Tuberculosis Treatment Compliance under Smartphone-based Video-observed Therapy versus Community-based Directly Observed Therapy: A Cluster Randomized Controlled Trial

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Abstract

Background: There are no recent studies comparing the compliance rates of both patients and observers in tuberculosis (TB) treatment between the video observed therapy (VOT) and directly observed therapy (DOT) programs.

Objective: We aimed to compare the average number of days that patients with pulmonary tuberculosis (TB) and their observers were compliant under VOT and DOT.

Methods: Patient and observer compliance with TB treatment between VOT and DOT programs were compared as the average number of VOT and DOT compliance days and sputum-conversion rate in a 60-day cluster randomized controlled trial with pulmonary TB patients (VOT=63, DOT=65) with positive sputum acid-fast bacilli smears and 38 observers, equally randomized into the VOT and DOT groups (each, n=1–5 patients). The VOT group submitted videos to observers via smartphones; the DOT group followed standard procedures. An intention-to-treat analysis assessed compliance of both patients and observers.

Results: The VOT group had higher average compliance than the DOT group (patients, mean difference [95% confidence interval, CI]: 15.2 [4.8–25.6] days; observers: 21.2 [13.5–28.9] days). The sputum-conversion rates in the VOT and DOT groups were 73.0% and 61.5%, respectively (P=0.167).

Conclusions: Smartphone-based VOT significantly outperformed community-based DOT in ensuring compliance with TB treatment among observers. However, the study was underpowered to confirm improved compliance among patients with pulmonary TB and to detect differences in sputum conversion rates. Clinical Trial: thaiclinicaltrials.org TCTR20210624002; https://www.thaiclinicaltrials.org/show/TCTR20210624002

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Abstract

Background: There are no recent studies comparing the compliance rates of both patients and observers in tuberculosis (TB) treatment between the video-observed therapy (VOT) and directly observed therapy (DOT) programs.
Objective: We primarily aimed to compare the average number of days that patients with pulmonary TB and their observers were compliant under VOT and DOT. The secondary objective was to compare the sputum conversion rate of patients under VOT with that of patients under DOT.
Methods: Patient and observer compliance with TB treatment between the VOT and DOT programs were compared based on the average number of VOT and DOT compliance days and sputum-conversion rates in a 60-day cluster randomized controlled trial with patients with pulmonary TB (VOT=63, DOT=65) with positive sputum acid-fast bacilli smears and 38 observers, equally randomized into the VOT and DOT groups (each, n=1–5 patients). The VOT group submitted videos to observers via smartphones; the DOT group followed standard procedures. An intention-to-treat analysis assessed the compliance of both the patients and the observers.
Results: The VOT group had higher average compliance than the DOT group did (patients, mean difference [95% confidence interval, CI]: 15.2 [4.8–25.6] days [*P*=0.005]; observers: 21.2 [13.5–28.9] days [*P*<0.001]). The sputum-conversion rates in the VOT and DOT groups were 73.0% and 61.5%, respectively (*P*=0.167).
Conclusions: Smartphone-based VOT significantly outperformed community-based DOT in ensuring compliance with TB treatment among observers. However, the study was underpowered to confirm improved compliance among patients with pulmonary TB and to detect differences in sputum conversion rates.
Trial Registration: thaiclinicaltrials.org TCTR20210624002; https://www.thaiclinicaltrials.org/show/TCTR20210624002

Keywords: video-enhanced therapy; tuberculosis; health care system; observed therapy; treatment compliance; lung disease; randomized trial; digital health; telehealth; telemedicine

Introduction

Video-observed therapy (VOT) facilitates remote monitoring of patients with tuberculosis (TB) [1] and constitutes an alternative program to directly observed therapy (DOT).[2] VOT has two forms: synchronous VOT (S-VOT) and asynchronous VOT (A-VOT).[1] In S-VOT, observers video-call their patients for real-time observation of drug administration, whereas with A-VOT, observers can review the video sent by the patients at any time. Globally, A-VOT is preferred over S-VOT, because it allows patients the flexibility to record drug-administration sessions, and the video can be reviewed multiple times.[3]

In Thailand, approximately 80,000 TB cases are reported annually.[4] Since 1996, the country has implemented DOT to ensure treatment adherence.[5] Despite evidence from two previous studies indicating the poor sustainability of DOT, no changes have been made due to the lack of alternative strategies and resources.[6,7] The National Tuberculosis Control Program Guideline recommends community-based DOT, observed by health personnel, as the preferred approach.[8] However, in 60–75% of TB cases, family-based DOT is utilized instead of health personnel observation, reflecting the complacency of the healthcare system.[9,10] Since 2015, VOT has been used in some areas, without, however, using an accountability system.[11] This system included irregular S-VOT utilizing the LINE (Line Corporation) app or an offline A-VOT that could not be audited daily.[11] The Thai video-observed therapy (TH VOT) system, an A-VOT system, has been devised and implemented in Songkhla province, serving as a testing area for the A-VOT system.[12,13] Rather than visiting patient homes in the community as in traditional DOT, or performing irregular VOT as previously done, observers can feasibly use the TH VOT system to reduce their travel expenses, and each VOT session performed can be daily audited.[12,13] The TH VOT system is usable and convenient for patients, especially for those who usually take medication late at night.[13] However, the system's effectiveness in improving medication adherence compared to the traditional community-based DOT remains unknown.

Prior research in Western countries has shown that A-VOT surpasses DOT in ensuring patient adherence, cost-effectiveness, and overall acceptance.[14–19] These investigations evaluated A-VOT based on observation counts. For comparison, counts under DOT, which follow strict regulations, such as those in the UK and United States, were also examined.[15,18] In contrast, the observation counts reported from DOT in Thailand are irregular, owing to a low level of accountability among observers.[6,7,12] Therefore, to evaluate the effectiveness of VOT compared to DOT, it is important to consider compliance from both the patients' and the observers' perspectives, unlike what has been evaluated in these prior studies.[15–18]

The primary objective of this trial was to compare the average number of days that patients with pulmonary TB and their observers were compliant under VOT and DOT. This was conducted during the intensive phase of treatment, which lasted 60 days, and followed the published protocol.[20] We assumed that medication adherence depended on the compliance of both patients and observers in both the VOT and DOT programs. The results of this study will help determine whether A-VOT can completely replace conventional DOT in Thailand. This is in line with the 'Thailand Operation Plan To End TB (2023–2027)," which aims at employing innovative technology to control TB.[21]

The secondary objective of this trial was to compare the clinical outcomes between the VOT and DOT groups. The clinical outcomes were sputum conversion and reporting of adverse events. This is useful for the future planning of the A-VOT system and for conducting further studies on a larger scale. The eligibility criteria and outcomes were registered before the commencement of the study (TCTR20210624002).[22]

Methods

Study Design

We conducted a cluster randomized controlled trial (RCT) in which an observer was assigned to a cluster of patients with pulmonary TB living in the same jurisdiction, using either DOT or VOT. The trial was registered in the Thai Clinical Trials Registry (TCTR20210624002). The trial protocol followed the CONSORT 2010 statement[23] and is available online at

researchprotocols.org.[20]

Study Setting

In Thailand, individuals diagnosed with TB receive definitive diagnostic evaluations at a hospital located within the jurisdiction of their place of residence. Subsequently, specialized nurses trained in tuberculosis care (TB nurse) at each hospital delegate a TB staff member (DOT observer) to administer DOT services to patients located within the corresponding Primary Care Unit (PCU) that aligns with the pertinent jurisdiction.
This study was conducted in the Hat Yai and Meuang Songkhla districts of Songkhla province, Southern Thailand, where a robust Internet network is available. Regarding telecommunications services in Thailand, both AIS and TrueMove H corporations offer 4G/5G networks with speeds that are well above the minimum requirement of 10 Mbps bandwidth for uploading videos from mobile phones.[24] All TB staff who served as the observers of this study had worked as DOT observers for at least 2 years. All participants were regular smartphone users.

Background of the Existing A-VOT in Thailand

In Thailand, the TH VOT mobile web system was developed for remote monitoring of anti-TB drug adherence.[12] This system is accessible through any mobile web browser and is available as an app on Google Play Store.[25] It utilizes user authentication via the widely-used LINE app, with daily LINE notifications for setting the times agreed-upon.[26–28] Patients upload videos of their medication intake to the server, which then alerts observers to review these videos. Our previous study, conducted in November 2021, found high patient compliance (approximately 70%) and moderate observer compliance (approximately 50–65%), despite the challenges posed by the Delta variant of the novel coronavirus.[13,29] The system, requiring roughly 1 min for patient video recording and 1.5 min for observer review, proved effective and faced no technical issues in areas with robust internet. It was particularly beneficial for patients taking medication late at night, allowing observers to review videos the following morning.[13] More details on system functions and usability are available online in our previous studies.[12,13,20]

Sampling Method and Recruitment Procedures

In our study area, we randomly selected 53 PCUs using a computer-generated list of random invitations. From these, we invited 38 observers from 38 PCUs based on the list of invitations, leaving 15 PCUs uninvolved. The randomized allocation lists, used for assigning PCUs at a 1:1 ratio to either the VOT or DOT group, were also generated by a computer. Patients with TB under the jurisdiction of the selected 38 PCUs were assessed for eligibility and subsequently invited to provide informed consent to participate in the study.

Participants

Observers (Cluster Level)

All 38 observers from randomly selected 38 PCUs consented to participate in the study, and 19 were allocated to the VOT group and the remaining 19 to the DOT group.

Patients (Individual Level)

Patients were considered eligible if they had newly active pulmonary TB with a positive acid-fast bacilli (AFB) sputum smear, were aged >18 years, owned a smartphone, could use the LINE application, and resided in the same jurisdiction as the observer. Participants were excluded if they had a condition that required specialist intervention, which precluded the 60-day follow-

up in intensive phase, rifampicin-resistant TB evaluated by a cartridge-based nucleic acid amplification test (Xpert MTB/RIF, Cepheid, Sunnyvale, California, USA), were unable to continue the treatment for 60 days, or had alcohol dependence.

Co-interventions

The patients were provided zipped bags daily for 60 days, each with a daily dose of their HRZE (isoniazid, rifampicin, pyrazinamide, and ethambutol) drug regimen.[12] Patients whose consent was registered in the database by a TB nurse were scheduled to take their medication (HRZE regimen) once daily. After each patient registration, the observer in the jurisdiction where the patient resided was notified through an auto-notification of the official LINE (either DOT or VOT).

For monetary compensation, the patients received 300 baht (US $8.68) immediately after registration to cover the cellular internet cost for the first month. Further compensation were paid once the patients completed their 60-day intensive treatment without discontinuing the assigned intervention. They received 300 baht (US $8.68) as a reimbursement for cellular internet cost in the second month and 400 baht (US $11.57) for transportation of the sputum specimen on 3 consecutive days.

The observers who observed medication administration among patients for at least 15 out of 60 daily sessions were compensated with 600 baht (US $17.36). They were also compensated for the cost of travel to visit their patients (4 baht or US $0.12 per kilometer).

Assigned Interventions

Cluster Level

VOT for Observers

To avoid a learning curve on the VOT side, the observers performed real or simulated activities for 1 month before the trial.[13]

After being notified of patient recruitment, the observers visited the patients at home on the first day. The observer would instruct the patient to re-demonstrate the learned procedures [12] as a means of verifying their correct understanding of how to record and upload the video. This training and validation process for independent execution typically required approximately 30 min. The observer and patient set a time range for taking the medication, after which, the system would send reminder notifications to both the patient and the observer via LINE. Next, the patient maintained a daily record of the drug-taking session, noted any adverse events, and sent a video to the observer through the TH VOT system. The observer reviewed the video, approved the session, and provided necessary advice through the LINE chat box. The observer followed up with a phone call if the patient failed to send the video within 30 min of the appointment. If the observers detected any mistakes performed by the patients, they would conduct a video call via LINE to correct the process; these video calls would take approximately 15 min.

DOT for Observers

Each patient and observer received a session booklet (more details in the protocol).[20] After being notified by the automatic system, the observer conducted a home-visit DOT as a routine service. To validate the observers' recorded information, the patient and observer were

requested to take a photo of the most recent page of the booklet and send it to the auditor through the official TH VOT LINE system every weekend. The auditor reviewed and recorded the number of daily compliance sessions in the database. Note that the observer was independently responsible for managing appointment times with their patients. There was no system support for scheduling appointments to mimic a conventional DOT.

Individual Level

VOT for Patients

After registration, patients in the VOT group were trained by their observer to record and upload a drug-taking video session according to the standard operating procedure (SOP).[12] Briefly, the patients had to set their video frame so that their face was clearly visible. All tablets and capsules should also be clearly visible. They then had to click the “record video” button to start video recording, noting that there is a warning below the button to complain of any non-serious adverse events that may have occurred during the video recording before taking the medication. Patients had to then pick up the pills and place them on their tongue. Next, they swallowed the pills using clear water from a (clear) glass, raised their tongue to show the sublingual area, and stuck out their tongue to show the palatal area. After the drug-taking process was completed, they had to click the “end recording” button to upload the video. After uploading the video to the TH VOT system, the patients could watch an instructional video to remind themselves of the serious adverse effects, which, should they experience, they must stop the medication and call the observer immediately.

DOT for Patients

For patients in the DOT group, the TB nurse provided a booklet to record their daily drug intake and whether the intake was observed by the assigned observer. The TB nurse requested the patients to return the booklet and all zipped bags on the follow-up day to claim compensation. Each weekend, the auditor notified the patients to capture and send a recent booklet page to the official LINE chat, to which the observers did not have access. All daily reports from patients were recorded without verification, treating them as self-administered treatment.

Procedures for the Auditor to Review Each Video/Picture Session

Sessions in the VOT Group

“Day” was used as the time unit for judging compliance, and local times (Greenwich Mean Time + 7 h) were recorded. The morning began at 12 AM (midnight) and the evening ended at 11:59 PM. However, daily compliance was judged as “achieved within the cut-off time” if the patients took their medication and submitted their videos before 6 AM on the following day. The auditor assessed the daily video sessions for both the patients and the observers based on the protocol.[20]

Sessions in the DOT Group

The auditor scored daily compliance weekly based on booklet photos sent by patients with TB and their observers. The patients were considered to have daily compliance as reported (no audit). The auditor would make a phone call to patients with TB to confirm whether they were observed as reported by their observer and to remind them to safely store the booklet and all zipped bags received from the TB clinic, as per the protocol.[20]

Follow-ups

Each patient was scheduled to return to the TB clinic for follow-up on day 61. One day before the scheduled visit, the TB nurse reminded the patients in the DOT group to return the booklet and zipped bags. A deep cough specimen was collected early in the morning for 3 consecutive days (from days 61 to 63). The sputum specimens were subjected to the AFB test. The patients were requested to notify their doctors about all adverse events that occurred at the start of treatment. Doctors recorded the reported adverse events from history using the electronic health record (EHR) system and suggested appropriate treatment. If a patient missed their follow-up appointment, the responsible TB nurse contacted them and recorded their reasons in the EHR.

Data Collection

Data regarding observational activities were recorded in the database, and data regarding clinical outcomes were documented in the EHR system of the participating hospitals. The records were retrieved for analysis at the end of the follow-up period.

Outcomes

Primary Outcomes

The data recorded by the auditor were compiled to understand patient and observer compliance in each arm. For the compliance of individual patients, the daily compliance scores rated by the auditor were summed. The mean number of compliance days was calculated for all patients.

Similarly, for compliance of individual observers, daily compliance scores rated by the auditor were calculated. A higher number of patient doses observed increased the mean number of compliance days for the entire group of observers (VOT or DOT).

Secondary Outcomes

The clinical outcomes retrieved from the EHR, the conversion of the AFB smear (three negative sputum smears, as mentioned above), the reporting of adverse events, missing follow-up visits, and death during the 60-day follow-up period were compared between the two groups.
The information retrieved from the EHR system was used to compare the reporting of adverse events by observers in the VOT and DOT groups.

Sample Size

Each jurisdictional area comprised 1,000–5,000 individuals. With an approximate annual TB incidence of 130 per 100,000 individuals in the Songkhla province,[30] the sample size estimate was based on the assumption that each cluster could recruit approximately 1–5 (mean=3) patients with TB within 9 months.
The sample size was calculated using the group-randomized control trial calculator.[31] The parameters are shown in the protocol.[20] The required number of clusters for each arm was 19. Thus, the number of patients with TB in each group was 57 (19 × 3). Using a sample size inflation factor of 20% to compensate for the uncertainty of the TB incidence in each jurisdictional area, a sample size of 70 patients with TB was estimated for each arm.

Cluster Randomized Allocation

Observers who consented to participate were randomly allocated to either the VOT or DOT

groups using a file generated using the R software (R Foundation for Statistical Computing, Vienna, Austria). The sequences were stored on a study server. Following the trial protocol, the participating observers registered themselves in the LINE system. After they pressed the "accept" button, the observers were informed about their allocated intervention group through the study LINE system.

Implementation of the Trial and Patient Information

The new patients with pulmonary TB were recruited to the VOT or DOT group by a TB nurse, depending on the jurisdiction of the observer's residence. Relevant information regarding the study was provided to the potential patients before the start of the trial, including highlighting who could observe them taking medication (their observer and auditor) along with possible assigned interventions (VOT or DOT). The observers' intervention group was excluded before they consented to participate. If the patients consented to participate, they were assigned to the same intervention group as the observer in their jurisdiction. The participants were free to refuse the intervention at any point after receiving instructions from the TB nurse. Those who refused to participate or withdrew from the study continued the traditional DOT without data collection compliance. However, clinical data were collected as permitted in accordance with the Thai Personal Data Protection Act, 2019.

Blinding

The observers disclosed their assigned interventions to auditors, TB nurses, and researchers. Next, the researchers trained the VOT observers to familiarize themselves with the TH VOT system[13]; the DOT observers were requested to perform traditional DOT as routine care. Therefore, none of the researchers or staff involved in the study were blinded to the assigned interventions.

Statistical Analysis

Patient and observer background information were summarized using descriptive statistics. An intention-to-treat analysis was conducted according to a randomized allocation. Thus, the participants were classified according to the intervention group to which they were assigned, regardless of whether they changed observation modality. We compared the mean number of compliance days between the two groups 60 days after treatment initiation. For a straightforward discussion, we also calculated the compliance rate (%) of each group using the following formula:

Sum of compliant days for each group × 100/ (Number of patients in each group × 60)

Our study was a cluster RCT; thus, the number of compliance days of patients and observers was nested in clusters. We analyzed the 60-day compliance, considering that the same observer may monitor more than one patient. The intervention effect was based on a linear mixed-effects model.[32] According to our study design, the intervention was a fixed effect, whereas the cluster level was a random effect. The estimated mean numbers of compliance days along with their standard errors for four groups of patients under VOT and those under DOT were derived from the model that accounted for the cluster effect.
The number of compliance days for each individual, adjusted for clustering effects, would be calculated based on the specified model. Subsequently, a quantile-quantile (Q-Q) plot would assess the normality of the estimated numbers for each group. If data points predominantly align with a reference line, suggesting normality, a t-test would be justified for comparing the estimated numbers under VOT versus DOT. Prior to conducting the t-test, the Breusch–Pagan

Test would evaluate homoscedasticity [33]; a p-value < 0.05 indicating heteroscedasticity necessitates the use of the Welch t-test, whereas homoscedastic conditions would permit the application of the Student's t-test. In cases where data markedly deviate from the reference line, indicating non-normality, non-parametric methods would be applied. Data visualization for this study was conducted as outlined in the protocol.[20]

Only descriptive statistical methods were used for the secondary outcomes because we did not have sufficient statistical power to detect small differences. The chi-squared test was employed for comparison; nevertheless, when the expected counts were less than 5, the Fisher's exact test was used.

We also conducted a power analysis using the methodology proposed by Rutterford et al. to assess the robustness of our findings.[34] For this analysis, the mean number of patients per cluster was employed, and an estimated intraclass correlation coefficient of 0.2 was used to calculate the statistical power, expressed as a percentage. Power calculations were not performed for rare outcomes in which no events occurred in either the DOT or VOT groups.

All analyses were performed using the epiDisplay (version 3.5.0.2),[35] tidyverse (version 1.3.1),[36] lmerTest (version 3.1.3),[37] and car (version 3.1-2) [38] packages in R language and environment version 4.1.1 (R Core Team (2021)). Statistical significance was established at a two-sided *p*-value of less than 0.05.

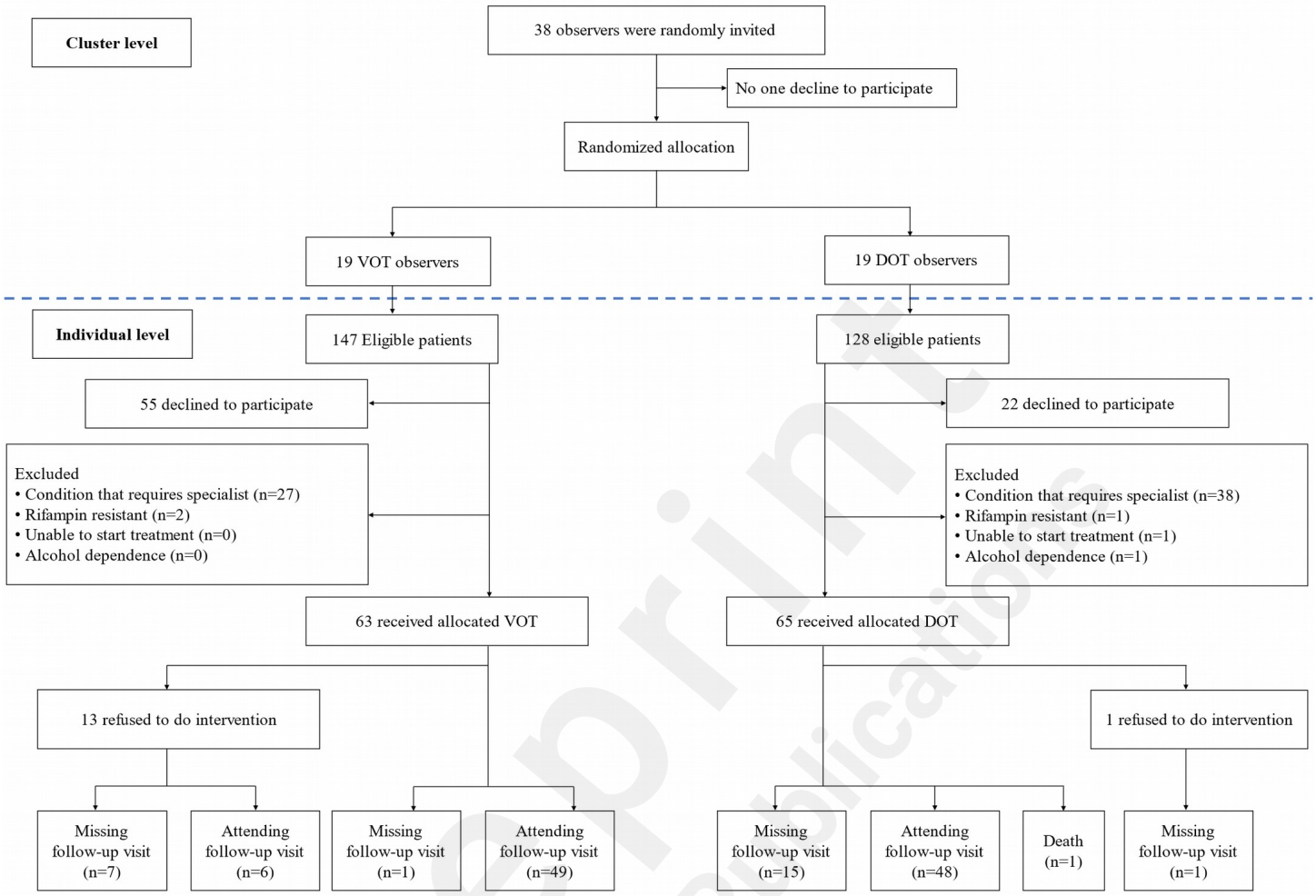
Deviation from the registered protocol

In this study, we added calculations for the compliance rate to provide more detail and readability than did the statistical analysis outlined in the registered protocol.

Ethics Approval

The Human Research Ethics Committee, Faculty of Medicine, Prince of the Songkla University approved the trial on February 19, 2021 (approval number 64-03618-9). All participants consented to participate in the trial and allowed access to their data in the electronic health records for this research, as well as to the reporting of results in a format in which individuals cannot be identified.

Results



Participants

Between January 2022 and May 2023, 38 observers from 38 PCUs participated in cluster randomization, with 19 assigned to the VOT group and 19 to the control group. The trial ended in July 2023 because of a limited budget. A flow diagram of the observers and patients is shown in Figure 1. Eventually, 92 of the 147 eligible patients in the VOT group and 106 of the 128 patients in the DOT group consented. Exclusion of patients who consented occurred mainly because they required hospitalization were transferred to the internal medicine department, which precluded participation in the 60-day intensive phase of VOT or DOT. Of the rest, 63 and 65 patients were recruited, respectively. None of the patients changed modality of observation. However, 13 patients in the VOT group refused to record videos because of miscommunication with the observers and lack of training with respect to video recording. In the DOT group, one patient refused the intervention after receiving a tutorial on the procedure because of personal concerns. One patient died of severe superimposed pneumonia.

Finally, 55 of the 63 individuals in the VOT group returned for a follow-up visit, compared with 48 of the 65 individuals in the DOT group. The number of missing follow-up cases was not significantly different between the two groups.

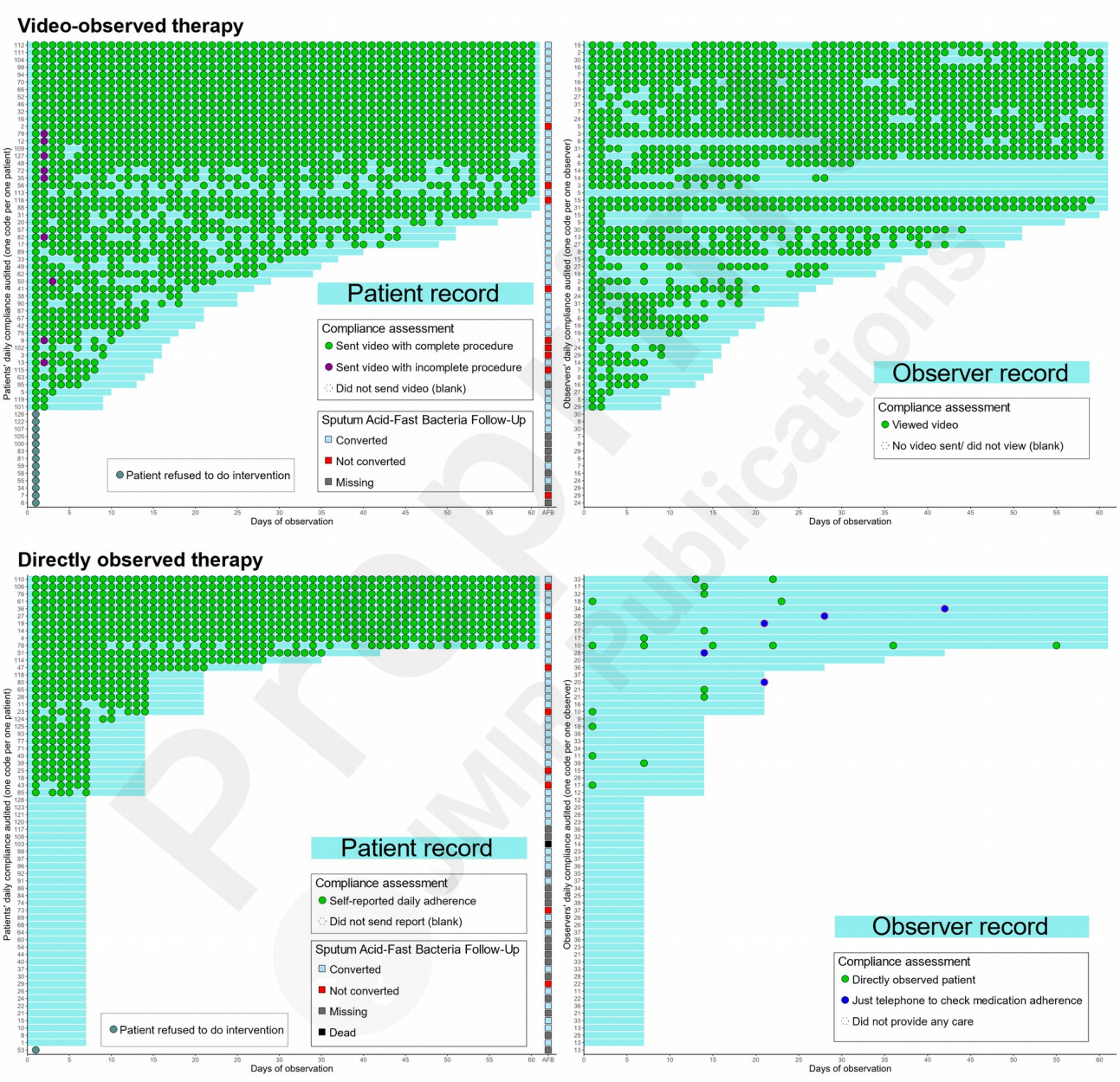
Table 1. Baseline characteristics of the participants

Characteristics	VOT	DOT
Observers		
Total number (N)	19	19
Age, years (mean ± SD)	37.6±4.9	35.6±7.1
Sex, n (%)		
Female	11 (57.9)	13 (68.4)
Male	8 (42.1)	6 (31.6)
Number of patients under supervision, median (IQR)	4 (2, 4)	4 (3, 4)
Patients with pulmonary tuberculosis		
Total number	63	65
Age, years (mean ± SD)	46.3±14.2	51.2±16
Sex, n (%)		
Female	21 (33.3)	17 (26.2)
Male	42 (66.7)	48 (73.8)
Weight, kg	54.3±11.1	52.6±8.5
Height, cm	163.2±10.9	159.9±9.3
Body mass index, kg/m^2	20.4±3.6	20.5±2.6
Pulmonary lesion, n (%)		
Left	35 (55.6)	27 (41.5)
Right	17 (27)	20 (30.8)
Both	11 (17.5)	18 (27.7)
Cavitary lesion, n (%)	26 (41.3)	22 (33.8)
Underlying disease, n (%)		
Diabetes mellitus	11 (17.5)	15 (23.1)
HIV infection	3 (4.8)	4 (6.2)
COPD	2 (3.2)	1 (1.5)
Any cancer	1 (1.6)	1 (1.5)
Number of tablets/capsules prescribed for daily administration, median (IQR)		
Isoniazid	3 (2, 3)	3 (2, 3)
Rifampicin	2 (1, 2)	2 (1, 2)
Pyrazinamide	3 (2, 3)	3 (2, 3)
Ethambutol	2 (2, 3)	2 (2, 2)

COPD, chronic obstructive pulmonary disease; DOT, directly observed therapy; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; VOT, video-observed therapy

All patients assigned to the allocations (63 in the VOT group and 65 in the DOT group) were followed up until the end of the trial. Data from all patients, including those who refused the intervention or died, were analyzed using an intention-to-treat approach.

Table 1 compares the baseline characteristics of the observers and patients in the VOT and DOT groups. The observers in both groups supervised a median of four patients each. None of the characteristics showed significant differences in distribution.



Overall Patient and Observer Compliance

Figure 2 shows the 60-day treatment compliance of the patients (left column) and their observers (right column) in the time series of green dots along the x-axis. The y-axis indicates individual records. On the patient side, the last point of the individual time series represents the follow-up AFB smear. Overall, patient compliance correlated with observer compliance. More than half of the patients were unavailable to answer phone calls twice, at

which point, they and their observers were discontinued from the compliance assessment.

Within the VOT group, no patient deviated from the recording protocol on day 1 of compliance assessment because of the oversight provided by their at-home observer. Subsequently, nine patients failed to comply with the recording protocol but were promptly corrected by their observers. Thereafter, the patients made no further mistakes. Remarkably, without considering the cluster effect, patient compliance rate in the VOT group approached 45.1% (1706/3780) over the 60-day period. In contrast, observer compliance rate was 35.2% (1330/3780).

On the other hand, patient compliance rate in the DOT group was 20.9% (815/3900) over the 60-day period. However, the patients were rarely observed by their observers (not including the blue dots in Figure 2) whose compliance rate was only 0.5% (21/3900). Over half of the patients initially received no attention. Only 14 of the 65 patients were observed. Within 60 days, the number of compliance days for the observers ranged from zero to six. Furthermore, some observers simply made a call to check whether their patients had taken their medication without conducting a home visit, but reported that the observation was complete (blue dots).

Outcomes

Table 2. Primary and secondary outcomes evaluated in this study

Outcomes	VOT	DOT	*P* value	Power (%)
Total (N)	63	65		
Primary outcomes				
Estimated mean compliance days per person, mean ± standard error[a]				
Patients	27.6 ± 4.4	12.4 ± 3.0	0.005	67.5
Observers	21.5 ± 3.5	0.3 ± 1.8	<0.001	90.4
Secondary outcomes				
Status at follow-up, n (%)				
AFB smear converted[b]	46 (73)	40 (61.5)	0.167	21.3
Missed the follow-up visit[b]	8 (12.7)	16 (24.6)	0.084	30.6
Death[c]	0 (0)	1 (1.5)	-	-
Reported adverse events during history taking by a doctor, n (%)				
Nausea[b]	10 (15.9)	6 (9.2)	0.256	16.0
Rash[b]	9 (14.3)	3 (4.6)	0.061	35.2
Pruritus[c]	5 (7.9)	4 (6.2)	0.742	5.0
Fatigue[c]	3 (4.8)	1 (1.5)	0.361	14.5
Blurred vision[c]	1 (1.6)	0 (0)	0.492	-
Numbness	1 (1.6)	0 (0)	0.492	-
Adverse event reported by observers, n (%)				

Outcomes	VOT	DOT	*P* value	Power (%)
Nausea[c]	3 (4.8)	0 (0)	0.116	-
Rash[c]	1 (1.6)	0 (0)	0.492	-
Pruritus	0 (0)	0 (0)	-	-
Fatigue[c]	1 (1.6)	0 (0)	0.492	-
Blurred vision	0 (0)	0 (0)	-	-
Numbness	0 (0)	0 (0)	-	-

[a]The mean ± standard error was calculated using mixed-model linear regression while considering clustering. Welch's t-test was performed.
[b]Chi-squared test was performed.
[c]Fisher's exact test was performed.
AFB, acid-fast bacilli; DOT, directly observed therapy; VOT, video-observed therapy

The cluster-adjusted number of compliance days for each group, as evidenced by Q-Q plots in Figure S1–4, is assumed to follow a normal distribution. For VOT versus DOT group comparison, there was evidence of heteroscedasticity by Breusch–Pagan test as P <0.001 for patient and observer comparisons. Welch t-test was employed for comparison of the primary outcomes. Table 2 presents a comparison of the primary and secondary outcomes of the VOT and DOT groups. When comparing the primary outcomes, the average compliance days adjusted for clustering for patients in the VOT group were significantly higher than for those in the DOT group, with a mean difference of 15.2 (95% confidence interval [CI]: 4.8–25.6). Similarly, VOT observers reported significantly higher average compliance days compared with almost none for DOT observers, with a mean difference of 21.2 (95% CI: 13.5–28.9). With the mean number of patients per cluster equal to 3, our study demonstrated sufficient statistical power (>80%) for detecting differences in compliance among observers.

Assessment of the follow-up secondary outcomes showed that 73% of the patients in the VOT group achieved sputum AFB smear conversion, compared with 61.5% of the patients in the DOT group (Table 2). The percentage of missed follow-up appointments was notably higher in the DOT cohort, at 24.6%, compared with the VOT cohort, at 12.7%. The number of adverse events reported by attending doctors was higher than that reported by observers. Overall, in the VOT group, 5 out of the 29 adverse events recorded by doctors were detected by observers (17.2%). Conversely, all the adverse events in the DOT group were overlooked by the observers. No statistical significance was detected for comparisons of all secondary outcomes.

Discussion

Principal Results

This study assessed medication adherence by evaluating compliance with the experimental intervention in both patients and their observers, using this as a surrogate outcome measure. We assumed that the higher compliance rates among both patients and observers

would indicate greater medication adherence in patients. Overall, patients in the VOT group had a notably higher average number of compliance days than those in the DOT group, consistent with the trend of the observers. However, this study was underpowered to detect improved compliance among the patients. The consent rate in the VOT group (92 out of 147, or 62%) was lower than that in the DOT group (106 out of 128, or 82%). This, combined with the fact that 13 VOT patients refused the intervention after consenting due to a lack of support from their observers, implies a need for increased effort from the TB nurse at the TB clinic and the observers to enhance patient acceptability of the A-VOT system.

The TH VOT system includes an on-screen reminder before the “record video” button is clicked, prompting patients to report any adverse events in the video before taking their medication. This reminder process was absent in the DOT group. As shown in Table 2, none of the reported adverse events were serious; most patients could endure them. However, without active inquiry about these events by their observers, the patients did not report them. The failure of patients to communicate their adverse events to the observers could be an important factor related to low treatment compliance. Without this care from the observers, patients were less likely to engage in observation therapy, as it would not differ from self-administered therapy (SAT). This issue could be partially mitigated by the reminder interface in the TH VOT system, which prompts users to record a daily video. However, the observers were able to detect only 17.2% of the adverse events retrospectively identified by doctors.

In this RCT, the patient characteristics were well-balanced between the VOT and DOT groups. In addition, compliance in both patients and their observers was assessed within clusters, which is more practical than assessing individual effects in a community-based DOT setting.[39] In the VOT group, better compliance was observed and a higher percentage of patients achieved positive AFB smear conversion, compared with the DOT group. However, this difference was not significant, potentially due to the limited sample size. The results also suggest a correlation between the compliance of patients and observers. This may indicate the influence of observers on patients in persuading them to adhere to the observation process. Observers in the VOT group reported approximately one-fifth of the adverse events recorded by doctors. In contrast, all these events were completely ignored by the observers in the DOT group. Therefore, training for both VOT and DOT, as well as quality control of the observers, are of utmost importance.

Previous studies in the UK and United States have shown that over half of the patients received successful observations in the intensive phase at a rate of 80% or higher.[15,18] However, our results are less than half of those reported. The possible reasons for this discrepancy include that in Thailand, compulsory observations are required only for patients with extensively drug-resistant TB.[40] The treatment efficacy of DOT in Thailand has shown no significant difference compared with that of SAT, particularly in non-clinic-based DOT, which often transitions into SAT.[5–7] Given this context, more suitable comparative studies for the findings with the intended-but-not-failed DOT would have been those exploring the differences in treatment outcomes between VOT and SAT. However, our literature search did not yield any published studies presenting this comparison.

Consequently, we referred to data from the United States, indicating that DOT, compared with SAT, resulted in a 40% increase in complete treatment (estimated as odds ratio-1) for individuals with latent tuberculosis infection (LTBI).[41] Assuming that VOT would be as effective as DOT (as VOT in the US has been shown to be equivalent to DOT[18,19]), we anticipated that VOT would similarly result in a 40% improvement in complete treatment over SAT in the US context. For our 2-month follow-up, which evaluated sputum conversion rates as a surrogate outcome for complete treatment, we hypothesized that these outcomes would parallel the complete treatment observed in the United States study. However, the TH VOT system demonstrated only an 18.7% improvement in successful treatment (calculated as (73−61.5)/61.5×100). Compared with those in the United States, this finding underscores the need for more concerted efforts and regulation to enhance treatment success rates in Thailand.

In addition, this study was conducted during the coronavirus disease (COVID-19) pandemic. Observers might have used the pandemic as a pretext for poor compliance on observation.[29] However, the COVID-19 pandemic was not the main cause of poor compliance among observers, as we noted the poor compliance in our pilot study even before the pandemic began.[12] Additionally, there has been evidence of poor compliance with DOT services among observers for more than 20 years.[6,7]

Limitations

The main limitation of this study was that the trial period was restricted to the first 2 months of TB treatment (intensive phase). However, although sputum conversion is an uncertain surrogate for successful treatment, many studies have shown that this rate correlates well with treatment success.[42–46] Moreover, blinding was not possible. Nevertheless, both groups were monitored by the same auditor; consequently, the Hawthorne effect should be balanced.[47] In addition, we could not differentiate between the daily doses that were not observed and those that were not taken. Finally, we inferred that the higher compliance of both patients and observers with the assigned intervention indicated better medication adherence. The difference in sputum conversion rate and reporting of adverse events should be interpreted with caution due to inadequate sample size.

The compliance of patients in the VOT group was directly recorded on video to ensure accuracy. In contrast, compliance in the DOT group was based solely on patient reports, which could not be verified. The statistics based on potential overreporting in the DOT group may have biased our results toward the underestimation of the superiority of the A-VOT system over DOT. This disparity in compliance quality limited the comparison of the two groups. Even so, the reported compliance in the DOT group may have been overestimated; however, it was still lower than that in the VOT group. This might be because the VOT system is more feasible than the traditional DOT and its notification system can enhance observer compliance.[13] Consequently, it may indirectly improve patient compliance through increased encouragement and response from observers.[48]

Staff time and effort to train and supervise drug intake should be considered during the

implementation of the A-VOT system. The A-VOT could reduce the travel time of the observers substantially. On the contrary, effort on training patients to use the A-VOT system, especially patients who are from a low socio-economic background, and session recording supervision by synchronous VOT may be necessary in the first few days, when patients are still unfamiliar with the system.

Conclusions

In Thailand, although A-VOT requires more initial effort and has lower acceptability, it was superior to traditional community-based DOT in ensuring treatment compliance among observers. Nonetheless, the study lacked the statistical power to validate enhanced adherence to treatment among patients with pulmonary TB and to detect differences in sputum conversion rates. In community-based DOT settings with robust internet availability, replacing the DOT program with the A-VOT system may improve medication adherence among patients with TB, although a more accountable system for the observers is needed.

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Contributions

PK defined the conceptual framework of the study, led the development of video-observed therapy, and handled data analysis. The responsibility for obtaining the necessary data permissions fell to both PK and VC, who also played key roles in interpreting the results of the analysis. The process of data specification and curation involved collaboration between PK and TP. The first draft of the manuscript was created by PK, whereas VC played an essential role by contributing to the academic discourse and offering critical evaluations of subsequent drafts. Final approval of the manuscript was obtained from all authors involved.

Conflicts of Interest

The development of the mobile app was supported by the Health Systems Research Institute of Thailand. This study was funded (Award Number D43 TW009522) by the Fogarty International Center and the U.S. National Institute of Allergy and Infectious Diseases, which are part of the U.S. National Institutes of Health. The content of the manuscript is solely the authors' responsibility and does not necessarily reflect the official views of the US National Institutes of Health. All authors declare no financial or non-financial competing interests.

Data Sharing

The data used in this study were de-identified to ensure patient confidentiality, in accordance with the Personal Data Protection Act B.E. 2562 of Thailand. Therefore, the data could not be used to indirectly identify a person, yet were sufficiently detailed to enable analysis and yield results consistent with the original data. The research data have been shared on GitHub.[49]

Abbreviations

AFB: acid-fast bacilli
A-VOT: asynchronous video-observed therapy
DOT: directly observed therapy
EHR: electronic health record
HRZE: isoniazid, rifampicin, pyrazinamide, and ethambutol
ICC: intracluster correlation coefficient
NTIP: National Tuberculosis Information Program
PCU: primary care unit
SOP: standard operating procedure
S-VOT: synchronous video-observed therapy
TB: tuberculosis
TH VOT: Thai video-observed therapy
VOT: video-observed therapy

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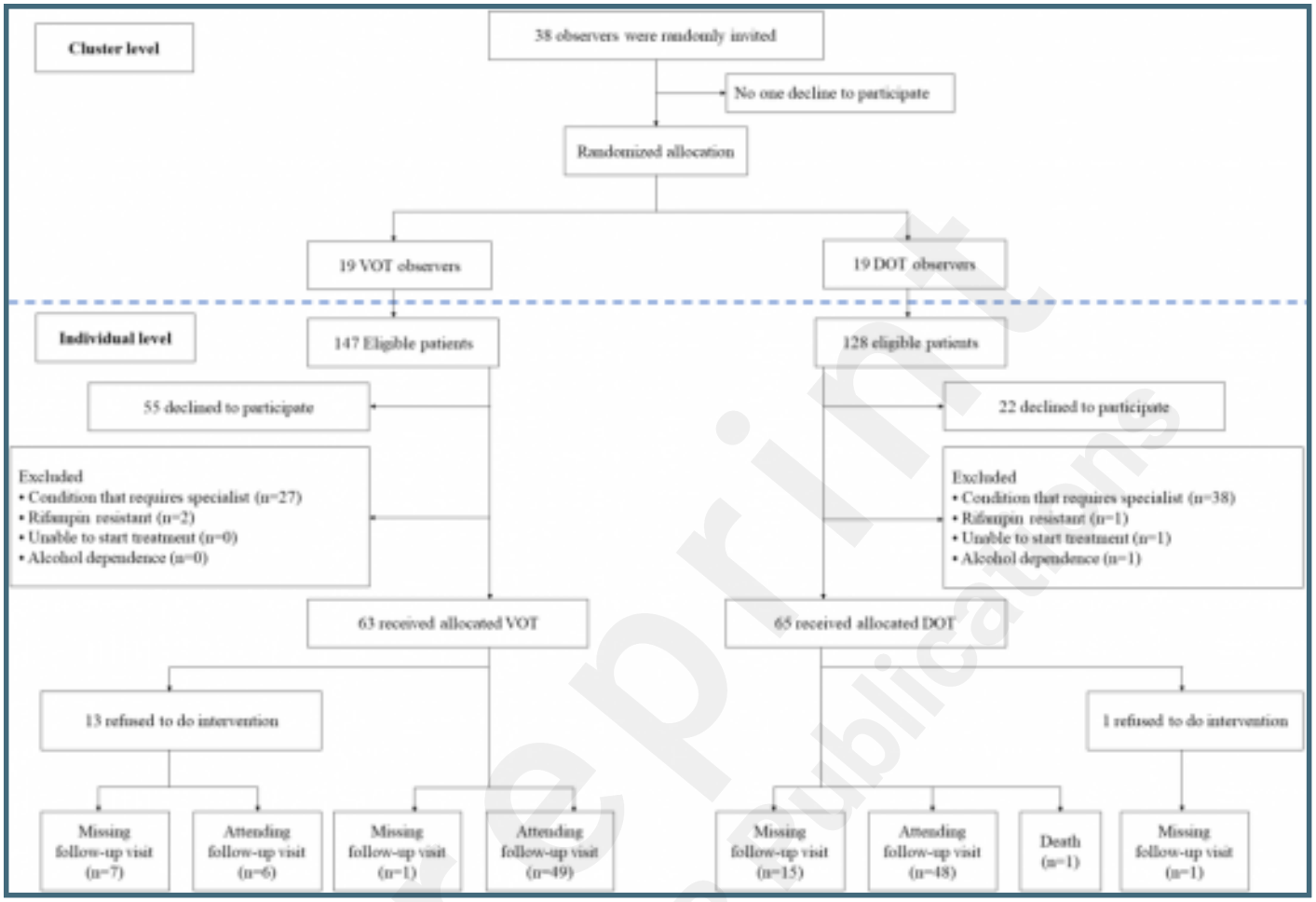
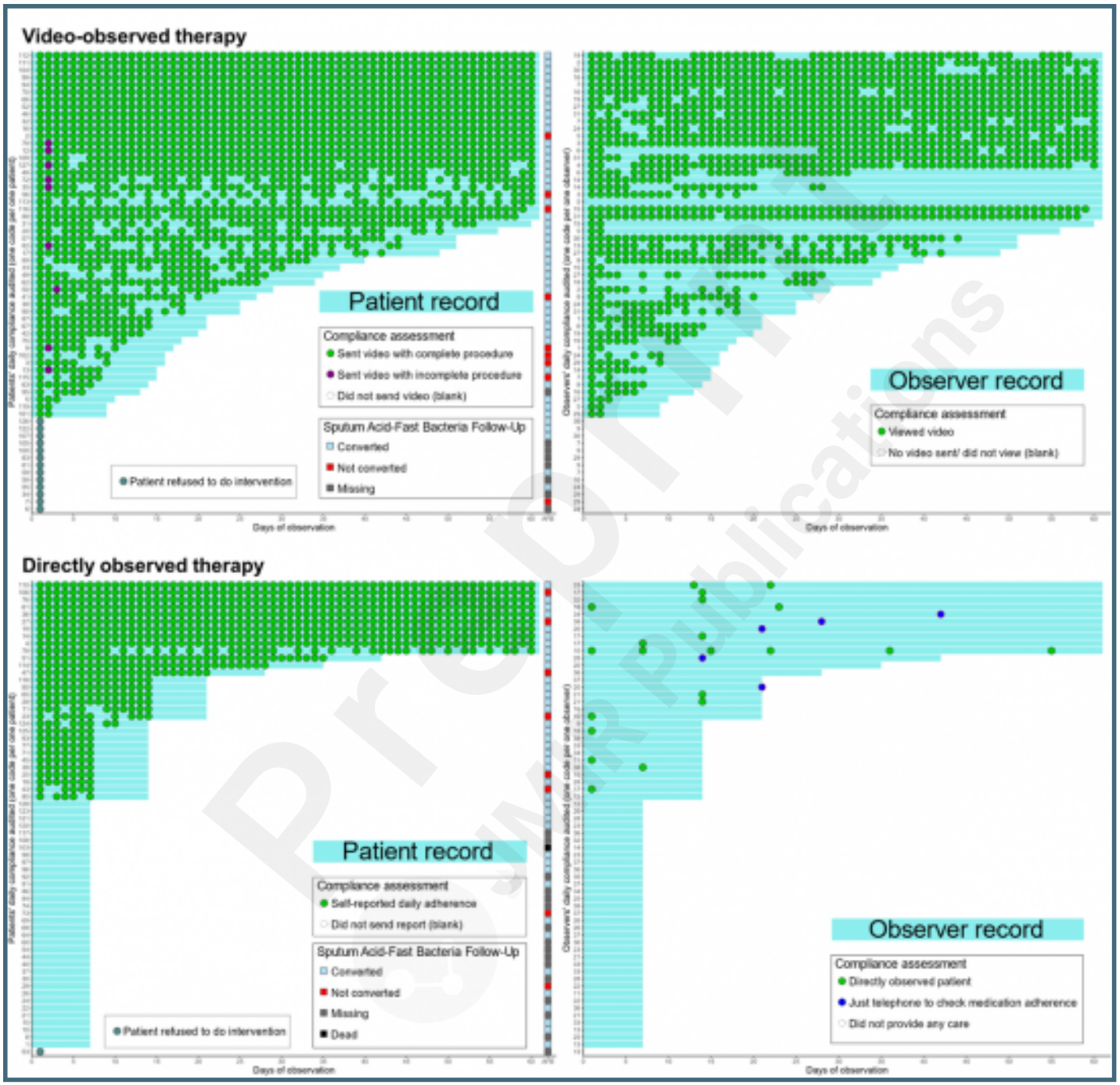
Supplementary Files

Figures

Study flow. DOT, directly observed therapy; VOT, video-observed therapy; Condition that requires specialist: All patients required hospitalization and were transferred to the internal medicine department; Follow-up visit: Sputum collection and clinical evaluation by a doctor.



Schematic depicting the 60-day treatment compliance of the patients and their observers in the video-observed therapy (VOT) and directly observed therapy (DOT) groups as well as the sputum follow-up results. The blue dots (representing only making a call and not conducting a home visit) were not counted as a compliance day.



Multimedia Appendixes

Checklist of the manuscript.
URL: http://asset.jmir.pub/assets/c2ab1a354964207fcddfad8d1cb23dc6.docx

TOC/Feature image for homepages

THVOT apps.