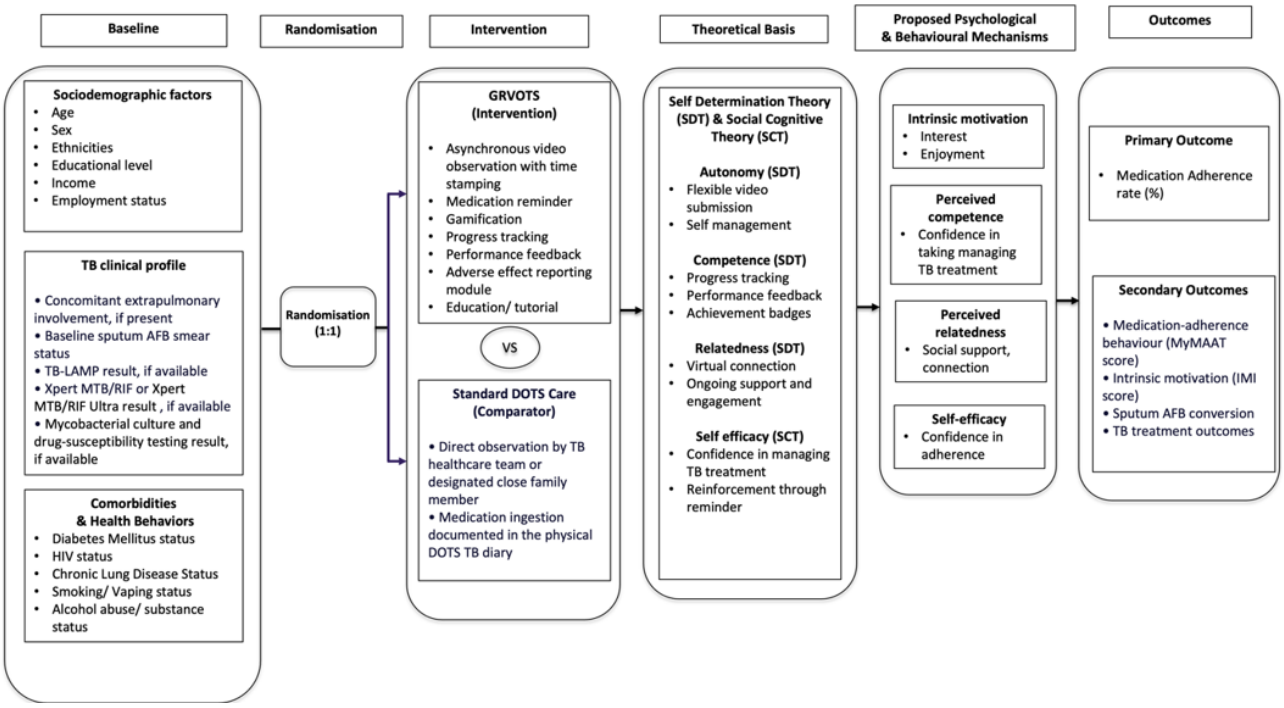


Figure 1. Conceptual framework illustrating the proposed pathways through which GRVOTS, informed by SDT and SCT, may influence psychological and behavioral mechanisms, medication adherence, and secondary TB outcomes compared with standard DOTS care (the authors' own elaboration)

approach can be adequately determined. As standard DOTS care represents an established comparator, a non-inferiority design is appropriate to determine whether medication adherence with GRVOTS is maintained within a prespecified non-inferiority margin relative to standard care, rather than requiring GRVOTS to demonstrate superiority.

Therefore, this study aims to determine whether GRVOTS is non-inferior to standard DOTS care, documented using the TB treatment diary, in maintaining medication adherence among adults with newly diagnosed DS-PTB in Klang Valley, Malaysia. Secondary outcomes include TB treatment outcomes, sputum acid-fast bacilli (AFB) conversion, medication-adherence behavior and intrinsic motivation. By providing randomized comparative evidence within the Malaysian healthcare setting, this study will address the uncertainty regarding the comparative effectiveness of a gamified video-observed treatment approach. The findings may inform consideration of the potential role of GRVOTS within patient-centered digital TB treatment support while recognizing the broader acceptability, resource, implementation and equity considerations associated with DATs.

Study Hypothesis

The study hypothesis is based on the primary outcome of medication adherence rate (%) and the prespecified non-inferiority margin of 15 percentage points.

Null hypothesis (H_0): The medication adherence rate among adults with DS-PTB receiving GRVOTS is inferior to that among participants receiving standard DOTS care documented using the TB diary by 15 percentage points or more.

Alternative hypothesis (H_1): The medication adherence rate among adults with DS-PTB receiving GRVOTS is non-inferior to that among participants receiving standard DOTS care documented using the TB diary, with the between-group difference remaining within the prespecified non-inferiority margin of 15 percentage points.

Non-inferiority will be concluded if the lower bound of the 95% CI for the between-group difference in medication adherence rate (GRVOTS minus standard DOTS care) is greater than -15 percentage points.

Study Objectives

To determine whether GRVOTS is non-inferior to standard DOTS care documented using the TB diary in maintaining medication adherence among adults with newly diagnosed DS-PTB in Klang Valley, Malaysia.

1. To compare the overall medication adherence rate (%) between the GRVOTS and standard DOTS care groups over the six-month treatment period.
2. To compare medication-adherence behavior, measured using the Malaysia medication adherence assessment tool (MyMAAT), and intrinsic motivation, measured using the intrinsic motivation inventory (IMI) between the GRVOTS and standard DOTS care groups throughout the treatment period.
3. To compare sputum AFB conversion and TB treatment outcomes between the GRVOTS and standard DOTS care groups.

Conceptual Framework

The conceptual framework for this study, informed by self-determination theory (SDT) and social cognitive theory (SCT), is depicted in **Figure 1** [35, 36]. Participants will be randomly assigned to either the GRVOTS group or the standard DOTS care group. The framework proposes that the components of GRVOTS, including asynchronous video-observed treatment, medication reminders, gamification features, treatment-progress monitoring, adverse-effect reporting and educational

support, may influence behavioral and motivational mechanisms relevant to medication adherence.

Within the framework, the motivational components of GRVOTS are expected to support autonomy, competence and relatedness, as described in SDT, while progress feedback, treatment monitoring and reinforcement may enhance self-efficacy in accordance with SCT. These mechanisms may contribute to greater intrinsic motivation, improved medication-adherence behavior and sustained engagement with anti-TB treatment throughout the treatment period. Medication-adherence behavior will be assessed using MyMAAT, while intrinsic motivation will be assessed using IMI.

Medication adherence rate (%) is the primary outcome and represents the principal endpoint for evaluating the non-inferiority of GRVOTS compared with standard DOTS care. Improved and sustained medication adherence may subsequently contribute to favorable clinical outcomes, including sputum AFB conversion and successful TB treatment outcomes. Sputum AFB conversion, TB treatment outcomes, medication-adherence behavior and intrinsic motivation are therefore evaluated as secondary outcomes that provide complementary behavioral, motivational, microbiological and clinical information on the effect of the intervention.

Sociodemographic and clinical characteristics that may influence medication adherence or treatment outcomes will be measured at baseline and considered as potential covariates where clinically and methodologically appropriate. The conceptual framework therefore links the GRVOTS intervention to motivational and behavioral mechanisms, medication adherence and subsequent clinical outcomes, while recognizing that these relationships may also be influenced by individual participant characteristics.

MATERIALS AND METHOD

Study Design

This study is a two-arm, parallel-group, open-label, non-inferiority randomized controlled trial with a 1:1 allocation ratio. The protocol adheres to the standard protocol items: recommendations for interventional trials (SPIRIT) guideline [37]. A non-inferiority design was selected because the primary research question is whether GRVOTS can maintain medication adherence within an acceptable margin compared with standard DOTS care.

GRVOTS is intended to complement standard DOTS care rather than replace it for all patients. In the Malaysian setting, digital treatment support may be particularly useful for patients who face difficulties with frequent in-person observation or who are at risk of treatment interruption or loss to follow-up. However, its use may be limited to some patients by factors such as Internet connectivity, access to suitable devices and digital capability. Consistent with WHO guidance, video-supported treatment should be implemented within a people-centered approach and selected according to individual patient needs, preferences, available resources and feasibility, rather than as a universal replacement for conventional treatment support [26].

A superiority design was not selected because the research question is whether GRVOTS can maintain medication adherence within the prespecified non-inferiority margin while offering practical advantages such as remote observation, reduced travel burden and greater flexibility. The non-inferiority design is therefore appropriate for evaluating GRVOTS as an additional patient-centered treatment-support option.

Study Setting

The trial will be conducted across 22 public healthcare facilities comprising health clinics (Klinik Kesihatan) and hospitals under the Selangor State Health Department and the Kuala Lumpur and Putrajaya Health Department in Klang Valley, Malaysia. A list of 99 facilities providing TB treatment services within the study area was obtained from the respective health authorities. Facilities reporting at least 10 TB cases annually were considered eligible for site selection. This minimum caseload criterion was applied to ensure a sufficient pool of potentially eligible participants and support recruitment feasibility within the predefined enrolment period, while avoiding the operational burden of initiating study procedures at very low-volume facilities that might contribute few or no participants. The criterion was not based on facility treatment performance or anticipated study outcomes. Eligible facilities were subsequently selected using simple random sampling.

Participating facilities provide routine TB services including diagnosis, treatment, treatment monitoring and follow-up care, and routinely report patient information to the national tuberculosis registry (NTBR). Healthcare personnel at participating facilities will continue to provide routine TB care in accordance with the Ministry of Health Malaysia TB management guideline [6]. The participating facilities are predominantly located in urban and peri-urban areas of Klang Valley. As the study was not designed to formally compare urban and rural clinics, potential differences in digital infrastructure, healthcare access and technical support should be considered when generalizing the findings to rural settings.

Study Duration

The study will be conducted from 15 July 2026 to 30 March 2027. Recruitment and enrolment of eligible participants will occur over a two-month period. Following randomization, participants will be followed prospectively throughout the standard six-month anti-TB treatment regimen, comprising a two-month intensive phase and a four-month continuation phase.

Study Population

The study population will comprise newly diagnosed adults with DS-PTB registered in the NTBR and receiving treatment at participating public health clinics and hospitals in Klang Valley.

Eligibility Criteria

Eligibility criteria were established to define a study population of adults with newly diagnosed DS-PTB who were suitable for either allocated treatment-support strategy and able to complete the required study procedures. Participants are recruited during the intensive phase of standard first-line anti-TB treatment. Access to a compatible smartphone with Internet connectivity and the ability to operate the device independently are mandatory because eligibility is determined before randomization and all enrolled participants must be capable of receiving the GRVOTS intervention if allocated to the intervention group. The inclusion and exclusion criteria are presented in **Table 1**.

Table 1. Eligibility criteria for study participants

Eligibility criteria	Study participants
Inclusion	• Aged ≥ 18 years • Newly diagnosed drug-susceptible pulmonary tuberculosis (DS-PTB) • Initiating or receiving standard first-line anti-tuberculosis treatment during the intensive phase • Able to communicate in Malay or English • Able to provide written informed consent • Able to operate a smartphone independently • Has access to a compatible smartphone with Internet connectivity
Exclusion	• Rifampicin-resistant or other drug-resistant TB, including multidrug-resistant TB, requiring a drug-resistant TB treatment regimen • Severe uncontrolled psychiatric illness or significant cognitive impairment that prevents provision of informed consent, independent use of the study application, or reliable completion of study procedures • Significant visual or physical impairment that prevents independent smartphone use or completion of the required study procedures

Human immunodeficiency virus (HIV) infection was not an exclusion criterion. Adults living with HIV who had newly diagnosed DS-PTB were eligible for participation provided that they fulfilled all other inclusion and exclusion criteria. HIV status was therefore recorded as a baseline clinical characteristic rather than used to determine study eligibility.

Adverse drug reactions occurring after randomization will not result in retrospective exclusion. Participants who develop adverse drug reactions will receive routine clinical assessment and management according to Ministry of Health Malaysia practice and will remain under study follow-up whenever possible. Any clinician-directed treatment interruption, drug substitution or modification of the anti-TB regimen will be documented separately and will not be classified as medication non-adherence.

Sample Size Determination

The sample size was calculated using the Cleveland clinic sample size calculator (RiskCalc) for a two-arm, parallel-group non-inferiority randomized controlled trial, with medication adherence rate (%) as the single primary outcome. The assumptions were first informed by the preceding GRVOTS single-arm study, in which 82 participants were enrolled and 71 completed the eight-week intervention, corresponding to a loss to follow-up of approximately 13.4% [34]. As the present study follows participants for six months, an attrition allowance of 20% was applied.

The preceding GRVOTS study reported a mean medication adherence rate of 90.87% (standard error 1.80%) among 71 participants [34], corresponding to an approximate SD of 15.2 percentage points. As this was a single-arm study with a shorter follow-up period, a slightly larger variability estimate was used for the present randomized trial. In the restricted analysis of [9], participants receiving video-observed therapy completed a mean of 86% of scheduled treatment observations, with an SD of 17 percentage points. Although the primary adherence outcome in that study used a binary threshold of at least 80% of scheduled observations, adherence was also reported as a continuous percentage measure. A common SD of 17 percentage points was therefore adopted for the present sample-size calculation and was broadly consistent with the preceding GRVOTS findings.

For planning purposes, no difference in mean medication adherence between the GRVOTS and standard DOTS TB diary groups was assumed. Using a non-inferiority margin of 15 percentage points, a one-sided significance level of 2.5%, 90% power and a 1:1 allocation ratio, the minimum required sample size was 54 participants, with 27 participants per group. After allowing for 20% attrition, the required sample size increased to 68 participants, with 34 participants per group, and was subsequently rounded up to 70 participants, with 35 participants in each study arm.

The 15-percentage-point non-inferiority margin represents the maximum allowable absolute reduction in medication adherence for GRVOTS to be considered non-inferior to standard DOTS care. A 10-percentage-point non-inferiority margin was used in a previous study comparing electronic directly observed therapy with in-person directly observed therapy [38], whereas another study applied a 20-percentage-point margin when comparing a digital medication-event reminder and monitor with standard directly observed therapy [39]. Therefore, a non-inferiority margin of 15 percentage points was selected for the present study, within the range used in previous digital tuberculosis adherence trials. The proposed margin was also discussed with clinicians and TB program personnel during study development and was considered clinically acceptable, considering the potential practical advantages of GRVOTS, including remote treatment observation, reduced travel burden, greater flexibility and improved patient engagement.

A formal preserved-fraction analysis was not undertaken because previous evidence does not provide a sufficiently reliable and directly comparable estimate of the effect of DOT on continuous percentage medication adherence. Previous studies have mainly reported cure, treatment success and treatment completion, and a Cochrane systematic review found no substantial improvement in cure or treatment completion with DOT compared with self-administered treatment [40]. Therefore, no specific proportion of a historical DOT effect is claimed to be preserved by the selected margin. Participants are individually randomized across 22 study facilities rather than by facility; therefore, no cluster design-effect adjustment was applied to the sample-size calculation. A reliable prior estimate of within-facility clustering in medication adherence was not available at the design stage.

Participant Recruitment and Enrolment

Eligible participants will be identified by the TB healthcare team at participating facilities during routine clinical care. Potentially eligible patients will be referred to the research team for screening against the study eligibility criteria. The research team will approach eligible patients during scheduled clinic visits and provide verbal and written information regarding the study objectives, procedures, duration, potential risks and benefits, and participant responsibilities. Individuals who express interest in participating will be given sufficient

time to review the participant information sheet and ask questions before deciding.

Written informed consent will be obtained from all participants prior to enrolment and completion of any study-related procedures. Following informed consent, participants will be assigned a unique study identification number and subsequently undergo randomization and allocation before completing the baseline assessment. Participation in the study is voluntary, and participants may withdraw from the study at any time without affecting their access to routine healthcare services. Participants in both study groups will receive a token of appreciation valued at RM5 upon completion of each scheduled assessment. No additional costs will be incurred by participants, as TB treatment and medications are provided through existing government healthcare services. Recruitment will continue until the target sample size of 70 participants (35 participants per group) has been achieved.

Randomization, Allocation Concealment, and Blinding

Following informed consent, participants will be randomly assigned in a 1:1 ratio to either the intervention group (GRVOTS) or the comparator group (DOTS TB diary). Baseline assessments will subsequently be conducted after allocation. A computer-generated randomization sequence with randomly varying block sizes of four and six will be generated prior to study commencement using sealed envelope randomization software [41]. The allocation sequence will be maintained in a password-protected electronic file and will remain inaccessible to personnel responsible for participant recruitment and enrolment until treatment allocation has been assigned.

Allocation concealment will be ensured through centralized randomization procedures. Treatment allocation will only be revealed after participant eligibility has been confirmed and written informed consent has been obtained. The principal investigator will then assign participants to the next available allocation in the pre-generated randomization sequence.

Due to the nature of the intervention, blinding of participants and intervention providers is not feasible; therefore, the study will be conducted as an open-label trial. The primary outcome, medication adherence, cannot be assessed under blinded conditions because adherence is measured using intervention-specific procedures. In the intervention group, adherence will be determined through review of submitted GRVOTS videos using the video count checklist (VCC), whereas adherence in the comparator group will be determined from the DOTS TB diary.

To minimize detection bias, objective clinical outcomes, including sputum AFB conversion and TB treatment outcomes, will be assessed by an independent assessor who is not involved in participant recruitment, intervention delivery, or follow-up activities and will remain blinded to treatment allocation. Outcome data will be coded using unique study identification numbers before assessment. Blinded statistical analysis will also be implemented. Before analysis, treatment groups will be recoded as group A and group B by a member of the research team who is not involved in statistical analysis. The study statistician will remain blinded to treatment allocation until completion of the primary analysis.

Intervention and Comparator Group

Intervention group: GRVOTS

Participants randomized to the intervention group will receive TB treatment monitoring through GRVOTS, a mobile health application that integrates asynchronous VDOT with automatic date and time stamping, medication reminders, gamification features (progress meter, performance progress bar, and achievement badge rewards), adverse effect reporting, and electronic study questionnaires [34]. An overview of the GRVOTS application and its principal components is presented in **Figure 2**.

Following enrolment, participants allocated to the intervention group will receive standardized training on the installation and use of GRVOTS, including the medication-ingestion recording procedure, video submission requirements and navigation of the application features. Embedded tutorial videos will remain available within the application to provide ongoing user support throughout the study period. Participants will be required to record and submit a daily medication-ingestion video using the camera embedded within the GRVOTS application. Videos cannot be uploaded from the smartphone gallery; therefore, all medication-ingestion recordings must be made in real time through the in-app camera.

To minimize the collection of unnecessary identifying information, participants will be instructed to record only the lower half of the face during medication ingestion. During each recording, participants will be required to display the prescribed TB medication pack and verbally confirm the relevant medication details, including the number and dosing schedule of the tablets. Before ingestion, participants will open the mouth and show the oral cavity, including the tongue, to demonstrate the absence of medication or other objects. Medication ingestion and swallowing will then be recorded continuously, followed by a second view of the oral cavity to provide visual evidence that the medication has been swallowed.

GRVOTS uses an asynchronous video-observation approach. Each video is assigned its original recording date and time when recorded through the application. If Internet connectivity is unavailable or insufficient for immediate transmission, the video is retained within the pending videos function together with its original timestamp and may be transmitted when connectivity is restored. Such a submission is therefore considered a delayed transmission of a video recorded in real time rather than a retrospective recording. If no medication-ingestion video is recorded for a scheduled dose, a retrospective replacement video cannot subsequently be uploaded from the smartphone gallery, and the corresponding dose will remain unverified.

Submitted videos will be reviewed by the principal investigator within 24 hours of receipt using predefined medication-ingestion verification criteria. A submission will be considered verified when the prescribed medication, pre-ingestion oral cavity, medication ingestion and swallowing, and post-ingestion oral cavity can be adequately observed. Incomplete, interrupted or otherwise unverifiable recordings will be classified as invalid and will not be counted as verified doses. Suspected duplicate submissions will also be reviewed and will not be counted as separate verified doses unless confirmed as distinct medication-ingestion events.

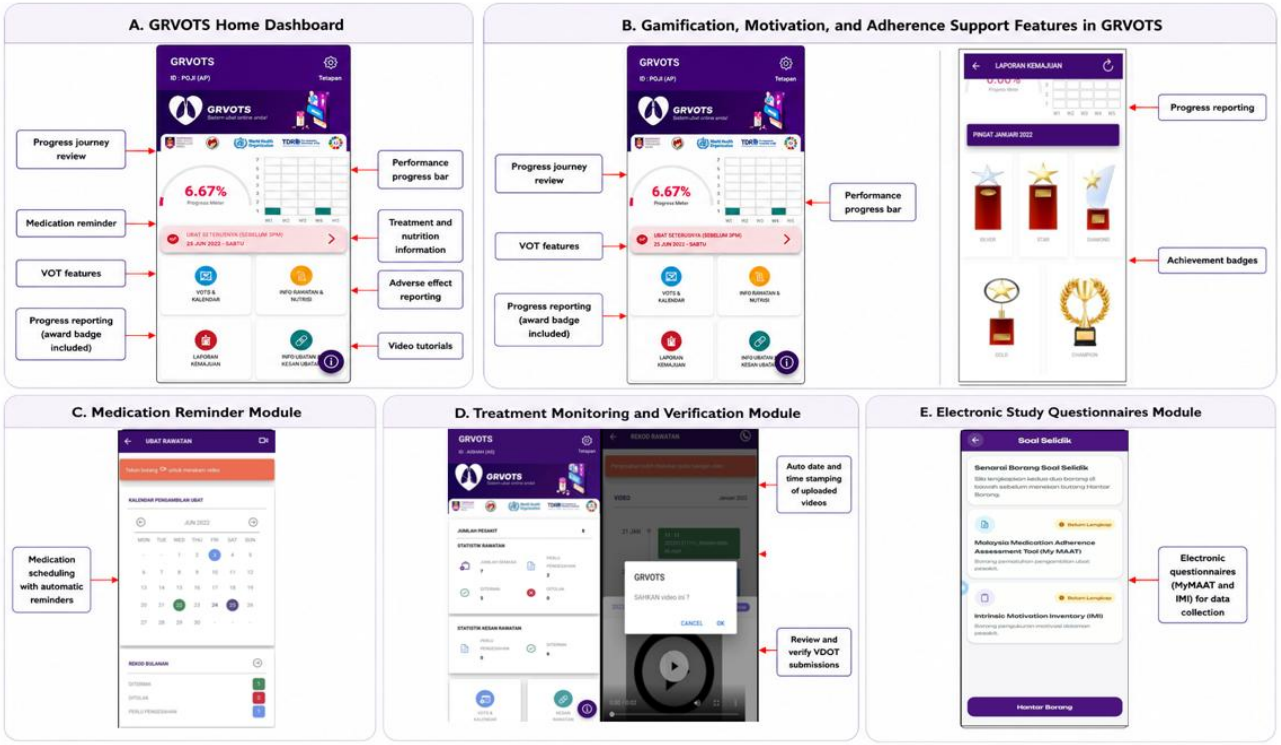


Figure 2. Overview of the GRVOTS application and its principal components: (A) GRVOTS home dashboard displaying the main navigation interface and treatment management functions; (B) Gamification, motivation, and adherence support features, including the progress meter, performance progress bar, and achievement badge rewards; (C) Medication reminder module providing treatment scheduling and reminder notifications; (D) Treatment monitoring and verification module for reviewing and validating submitted VDOT recordings, including automatic date and time stamping of uploaded videos, and monitoring patient-reported adverse effects; and (E) Electronic study questionnaire module for administering (the authors' own compilation based on the GRVOTS application development study [13])

GRVOTS does not incorporate automated facial-recognition technology. Each submission is linked to the participant's registered account and restricted to recordings generated through the in-app camera. Verification therefore relies on the participant-specific account, original recording timestamp, submission metadata and manual assessment of the predefined medication-ingestion sequence rather than automated facial recognition.

Verified video submissions will be documented in the VCC, which will serve as the adherence record for the intervention group. The participant-facing GRVOTS interface provides visual feedback on adherence performance and treatment progress. The current GRVOTS implementation also includes a password-protected web-based administrative interface that enables the principal investigator to monitor participant activity and identify missed medication-video submissions or scheduled study activities for follow-up.

In addition to video-based adherence monitoring, GRVOTS incorporates several features designed to support treatment engagement. These include medication reminder notifications, a progress meter that tracks treatment progress, a performance progress bar that provides feedback on adherence performance, and an achievement badge system comprising five levels (silver, star, gold, diamond, and champion) awarded according to sustained medication adherence. Educational tutorial videos are also accessible within the application to reinforce participant understanding of its functions. Participants may report symptoms or potential anti-TB medication-related adverse effects through the adverse effect reporting module. Reports will be reviewed by the principal investigator within 24 hours. Participants reporting potentially significant symptoms will be advised to seek assessment of their respective healthcare facilities, and the designated TB healthcare team will be notified where appropriate. The GRVOTS intervention does not modify the prescribed TB treatment regimen, and all clinical decisions regarding treatment continuation, interruption, or modification will remain under the responsibility of the treating healthcare team in accordance with routine clinical practice and Ministry of Health Malaysia guidelines.

The MyMAAT and IMI questionnaires will be administered electronically through GRVOTS at prespecified follow-up time points. Automated notifications will remind participants to complete the questionnaires, and completion status will be monitored through the study system. Participants with missed video submissions or scheduled study activities will be contacted by the principal investigator for follow-up and technical support as required.

Comparator group: Standard DOTS care (DOTS TB diary)

Participants randomized to the comparator group will receive standard TB treatment monitoring in accordance with the current Ministry of Health Malaysia TB management guidelines [6]. Medication ingestion will be directly observed by the TB healthcare team or by a close family member designated as the treatment supervisor. Each scheduled dose will be documented in the physical DOTS TB diary following observed medication ingestion, and the diary will serve as the primary source of adherence data for participants in the comparator group throughout the study period.

	Enrollment		Post-randomisation								
TIMEPOINT	***0*** screening	***0*** consent	***T0*** baseline	***T1*** 2 weeks	***T2*** 4 weeks	***T3*** 6 weeks	***T4*** 2 months	***T5*** 3 months	***T6*** 4 months	***T7*** 5 months	***T8*** 6 months
ENROLLMENT:											
Eligibility screen	X										
Informed consent		X									
Randomisation		X									
Allocation		X									
INTERVENTION/ COMPARATOR:											
[GRVOTS][a]			X →	→	→	→	→	→	→	→	X
[DOTS TB Diary][b]			X →	→	→	→	→	→	→	→	X
ASSESSMENTS:											
[MyMAAT questionnaire]			X	X	X	X	X	X	X	X	X
[IMI questionnaire]			X	X	X	X	X	X	X	X	X
[Daily GRVOTS Video submission/Video Count Checklist]			X	X	X	X	X	X	X	X	X
[Daily DOTS TB diary entry]			X	X	X	X	X	X	X	X	X
[Sputum Conversion Checklist]				X			X			X	
[Treatment Outcome Checklist]											X

Arrow indicates continuous delivery of TB medication and GRVOTS
Arrow indicates continuous delivery of TB medication and DOTS TB Diary

Figure 3. Participant timeline: Schedule of enrolment, interventions, and assessments from screening to month 6 (the authors' own elaboration based on the SPIRIT 2025 guidelines)

The setting for daily supervision may vary according to routine clinical arrangements and individual participant circumstances, including healthcare-facility- or home-based supervision. Regardless of the observation setting, adherence verification will remain based on directly observed medication ingestion documented in the physical DOTS TB diary. Scheduled clinical follow-up and case-holding review will be conducted in person at the treating clinic, where participants will be reviewed by the medical officer or specialist according to routine TB care. Any variation in the routine delivery of DOTS across participating facilities will be documented descriptively. Any alternative treatment-support modality initiated by the treating TB team during follow-up for clinical or service-related reasons will be recorded separately as a deviation from the allocated treatment-support strategy.

Medication adherence will be determined from the number of prescribed doses documented as observed in the DOTS TB diary relative to the total number of prescribed doses expected during the study observation period. Diary entries will be verified against corresponding routine treatment records by the treating TB team where required. The MyMAAT and IMI will be administered at predetermined follow-up time points. Participants will complete paper-based questionnaires during routine follow-up visits, and the completed questionnaires will subsequently be collected by the research team for analysis. Questionnaire responses will be used for outcome assessment as described in the Outcomes section. Participants in both study groups will continue to receive routine TB investigations, anti-TB medications and clinical care in accordance with the Malaysia clinical practice guidelines [6]. Participation in the trial will not restrict the use of concomitant treatments or other clinically indicated care considered necessary by the treating clinical team.

Follow-Up Assessment

Each participant will be followed for a total duration of six months, corresponding to the standard course of first-line TB treatment. Data collection will be conducted at nine assessment time points, comprising one baseline assessment (T0) and eight follow-up assessments (T1-T8). Participants in both the intervention and comparator groups will undergo four follow-up assessments at two-week intervals during the intensive phase of treatment, followed by four follow-up assessments at monthly intervals during the continuation phase. More frequent assessments during the intensive phase are intended to facilitate early identification of adherence issues and treatment-related challenges, while monthly assessments during the continuation phase support continued adherence monitoring throughout the remainder of treatment.

At each follow-up assessment, study outcomes and relevant study instruments will be administered according to the predefined study schedule. Medication adherence will be assessed using verified video submissions documented in the VCC for participants in the intervention group and the DOTS TB diary for participants in the comparator group. The MyMAAT and IMI will be administered at all assessment time points. Sputum conversion and treatment outcomes will be assessed according to the study schedule and routine clinical practice.

The SPIRIT schedule of enrolment, interventions, and assessments is presented in **Figure 3**, while the participant flow through screening, enrolment, randomization, allocation, follow-up, and analysis is illustrated in **Figure 4**.

Primary Outcome

The study has a single primary outcome: medication adherence rate (%) over the study observation period.

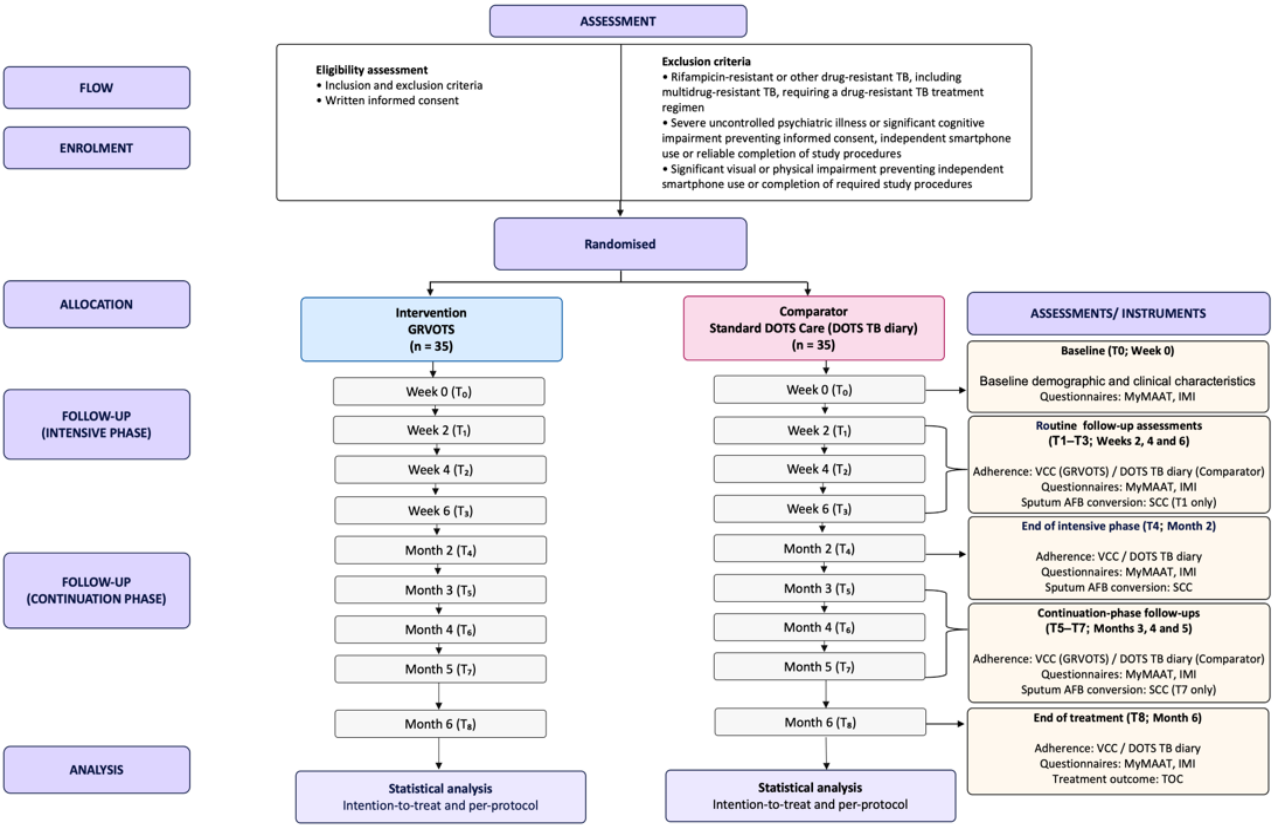


Figure 4. Participant flow through screening, enrolment, randomization, allocation, follow-up, and analysis (the authors' own elaboration)

Medication adherence rate will be assessed throughout the study period as the proportion of verified medication doses relative to the total number of expected medication doses and expressed as a percentage. For participants in the GRVOTS group, adherence rate will be calculated as the proportion of verified medication ingestion videos submitted relative to the total number of expected video submissions [9]. For participants in the DOTS TB diary group, adherence rate will be defined as the proportion of observed doses recorded in the DOTS TB diary relative to the total number of doses expected during the study period [42]. Medication adherence rate will be calculated using the following formula: Medication adherence rate (%) = (number of verified prescribed doses taken ÷ total number of prescribed doses expected during the study observation period) × 100.

For participants allocated to the GRVOTS group, a prescribed dose will be considered verified when the submitted medication-ingestion video fulfils the predefined verification criteria. These include presentation of the prescribed medication, demonstration of the oral cavity before ingestion, visible medication ingestion and swallowing, and demonstration of the oral cavity following ingestion. For participants allocated to the comparator group, medication-taking will be determined from entries in the physical DOTS TB diary and corresponding routine treatment records verified by the treating TB team. Prescribed doses formally withheld by the treating clinician because of an adverse drug reaction or other clinical indication will be documented separately and will not be classified as missed doses due to medication non-adherence.

Consistent with previous literature, an adherence rate of ≥ 80% will additionally be used to describe participants achieving optimal medication adherence [9]. However, this threshold will not be used to determine the primary non-inferiority conclusion. The primary non-inferiority analysis will be based solely on the between group difference in medication adherence rate. The treatment effect will be expressed as the mean difference in adherence between the GRVOTS and standard DOTS groups (GRVOTS minus standard DOTS), together with its 95% CI. GRVOTS will be considered non-inferior to standard DOTS if the lower bound of the 95% CI is greater than the prespecified non-inferiority margin of −15 percentage points. As a single primary endpoint is prespecified, no multiplicity adjustment is required for the primary non-inferiority hypothesis.

Secondary Outcomes

The secondary outcomes are medication-adherence behavior score, intrinsic motivation, sputum AFB conversion and TB treatment outcomes. These outcomes will provide complementary information on behavioral, motivational, microbiological and clinical aspects of the intervention but will not be used to determine the primary conclusion of non-inferiority. Medication-adherence behavior will be assessed using the validated MyMAAT [43]. The MyMAAT consists of 12 items rated on a 5-point Likert scale, producing a total score ranging from 12 to 60. Scores of 54-60 indicate adherence, whereas scores of 12-53 indicate non-adherence to anti-TB medication. MyMAAT will be treated as a secondary patient-reported measure of medication-adherence behavior and will not contribute to the determination of non-inferiority.

Intrinsic motivation towards medication-taking will be assessed using the IMI, which has been used previously in the GRVOTS study [34]. The IMI consists of 22 items rated on a 7-

Table 2. Study outcomes and corresponding measurement instruments

Outcome	Instruments
Medication adherence rate (%)	Video count checklist (VCC); DOTS TB diary for the standard DOTS care group
Medication adherence score	Malaysia medication adherence assessment tool (MyMAAT)
Tuberculosis treatment outcomes	Treatment outcome checklist (TOC)
Sputum AFB conversion	Sputum conversion checklist (SCC)
Intrinsic motivation	Intrinsic motivation inventory (IMI)
Baseline characteristics	Baseline characteristics form

point Likert scale, with higher scores indicating greater intrinsic motivation towards the medication-taking task. IMI measurements will be obtained at the prespecified study time points to assess changes in intrinsic motivation during treatment. Sputum AFB conversion will be assessed at the prespecified follow-up time points: T1 (2 weeks), T4 (2 months), and T7 (5 months). Among participants with sputum smear-positive pulmonary TB at baseline, conversion will be defined as a change from a positive sputum AFB smear at baseline to a negative sputum AFB smear during follow-up [6]. Sputum AFB results will be obtained from routine clinical records and recorded using the sputum conversion checklist (SCC).

TB treatment outcomes will be assessed at the end of treatment using the outcome classifications adopted by the NTBR, including cured, treatment completed, treatment success, treatment failure, loss to follow-up, died, transferred out, and change of diagnosis [6]. Treatment outcomes will be obtained from routine TB records and documented using the treatment outcome checklist (TOC). Adverse events occurring during anti-TB treatment will be documented throughout the study period as part of safety monitoring and managed according to routine clinical practice by the treating clinical team. Clinically indicated treatment interruptions, drug substitutions or regimen modifications will be recorded separately and will not be classified as medication non-adherence.

No formal multiplicity adjustment will be applied across the secondary outcomes. Secondary analyses will therefore be considered supportive and will be interpreted cautiously in view of the multiple comparisons, with effect estimates and corresponding 95% CIs reported where appropriate. The study instruments comprise the baseline characteristics form, VCC, DOTS TB diary, MyMAAT, IMI, SCC, and TOC. A summary of the study outcomes, their measurement time points and corresponding instruments is presented in **Table 2**.

Data Collection Procedures

Baseline assessment

Following written informed consent, randomization, and allocation, baseline demographic and clinical information will be collected at T0 using the baseline characteristics form and participants' medical records. Baseline variables will include age, sex, ethnicity, educational level, household income, employment status, chest radiography findings, baseline microbiological results including sputum AFB smear, TB loop-mediated isothermal amplification (TB-LAMP), Xpert MTB/RIF, or Xpert MTB/RIF Ultra, and mycobacterial culture and drug-susceptibility testing where available, bacille Calmette-Guérin scar status, Mantoux test results, and other relevant clinical characteristics including diabetes mellitus, smoking status and HIV status. At baseline, participants in both study groups will complete the MyMAAT and IMI questionnaires.

Follow-up assessment

Follow-up assessments will be conducted according to the predefined study schedule presented in **Figure 3**. GRVOTS adherence will be monitored through verified daily video submissions recorded in the VCC, while comparator adherence will be documented in the DOTS TB diary. MyMAAT and IMI will be administered at prespecified time points, and sputum AFB conversion and TB treatment outcomes will be obtained from routine clinical records according to the study schedule.

Measures to minimize bias

Several measures will be implemented to minimize potential sources of bias. Selection bias will be reduced through predefined eligibility criteria, computer-generated randomization and allocation concealment until assignment. Randomization using varying block sizes will maintain balanced allocation while reducing the predictability of subsequent assignments. Baseline characteristics will be summarized descriptively by randomized treatment group.

Owing to the nature of the intervention, blinding of participants and personnel delivering the treatment-support strategies is not feasible. Observation bias, including behavioral modification resulting from participants being aware that their medication-taking behavior is being monitored, may therefore occur. This possibility is particularly relevant because medication ingestion is directly observed through GRVOTS video submissions in the intervention group and through conventional DOTS supervision in the comparator group. Standardized instructions and predefined adherence-verification procedures will be used to minimize differential observation practices between participants; however, the potential influence of being observed cannot be completely eliminated and will be acknowledged when interpreting the findings.

Participant self-reporting bias will be distinguished from observation bias. Self-reported measures, particularly the MyMAAT and IMI, may be susceptible to recall or socially desirable responding [34, 43]. These outcomes will therefore be assessed using standardized, validated questionnaires administered according to the same prespecified schedule in both groups. Importantly, self-reported adherence assessed using MyMAAT is a secondary outcome and will not be used to determine the primary non-inferiority conclusion, which will be based on verified medication adherence.

Potential selective outcome reporting bias will be minimized through prospective specification of the primary and secondary outcomes, measurement time points and planned statistical analyses in the study protocol and trial registration. The primary endpoint and prespecified non-inferiority margin will remain unchanged during analysis, and all prespecified outcomes will be reported irrespective of the direction or statistical significance of the findings. Any

deviations from the prespecified protocol or statistical analysis plan will be documented and reported transparently [44].

Detection and measurement bias will be minimized through predefined outcome definitions and standardized measurement procedures. For the primary outcome, GRVOTS doses will be verified using predefined video-ingestion criteria, while comparator-group doses will be determined from the physical DOTS TB diary and corresponding routine treatment records verified by the treating TB team. Because the mode of adherence ascertainment differs by allocated intervention, complete blinding of primary adherence assessment is not feasible. Where applicable, objective clinical outcomes, including sputum AFB conversion and final TB treatment outcomes, will be obtained from routine clinical records, and statistical analysis will be performed with treatment groups masked to the statistician where feasible.

Attrition bias will be minimized through scheduled follow-up, reminder notifications and follow-up of participants with missed study assessments. Reasons for withdrawal, loss to follow-up and missing outcome data will be documented by treatment group. The primary non-inferiority analysis will be conducted using both intention-to-treat (ITT) and per-protocol (PP) populations, as concordance between these analyses is recommended when interpreting non-inferiority trials [44]. Missing data will be addressed according to the prespecified statistical analysis plan.

Participant Withdrawal

Participants may withdraw from the study at any time without providing a reason and without affecting their access to routine TB care or other healthcare services. The investigator may also discontinue a participant from study procedures if continued participation is considered unsafe or if the participant is unable to comply with study requirements.

Reasons for withdrawal may include participant request, inability to comply with study procedures, loss to follow-up, major protocol deviations, or safety concerns identified by the research team. Participants in the GRVOTS group may also choose to withdraw if they are unwilling to continue submitting medication ingestion videos or have concerns regarding privacy and confidentiality despite the safeguards implemented in the study.

Participants who discontinue the intervention will continue to receive routine TB care in accordance with Ministry of Health Malaysia guidelines. Where possible, participants who discontinue the intervention will be invited to continue outcome assessments. Data collected before withdrawal will be retained for analysis unless the participant requests otherwise, subject to applicable ethical and regulatory requirements.

Data Management

Data will be collected using the GRVOTS application, VCC, DOTS TB diary, MyMAAT, IMI, SCC and TOC. Electronic study data will be entered into a secure Microsoft Excel database (Microsoft Corporation, Redmond, WA, USA) and subsequently analyzed using IBM SPSS Statistics for Macintosh, version 28.0 (IBM Corp., Armonk, NY, USA).

Periodic data audits will be conducted to assess data accuracy, completeness and consistency. Discrepancies will be resolved by cross-checking against the relevant source documents. Before statistical analysis, data-cleaning procedures will be undertaken to identify missing values, duplicate records, data-entry errors and outliers. Data used for analysis will be de-identified and linked to participants using a unique study identification number.

Data security, storage, and confidentiality

Participants allocated to GRVOTS will submit medication-ingestion videos through the application. To minimize the collection of unnecessary identifiable information, participants will be instructed to record only the lower half of their face during medication ingestion. Videos must be recorded directly using the GRVOTS in-app camera and cannot be uploaded from the smartphone gallery. Participants will also be instructed not to transmit or share study videos through external messaging applications, email, social media or file-sharing platforms.

As preventive measures against accidental or unauthorized disclosure, medication-ingestion videos will be encrypted during transmission using HTTPS/TLS secure communication protocols and stored on a secure cloud-based server hosted by DigitalOcean. Access to uploaded videos will be through the password-protected GRVOTS dashboard and restricted to the principal investigator. Videos will be reviewed solely for medication-adherence verification and will not be used for purposes outside the study.

Direct personal identifiers, including participant names, identification card numbers and contact information, will be collected only for participant verification, study administration and follow-up. These identifiers will be stored separately from research outcome data and will not be included in the analytical dataset. Electronic study data will be stored on password-protected computers with access restricted to authorized research personnel, while paper-based study documents will be stored in locked cabinets within secure research facilities. These measures are intended to further reduce the risk of accidental disclosure of identifiable participant information.

Video recordings will be retained on the secure cloud server for the duration of the study and permanently deleted following completion of all study-related requirements. Secure backup procedures will be maintained to reduce the risk of data loss and support data recovery where required. Any backup copies containing video data will be permanently deleted at the same time as the original recordings. De-identified analytical study data will be retained for five years following publication of the study findings and subsequently destroyed in accordance with institutional data-retention requirements.

If a video inadvertently captures additional identifying features beyond the intended recording area, the recording will remain within the secure GRVOTS system and will be used solely for medication-adherence verification. The participant will be reminded of the recommended recording procedure at subsequent follow-up.

In the event of suspected unauthorized access, disclosure or other data-security incident, access will be restricted where necessary and the incident will be investigated promptly. The principal investigator will work with the GRVOTS application developer and, where required, the cloud-hosting provider to determine the nature and extent of the incident, identify potentially affected data, implement corrective security measures, and reduce the risk of recurrence. Any significant

data-security incident will be managed and reported in accordance with applicable institutional, ethical and regulatory requirements.

Statistical Analysis

Data will be analyzed using IBM SPSS Statistics version 28.0 and reported in accordance with CONSORT 2025 statement [45] and recommendations relevant to non-inferiority trials [44]. Continuous variables will be summarized using mean and SD or median and interquartile range, as appropriate, while categorical variables will be presented as frequencies and percentages. Baseline characteristics will be presented descriptively by randomized treatment group, without formal significance testing of baseline differences.

The primary non-inferiority analysis will be conducted using both the ITT and PP populations. The ITT population will include all randomized participants analyzed according to their originally allocated treatment group. The PP population will include participants who receive the allocated treatment-support strategy without major protocol deviations that could affect evaluation of the primary outcome. Major protocol deviations will be prespecified before database lock. Medication non-adherence itself will not constitute a protocol deviation because medication adherence is the primary outcome.

The single primary outcome is the overall medication adherence rate (%) during the six-month treatment period. For each participant, medication adherence will be calculated as the number of prescribed anti-TB doses verified as taken divided by the total number of prescribed doses expected during the study observation period, multiplied by 100. The primary treatment effect will be expressed as the difference in mean overall medication adherence rate between the GRVOTS and standard DOTS care groups, calculated as GRVOTS minus standard DOTS, with the corresponding two-sided 95% CI.

Non-inferiority will be assessed using the prespecified absolute margin of 15 percentage points. GRVOTS will be considered non-inferior to standard DOTS care if the lower bound of the two-sided 95% CI for the between-group difference in mean overall medication adherence rate is greater than -15 percentage points, corresponding to a one-sided significance level of 2.5%. Non-inferiority will be assessed in both the ITT and PP populations.

As a supportive longitudinal analysis, medication adherence across the prespecified follow-up periods will be analyzed using generalized estimating equations (GEE). An exchangeable working correlation structure will be used to account for within-participant correlation across repeated measurements. The model will include treatment group, time and the treatment-group-by-time interaction. Robust standard errors and corresponding 95% CIs will be reported.

Missing outcome data will be examined according to their extent, pattern and documented reasons. If primary outcome data are missing, multiple imputation will be performed as a sensitivity analysis under a missing-at-random assumption. The imputation model will include treatment allocation, available adherence measurements and relevant baseline variables associated with the outcome or missingness. A complete-case analysis may additionally be conducted as a supplementary sensitivity analysis.

Secondary outcomes will be analyzed according to their measurement scale and timing. Repeated MyMAAT and IMI measurements will be analyzed using GEE with an exchangeable working correlation structure, including treatment group, time and the treatment-group-by-time interaction. Sputum AFB conversion during treatment follow-up will be evaluated among participants who are sputum smear-positive at baseline and have subsequent sputum AFB results available. The proportion achieving sputum AFB conversion will be compared between treatment groups using the chi-square test or Fisher's exact test, as appropriate. TB treatment outcomes at the end of treatment will be summarized by treatment group and compared according to their categorical distribution, with effect estimates and 95% CIs reported where appropriate.

The study has a single primary endpoint; therefore, no multiplicity adjustment will be applied to the primary analysis. Secondary outcome analyses will be considered supportive and interpreted in the context of multiple comparisons. Participants will be individually randomized rather than randomized by study facility. As a sensitivity analysis, potential study-site effects will be examined where supported by the available data. All statistical tests other than the non-inferiority hypothesis will use a two-sided significance level of 0.05. Effect estimates will be reported with corresponding 95% CIs. No subgroup analyses are prespecified.

Ethical Consideration

The trial was prospectively registered with the Thai clinical trials registry (TCTR20260411006) and received ethical approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia (Ref: NMRR-26-00717-KVJ), and the Universiti Teknologi MARA Research Ethics Committee (ref: REC/08/2024 [PG/MR/407]). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the Malaysian code of responsible conduct in research.

Written informed consent will be obtained from all participants before enrolment and randomization. During the consent process, participants will be informed that those allocated to GRVOTS will be required to record and submit daily medication-ingestion videos. Participants will be informed that these recordings may contain identifiable information, including facial features and voice, and will receive information regarding the purpose of video collection, methods of transmission and storage, authorized access, duration of retention and procedures for permanent deletion.

Participation will be voluntary, and participants may withdraw from the study at any time without affecting their routine TB treatment or access to healthcare services. Withdrawal from the study will not result in retrospective exclusion of data already collected unless otherwise required by applicable ethical or regulatory requirements.

No identifiable video recording, image or other directly identifying participant information will be included in publications, presentations or reports without additional appropriate consent. Participants may request a summary of the overall study findings following completion of the study. Study findings will be disseminated through peer-reviewed publications, scientific presentations and reports to the Ministry of Health Malaysia.

Any substantial protocol amendments involving changes to the study objectives, eligibility criteria, interventions, outcome measures or statistical analysis plan will require

approval from the relevant ethics committees before implementation. Where applicable, approved amendments will also be updated in the trial registry.

RESULTS

As this is a study protocol, no results are available at the time of publication. It is hypothesized that GRVOTS will be non-inferior to the standard DOTS care with respect to medication adherence.

DISCUSSION

Expected Contributions

Achieving and sustaining medication adherence remains an important challenge in TB control. Although standard DOTS care provides structured treatment supervision, its implementation may impose practical burdens related to travel, employment, transportation costs and perceived stigma, which may affect treatment continuity and adherence[15, 46, 47]. DATs may reduce the need for repeated face-to-face observation, but evidence on gamified video-based treatment support remains limited, particularly within routine TB services in low- and middle-income settings.

This study addresses this evidence gap by evaluating GRVOTS, which integrates asynchronous video observation, medication reminders, gamification, treatment-progress monitoring, adverse-effect reporting and electronic follow-up within a single digital intervention. The non-inferiority design will determine whether GRVOTS can maintain medication adherence within the prespecified non-inferiority margin compared with standard DOTS care documented using the physical TB diary. Secondary outcomes will provide complementary information on medication-adherence behavior, intrinsic motivation, sputum AFB conversion and TB treatment outcomes.

Beyond medication verification, asynchronous observation may provide greater flexibility and reduce some of the logistical burden associated with conventional treatment supervision. The monitoring function may also support case-holding by facilitating the identification and timely follow-up of participants with missed medication submissions or treatment-monitoring activities [13]. However, whether this function reduces treatment interruption or loss to follow-up is not directly evaluated in the present trial and will require further study.

Strengths of the Study

This study has several methodological strengths. First, it uses an individually randomized controlled trial design with allocation concealment and a prespecified non-inferiority margin. Medication adherence is defined as the single primary endpoint, and both ITT and PP analyses are planned to strengthen the interpretation of non-inferiority. Adherence is assessed using prespecified intervention-specific methods: verified GRVOTS video submissions in the intervention group and DOTS TB diary records in the comparator group.

Second, GRVOTS was developed through a structured, theory-informed process incorporating gamification, motivational and technological design elements, with its components undergoing expert content validation before clinical evaluation [13]. The present trial also builds on previous preliminary intervention evidence for GRVOTS [34], allowing its comparative effectiveness to be evaluated using a randomized design. The current implementation incorporates a Pending Videos function that allows videos recorded within the application to be transmitted after temporary loss of connectivity while preserving their original recording date and time. This supports operational feasibility in situations where Internet connectivity is intermittent while maintaining the distinction between delayed transmission and retrospective recording.

Third, validated instruments, including MyMAAT and IMI, are used alongside adherence measures to assess behavioral and motivational outcomes. The trial is also conducted across multiple healthcare facilities in Klang Valley, has been prospectively registered, and prespecifies its primary endpoint, non-inferiority margin and analytical approach, thereby strengthening methodological transparency.

Potential Limitations

Several limitations should be considered. Blinding of participants and personnel delivering treatment support is not feasible, which may introduce performance and observation bias. Participants may modify medication-taking behavior because they are aware that adherence is being observed. Self-reported secondary outcomes, including MyMAAT and IMI, may also be affected by recall and social desirability bias, although they do not determine the primary non-inferiority conclusion

Digital access represents an additional limitation. Eligibility requires access to a compatible smartphone, Internet connectivity and the ability to operate the device independently. Individuals with limited digital access or literacy may therefore be under-represented, limiting generalizability to populations experiencing greater socioeconomic or digital disadvantage. Although the Pending Videos function can mitigate temporary connectivity interruptions, it cannot overcome the absence of a suitable device or Internet access.

The study is conducted predominantly in urban and peri-urban facilities in Klang Valley, and the findings may not be directly generalizable to rural or lower-resource settings. In addition, the study does not include a formal economic evaluation; therefore, long-term cost-effectiveness and financial sustainability cannot be determined

Scalability, Equity, Sustainability, and Program Integration

Wider implementation of GRVOTS, particularly in rural and lower-resource settings, would require adequate digital access, digital literacy, healthcare-worker capacity and reliable technical infrastructure. Equity remains an important consideration because patients without suitable smartphones, affordable Internet connectivity or sufficient digital literacy may be unable to use the intervention. GRVOTS should therefore be considered as an additional treatment-support option rather than a universal replacement for standard DOTS care, with non-digital alternatives retained for patients unable or unwilling to use digital monitoring.

Long-term sustainability would also depend on integration with existing national tuberculosis program and digital-health infrastructure, together with clear arrangements for system ownership, data governance and technical support. Potential

integration of selected GRVOTS functions, including adherence monitoring and case-holding support, within platforms such as MySejahtera may facilitate alignment with routine TB workflows, subject to appropriate program, technical, governance and regulatory approval. Such integration would require further assessment of interoperability, cybersecurity, healthcare-worker workflow and data stewardship.

Sustainability after research funding ends would additionally depend on a viable long-term financing and maintenance model. Recurrent requirements would include server hosting, video storage, software updates, cybersecurity, technical maintenance, user support and staff training. These operational and financial requirements will need to be evaluated alongside effectiveness before wider program-level implementation.

Public Health Implications

If GRVOTS is demonstrated to be non-inferior to standard DOTS care for medication adherence, the findings may support its further evaluation as a flexible treatment-support option for digitally eligible patients. Its potential value lies not only in remote medication observation but also in supporting treatment monitoring and timely follow-up within a patient-centered model of TB care. Wider implementation should nevertheless be guided by evidence on acceptability, equity, cost-effectiveness, program feasibility and sustainability. Further research should evaluate GRVOTS in rural and lower-resource populations and determine how it can be integrated sustainably within routine TB services.

CONCLUSION

Medication adherence is a key determinant of successful TB treatment and remains a major challenge despite the widespread implementation of the DOTS strategy. This protocol describes a non-inferiority randomized controlled trial that will evaluate whether GRVOTS is non-inferior to standard DOTS care in maintaining medication adherence. Secondary outcomes will evaluate medication-adherence behavior, intrinsic motivation, sputum AFB conversion and TB treatment outcomes. The findings will contribute to the evidence on DATs and may inform the integration of patient-centered, technology-assisted approaches into routine TB care in Malaysia. The open-label design and inclusion of participants with access to a smartphone may limit the generalizability of the study findings. Future studies should evaluate the effectiveness and implementation of similar digital adherence interventions in broader populations and healthcare settings.

Author contributions: **NAAM:** conceptualization, methodology, visualization, writing – original draft; **SAA & MRI:** conceptualization, methodology, writing – review & editing; **SMH, ZAB, HY, KI, & SMY:** writing – review & editing; **NI:** conceptualization, methodology, supervision, writing – review & editing. All authors have agreed with the results and conclusions.

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Ethical statement: This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (ref: NMRR-26-00717-KVJ), and the Universiti Teknologi MARA Research Ethics Committee (REC/08/2024 [PG/MR/407]). Written informed consent will be obtained from all participants. Participant confidentiality will be maintained through secure data storage and restricted access to authorized research personnel.

AI statement: The authors declared that generative AI was used solely for language editing and to assist with figure arrangement. All scientific analyses, interpretations, and decisions regarding manuscript content were made independently by the authors. All figures were conceptualised by the authors and prepared using original materials provided by the authors. No AI-generated images were used.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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