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Effectiveness of digital adherence technologies in improving TB treatment outcomes in four countries: a pragmatic cluster randomized trial protocol

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Abstract

Introduction

Successful treatment of tuberculosis (TB) depends to a large extent on good adherence to treatment regimens which in many countries relies on directly observed treatment (DOT). This in turn requires frequent visits to health facilities. High costs to patients, stigma, and burden to the health system challenged the DOT approach. Digital adherence technologies (DATs) have emerged as possibly more feasible alternatives to DOT but there is conflicting evidence on their effectiveness and feasibility. Our primary objective is to evaluate whether the implementation of DATs with daily monitoring and a differentiated response to patient adherence would reduce poor treatment outcomes compared with the standard of care (SOC). Our secondary objectives include: to evaluate the proportion of patients lost to follow-up; to compare effectiveness by DAT type; to evaluate the feasibility and acceptability of DATs; to describe factors affecting the longitudinal engagement of patients with the intervention; and to use a simple model to estimate the epidemiological impact and cost-effectiveness of the intervention from a health system perspective.

Methods and analysis

This is a pragmatic multi-country two-arm cluster-randomized trial, with health facilities as the unit of randomization. Facilities will first be randomized to either the DAT or SOC arm, and then the DAT arm will be further randomized into medication sleeve/labels or smart pill box in a 1:1:2 ratio for the smart pill box, medication sleeve/label or the SOC respectively. We will use data from the digital adherence platform and a separate research database of data available from routine data collection. In the main analysis, we will employ an intention-to-treat approach to evaluate treatment outcomes.

Ethics and dissemination

The study has been approved by the WHO Ethical Review Committee (0003296), and by country-specific committees. The results will be shared at national and international meetings and will be published in peer-reviewed journals.

Trial registration number: ISRCTN17706019

Strengths and limitations of this study

- This is a multi-country trial using rigorous methods to evaluate the effectiveness of DAT on treatment outcomes, going beyond measuring improvements in adherence to treatment
- The study will provide important evidence on patient and provider acceptability and feasibility necessary to provide country level guidance on decisions to adopt, implement and scale-up DATs across varying contexts
- Changes in the standard of care across countries due to the COVID-19 may have a confounding effect as some of the changes included the use of digital technologies

Introduction

About a quarter of the world population is infected with mycobacterium tuberculosis bacilli, and about 10 million people develop active tuberculosis (TB) each year.Of those with active TB, about a third are not detected by the health system. Furthermore, >10% of those detected are not successfully treated. (1) As a result, the global TB treatment success rate remained below the 20% reduction interim target between 2015 and 2020. (2)

To improve treatment outcomes, directly observed treatment (DOT) has been the standard recommendation since 1995. (3) However, DOT is no longer held as an adequate patient-centered model for TB care. (4) DOT by health care workers present challenges to patients owing to transportation costs, and lost income due to clinic appointments which can contribute to non-adherence. The evidence that DOT substantially improves treatment completion or cure relative to self-administration is mixed. (5, 6)

In recent years, digital adherence technologies (DATs) such as electronic medication monitors and text messaging, have emerged as alternatives to DOT. (7) Electronic medication boxes are medication monitoring devices that store TB medications, give audio-visual reminders to the patient, and record and transmits patients' dosing history. The medication sleeve is a type of electronic medication monitor that consists of medication blisters wrapped in special envelopes with printed codes. Patients use these codes when making a toll-free call/text to let their health care provider know when they have taken their medication. (7) In addition to reminding patients to take their TB medications, DATs provide mechanisms for compiling patient dosing histories that provide their health care providers with the ability to monitor adherence and to provide prioritized follow-up differentiated care. While the use of DATs is recommended, evidence that such technologies improve treatment outcomes is still limited.

Recent randomized studies in countries in Africa and Asia documented mixed results regarding effectiveness of medication monitoring to reduce poor medication adherence. (8-14) For the purposes of informing policy makers with information about if when and where to use DATs, inference from RCTs is difficult due to the fact

that RCTs often do not reflect the real-life circumstances under which such tools would be employed in programmatic settings. Furthermore, the patient and health-care provider acceptability and uptake of these tools have been shown to be variable in different countries and settings. (15-17). Cultural or material circumstances may operate differently on the utility or acceptability of DATs to deliver the targeted treatment support. Data from individual randomized trials often do not provide country programs with the information needed to replicate their success in real-life settings and specific contexts. A pragmatic trial design implemented under real-life situation therefore is useful to provide the necessary evidence that can transform the way treatment support is provided in high TB burden settings.

The Adherence Support Coalition to End TB (ASCENT) study will evaluate effectiveness of medication sleeves/labels and smart pill boxes linked to a web-based adherence platform, to create a differentiated care response to patient adherence in relation to end of treatment outcomes. A related study in Ethiopia will go further to provide effectiveness in relation to disease free outcomes. (18). In addition to effectiveness, ASCENT will collect data on DAT engagement and fidelity to the adherence tools, costs, and projections of epidemiological impact and cost-effectiveness. Taken together, the ASCENT studies will provide valuable evidence of effectiveness as well as patient and provider acceptability and feasibility necessary to provide country level guidance on decisions to adopt, implement and scale-up DATs across varying contexts around the world.

Objectives

The primary objective of this study is to evaluate whether the implementation of DAT with daily monitoring and differentiated response to patient adherence decreases the proportion of patients with poor treatment outcome compared to the standard of care in their respective countries. Poor treatment outcome is a composite of treatment outcomes that include death, treatment failure, or loss to follow-up (LTFU). The secondary objectives include evaluating individual components of the composite outcomes i.e., the proportion of patients LTFU, and time to treatment completion. Additionally, we will evaluate the effect of the individual DAT systems employed, medication labels or smart pill box, in relation to the SOC. Furthermore, we will

describe: the longitudinal engagement of patients with the DAT; the fidelity to the intervention including device and technological failures (e.g., poor cellular service coverage); the wider epidemiological impact of the interventions through mathematical models; the cost-effectiveness of the intervention from a health system perspective; and evaluate the feasibility and acceptability of DATs for patients as well as health care workers.

Methods/ Design

Study design

Figure 1 shows an overview of the study design. These are pragmatic two-arm cluster-randomized trials, with health facilities as the unit of randomization, conducted in four countries. Facilities in each country were randomized (1:1) to either the intervention (DAT) or SOC arm. A second randomization among the intervention arm clusters (1:1) was conducted to determine which of two interventions to employ (medication sleeve/label or smart pill box). In each country facilities from multiple regions/districts were randomized using stratification and restriction. Since labels were not implemented in Ukraine, the randomization was 1:1.

Study setting

The study is operating in four countries that are among the top 30 high-burden TB or MDR-TB countries: Ukraine, Tanzania, South Africa and the Philippines. These countries were selected based on epidemiological, socio- economic, geographic, infrastructural and health system factors. Facilities will include a mix of both large and small, urban and rural facilities. Eligible facilities needed to have previously notified TB patients and expressed willingness and capability to participate in study activities.

Study population

All adult DS-TB patients in the intervention and standard of care facilities contribute to the effectiveness evaluation using their treatment outcomes as reflected in the TB registries, typically after 6 months. Participation in using the DAT intervention is extended to all adult DS-TB patients in the selected intervention facilities upon initiation of their therapy. In Ukraine where patients start treatment as inpatients, participants start the intervention at discharge. Those providing consent will be enrolled onto the ASCENT adherence platform and provided with the DAT.

Interventions

In three countries (South Africa, Tanzania, and Philippines) facilities will be randomized to one of two technologies (smart pill box or medication sleeve/label) to transmit to the ASCENT web-based digital adherence platform for treatment adherence monitoring. This allows the TB care provider to use the ASCENT adherence data platform to evaluate daily dosing and offer differentiated care specific to the country as appropriate. In Ukraine, all Rayons (analogous to facilities) randomized to the DAT intervention will employ the smart-pill box, because fixed dose combinations do not exist for DS TB and would not be suitable for medication sleeves/labels.

The implementation starts with a run-in phase when in-country staff are trained, and the DAT adherence platform is integrated into the patient care pathway, followed by the main enrolment phase. After an introduction to the study and providing written consent, all adults (locally defined) diagnosed with DS-TB are offered the DAT technology and differentiated care intervention. By providing written informed consent, patients agree to use the DAT assigned to the facility during their TB treatment, and for researchers to (a) access their de-identified dosing history data on

the ASCENT adherence platform to support the health facility staff to operationalize the DAT intervention and (b) use this de-identified data as well as accessing data on treatment outcomes to evaluate effectiveness and fidelity of the intervention.

Figure 1- overview of the study design

Intervention arm 1 – smart pill box (all countries)

Upon providing informed consent, participants receive a smart pill box ((also known as the Medication Event Reminder Monitor system or MERM). The TB drugs are placed in the smart pill box that is configured to routinely signal a reminder to the patient by either an audible signal (beep) and/or a blinking light once a day at a time based on the patient's preference. On a daily basis, an electronic device embedded in the box sends a signal through a built-in mobile internet connection with all box openings of the patient to the ASCENT digital adherence platform. If the internet connectivity is unavailable, the opening events are stored on the device to be uploaded upon resumption of connectivity.

Intervention arm 2 – medication sleeves/labels

Upon providing informed consent, participants with secure access to a mobile phone employ one of two analogous methods to send notification of their dosing to the ASCENT platform. Participants who do not have access to a mobile phone are given a smart pill box.

Medication sleeves- participants have their Fixed Dose Combination (FDC) blister pack containing their medication placed in a custom card-stock medication sleeve with a series of unpredictable hidden codes that are revealed only upon removal of the daily pill.

Medication labels - In countries where the FDC packaging was variable and therefore difficult to reliably supply custom cardstock, we employed a modified system. Participants have a label, containing a code, placed on each of their fixed-dosed blister-packaged TB medication.

For both methods, when their daily dose is taken, participants message the code using a toll-free text, which automatically logs their daily dose to the ASCENT web-based application. Box open or short message service (SMS) sent by patient is assumed to be dose taken.

The Standard of Care arm

Patients in health facilities randomized to the control arm receive the current standard of care according to their country guidelines. In the Philippines and Tanzania, a treatment partner (TP) is identified by the patient and Public Health Nurse and patients are either observed by the TP or self-administer "with trust". In South Africa patients employ self-administration, recording their taking medication on a TB card. Non-adherence according to this may prompt DOT (either at home or in the clinic). In Ukraine, outpatient adherence is monitored using either home-based or facility-based DOT.

Differentiated care delivery based on adherence to treatment

Patients utilizing the DAT at facilities randomized to the intervention arm have their adherence data recorded on the ASCENT adherence platform. These data are displayed in real-time in a single view via the mobile Android app to allow health care providers to visualize the data analytics and evaluate their medication taking behavior. Health care providers are then able to identify patients who have not taken their medication according to the patient calendar or by viewing Task Lists that contain patients with 1, 2 or 3 days of non-adherence. They then employ constructive measures to encourage timely medication adherence according to the differentiated response algorithm approved by the National TB Program (NTP). These measures include messaging educational reinforcements, reminders, phone calls and home visits progressively. Each country has a differentiated response algorithm that has been arrived at in consultation with the community advisory board, civil society stake holders, and approved by the country NTP.

Randomization

Randomization of clusters (treatment facilities or Rayons in Ukraine) to intervention or SOC arm were conducted by stratification and restriction in order to ensure balance between the intervention arms and SOC arm. Studies in the Philippines, Ukraine and Tanzania were stratified by poor treatment outcome and South Africa and the Philippines by province. Restriction varied by country based on evaluation of predictors of outcomes utilizing existing notification data. The stratification and restriction variables are shown in Table 1.

Table 1. Stratification and restriction variables per country

Country	Stratification variables	Restriction variables
Philippines	Province; poor treatment outcome*	Poor treatment outcome*; number of DS-TB notifications; facility type
Ukraine	Poor treatment outcome	Treatment failure*; number of DS-TB notifications; Oblast (district)
Tanzania	Poor treatment outcome	treatment failure*; number of DS-TB notifications; urban (vs rural); HIV co-infection rate; facility serving mining communities.
South Africa	Province (2 strata)	Treatment success*; urban/rural, number of DS-TB notifications; facility type

* Using data from a 12–18-month period abstracted from the TB register pre-implementation of the intervention

Trial outcomes

Primary outcome

The primary endpoint is a poor end of treatment outcome, a composite indicator that includes documented treatment failure, lost to follow-up or death.

Secondary outcomes

Secondary outcomes – effectiveness and feasibility

- The proportion of adult DS-TB patients who are lost to follow-up during treatment

- Time to treatment completion, among DS-TB patients
- The proportion of adult DS-TB patients with poor treatment outcomes for standard of care versus (1) medication sleeves/labels and (2) smart pill box
- Intervention arm only:
- Patterns of longitudinal technology engagement in the intensive- and continuation phase
- The proportion of patients who had a differentiated response due to non-adherence, among all patients and among non-adherent patients
- The proportion of patients who received phone calls, home visits, and motivational counselling due to non-adherence

Secondary outcomes - impact modelling

- The change in the incidence of TB arising from the impact that DATs may have on TB transmission compared to current standard of care if the intervention were to be scaled up
- A simplified cost-effectiveness of DAT compared to standard of care relative, considering changes in relevant cost drivers such as number of clinic visits, technology and training costs.

Secondary outcomes – DR-TB patients

- Patterns of longitudinal technology engagement in the intensive- and continuation phase
- The proportion of adult DR-TB patients with poor (interim) treatment outcomes

There are several secondary outcomes which will be assessed in sub studies described further below.

Sample size

For each country, we collected data from the TB registries in health facilities of the selected regions/districts to provide an estimate of the harmonic mean of the number of DS-TB registrations over an 18-month period and the percentage with poor treatment outcome (treatment failure, and death and lost to follow-up during treatment). We assumed a (conservative) coefficient of variation of poor outcome of

0.35 to arrive at the number of facilities in each of arm (DAT or Control) required to detect a reduction in the percentage with poor treatment outcome by 30% with 90% power and a type 1 error of 5%. Notable exceptions were applied to Ukraine, where health facilities are administered within rayons and randomization occurred at this level instead of the health facility level in other countries (Table 2). In Ukraine, due to the high proportion with poor outcomes, the study was powered to detect a reduction of 50%.

Table 2. Estimated cluster size and associated assumptions per country

Country	Harmonic Mean for the number of DS-TB registrations over 18 months	Standard of care: poor treatment outcomes (%)	Intervention: poor treatment outcomes (%)	Clusters (facilities) per arm: 90% power
Philippines	350	9%	6.3%	31
Tanzania	113	12%	8.4%	38
South Africa	253	25%	17.4%	29
Ukraine	176	31%	15.0%	8 (Rayons)

Study procedures

Study procedures in SOC and intervention facilities

The four countries followed the same basic study procedures. In the SOC facilities, the procedures imposed by the study are minimal in order to reflect the standard practices relevant as the counterfactual experience for the intervention facilities. Table 3 summarizes procedures in the SOC and intervention facilities.

Study procedures in the intervention facilities were similarly minimized to include the necessary informed consent. All patients at both intervention and SOC arms received the same anti-TB treatment regimens according to their country NTP guidelines. This included employing fixed-dose combinations in three countries (The Philippines, Tanzania, and South Africa) and loose doses in Ukraine. At treatment initiation,

patients receive the same basic education based on NTP guidelines to ensure the same basic understanding of their tuberculosis and the importance of adherence to their treatment. TB focal persons and other health care staff underwent training for this in order to ensure a comparable baseline against which improvement from the DAT intervention.

Also, in both SOC and DAT facilities, the same information in the form of prominently displayed posters informing TB patients that the facility is participating in research and that information about their final de-identified treatment outcome will be collected. Patients were given the option to opt-out if they do not want that their data to be used for research purposes. Specifically, the poster states: "*If you are diagnosed with TB, information about the results of your treatment will be collected without using your name. If you would like the results of your treatment not to be used for this research, please inform the people giving you your TB care*".

Table 3: Comparison of activities between intervention and standard of care facilities

Activities	Intervention facility	Standard of care facility
Counselling for TB adherence	Initial patient education on adherence counselling will be provided as per standard of care	Initial patient education on adherence counselling will be provided
Registration and informed consent	Adult patients in the intervention arm who agree to use of the DAT provide consent Patient will be registered on ASCENT adherence platform and upon registration receive confirmation verbally and/or by text message	-
Explain DAT	HCW explains how patient can use DAT (standardised script) and pictorial leaflet	-
Treatment provision	Self-administration of TB medication with support of DAT	As per standard of care (DOT at health facility or patient' home or self-administration) dependent on country
Provide TB medication	As per standard of care	As per standard of care
Daily dosing reminder	A reminder message to patient will be sent in case a dose was not recorded on the platform. Depending on patient preference, the smart pill box can also remind patients for medication intake using LED and/or sound	-
Follow-up visits for treatment	Patients will be provided a return date to visit the health facility for refill	As per standard of care
Follow-up visit for treatment reminders	Depending on the DAT-, patient- and health care worker preferences, patients can receive a reminder for follow-up visit via text message or via DAT.	-
Patient adherence data	Information on adherence will be collected via DAT and real-time available via ASCENT adherence platform for health staff	As per standard of care (pill counts, patient treatment cards etc). Only available when patient visits health facility
Follow up visit(s) during treatment	Health care workers have access to the ASCENT adherence platform and will use the patient' adherence calendar for counselling	Health care workers will review the patient's verbal report on adherence and counsel patients accordingly
Education and motivational messages	Patients can receive periodic educational and motivational messages	-
Patient access to adherence information	Patients can have access to their own adherence data	-

Study procedures in intervention facilities only

All TB patients at the participating facilities are screened by the TB care provider (TB focal person) for eligibility. All adults (as defined by national law, male and female) with DS-TB who are initiated on TB treatment at the health facility are eligible for inclusion in the study. We have made the inclusion criteria as inclusive as possible in order to reflect the real-world impact of the digital adherence technology. There are no specific exclusion criteria. Eligible patients are offered enrollment in the study followed by the process to obtain written informed consent. Consented participants are then registered onto the ASCENT adherence platform.

In facilities that are randomized to the smart pill box; consented participants are given their TB medication and instructional booklet inside the box. Upon each opening, the box sends a signal to the ASCENT platform that is recorded in a digital log for the patient. Participants are asked to bring the box with them at each visit for medication refill and to return the box at completion of therapy.

In facilities randomized to the medication sleeve/label, participants are provided their medication with packaging (either sleeve or label) that provides instructions, phone numbers and codes along with instructional booklet. Instructions direct participants upon taking their medication every day to send the code to the number using text messaging that records the dose on the ASCENT platform. Those patients who do not own a phone or who are uncomfortable using a shared phone are allowed to use a smart pill box. Patients in the intervention arm – either smart pill box or medication sleeve/label – can also receive reminder messages via SMS.

Adverse consequences of the trial include inadvertent disclosure of TB status due to the association of the DAT with TB treatment and/or receiving SMSs related to TB treatment. These events are collected by the health care workers in a "social harms register" at facility and monitored by study personnel either during phone calls or periodic visits to facilities.

Patients enrolled in the DAT employ self-administration of TB medication using the DAT and support according to the differentiated response according to the data logged to the ASCENT platform. Participants at SOC facilities and those at DAT

facilities who do not consent to use the DAT take their medication according to standard of care for the facility and under the NTP guidelines (See supplemental information). Adherence data and treatment follow-up is also according to the country specific NTP guidelines.

Data Management

Data from the DATs will be collected from the ASCENT adherence platform (patients on the intervention only) using the Everwell Hub, a cloud-based or in-country (Tanzania) hosted infrastructure according to country regulations. Patient data are collected on the ASCENT adherence platform, with permission from the participant provided in the informed consent. The ASCENT platform allows the TB health care providers to review patient medication adherence logged from the DAT and track SMS communications with patients. Data privacy is protected with access to the platform being password protected with defined data access that allows health care providers, but not researchers, to view personal identifying data.

Treatment outcome data are from the routine reporting to the NTP and are electronic in the Philippines and Ukraine and abstracted from paper TB registers in Tanzania and South Africa. These data are collected for all patients (excluding those who opt-out) and are imported/entered into the ASCENT research database hosted in-country using REDcap, a secure web database application. (19)

The routine data in the ASCENT research database are linked to deidentified individual patient data from the ASCENT platform using a corresponding electronic or paper record that has the TB registration number and ASCENT platform ID.

Trial Governance

A Technical Advisory Group (TAG) has been set up to provide oversight, monitor and oversee progress for this four-country study and its companion study in Ethiopia. The TAG meets every 6 months and is composed of representatives from the five countries and chaired by a senior researcher in Uganda.

Diverse in-country stakeholders provide input to the study through a Community Advisory Board (CAB) and/or other Civil Society Organizations (Tanzania). Consultation was sought in order to involve former TB patients and their care providers and various other stakeholders. The CABs were engaged beginning in the preparatory phase to provide input and advice into the facility selection and randomization procedures. They were further consulted after the preparatory phase in order to arrive at the specific country differentiated response algorithm.

Statistical Analysis Plan

Statistical analyses will employ appropriate methods for the cluster randomized trial design. We will conduct an intention-to-treat approach to evaluate treatment outcomes in the DAT arm relative to the SOC. Additionally, two separate analyses will be performed to evaluate the individual DAT - smart pill box or medication label/sleeve – in relation to the SOC. For South Africa, Tanzania and the Philippines we will employ a logistic regression model with random effects (to account for clustering at the facility-level) to estimate the respective intervention effect as an odds ratio and associated 95% confidence interval adjusted for variables employed in randomization strata. Adjustment for other patient level covariates will be employed where imbalance exists between the study arms. Sub-group analyses will be examined to examine heterogeneity of effect among patient characteristics including, urban/rural, gender and country specific health care delivery circumstances, and type of TB (pulmonary or extra-pulmonary). (20) A detailed statistical analysis plan will be finalized before the end of follow-up and data are unblinded.

Sub-studies

As part of the process evaluation of DAT interventions in each of the four countries, a series of sub-studies are administered by ASCENT research personnel to a sub-set of patients, health care workers and key stakeholders in a selection of facilities employed in the effectiveness evaluation. In sub-study 1, acceptability and feasibility data will be collected from TB patients. In sub-study 2, qualitative methods will explore the TB patient experience using the DAT and explore differences in the experience by gender. In sub-study 3, qualitative methods will explore the acceptability and

feasibility of implementing DAT and differentiated response among the health care workers providing TB care and relevant stakeholders.

Economic Evaluation and Impact Modelling

The decision to scale-up DATs in countries will need to consider the benefit to both the health system as well as to the individual. As TB is known to disproportionately affect the poor, the use of DATs may decrease the economic burden placed on TB patients and address the END TB Strategy milestone of eliminating families facing catastrophic health costs due to TB. We will use effectiveness data as well as estimates of costs incurred by patients (collected in sub-study 1) and the service level costs to estimate the cost-effectiveness of utilizing DATs relative to the standard of care.

To the extent that DATs may impact treatment outcomes, it will be useful to understand the result on TB epidemiology in the country. The change in the treatment outcome from DAT relative to the SOC will inform a simple cohort model, in order to project the epidemiological impact, in terms of cases, incidence and prevalence, of scaling up of DAT in the respective countries.

Ethical considerations and dissemination

The study has been approved by the WHO Ethical Review Committee (0003296) and London School of Hygiene & Tropical Medicine Ethics Committee, United Kingdom (19135) following external peer review. Individual protocols have been reviewed and approved by relevant country specific committees: Single Joint Research Ethics Board (Philippines SJREB 2019-57); Wits Human Research Ethics Committee (South Africa AUR2-1-268); Tanzania Medical Research Coordinating Committee (MRCC) at National Institute for Medical Research, Dar es Salaam (Tanzania NIMR/HQ/R.8a/Vol.IX/3431); and Ukraine Ethics Committee of Public Health Center of the MOH of Ukraine (Ukraine IRB 2019-33).

Written informed consents of TB patients for the main effectiveness study are collected from TB patients by the TB care providers at the intervention facilities. In

addition, a waiver of consent was obtained to access TB register data. Patients agree to use the DAT and consent to have researchers use anonymized data collected to the ASCENT Adherence platform. Informed consents for the sub-studies are collected by research associates prior to the interviews. The individual-level data sets visible to research staff to monitor the study and conduct analysis are de-identified. All databases are maintained in password-protected systems. Where paper records exist, they are stored in the participating facilities in locked cabinets with access permitted to only relevant facility health care providers and research team members.

The research findings will be presented first to national stakeholders, and disseminated to the Community Advisory Board, stakeholders and participants in each country at local meetings, and presented at national and international conferences. The primary results of the study will be written as country-specific articles for submission to suitable scientific journals along with deidentified research datasets for the sake of reproducibility. Exclusive use of the data for further publications will be given to the ASCENT consortium as well as the country's local research community. Major changes to the study are communicated to the CAB and TAG, updated to the protocol and trial registration, and reported to the ethics committee for approval.

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Contributorship statement

DJ contributed to designing the study, supervised implementation, wrote the first and subsequent drafts and approved the final version. JL led the designing of the study, coordinated ethical review processes, contributed to acquisition of resources, initiated the write up of the first draft of the manuscript, and approved the final version. KvK led acquisition of resources, contributed to study design, oversaw project implementation, reviewed the first and subsequent drafts, and approved the final draft. JvR contributed to resource acquisition and supervision of implementation and reviewed the draft manuscript. CFM and MQ designed the transmission modelling, contributed to supervising implementation, reviewed the draft manuscript, and approved the final version. SC and NM contributed to study design, supervised

implementation in South Africa, and reviewed and approved the manuscript. KG, YT and AB supervised study implementation in Ukraine, and reviewed and approved the manuscript. AMCG and LM supervised study implementation in the Philippines and Tanzania respectively and reviewed and approved the manuscript. KF contributed to designing the study, developed statistical analysis plans, supervised implementation, and reviewed and approved the manuscript. The contents of the article are the responsibility of the authors alone and do not necessarily reflect the views of donors or employers of the authors.

Competing interests

We declare we have no competing interest.

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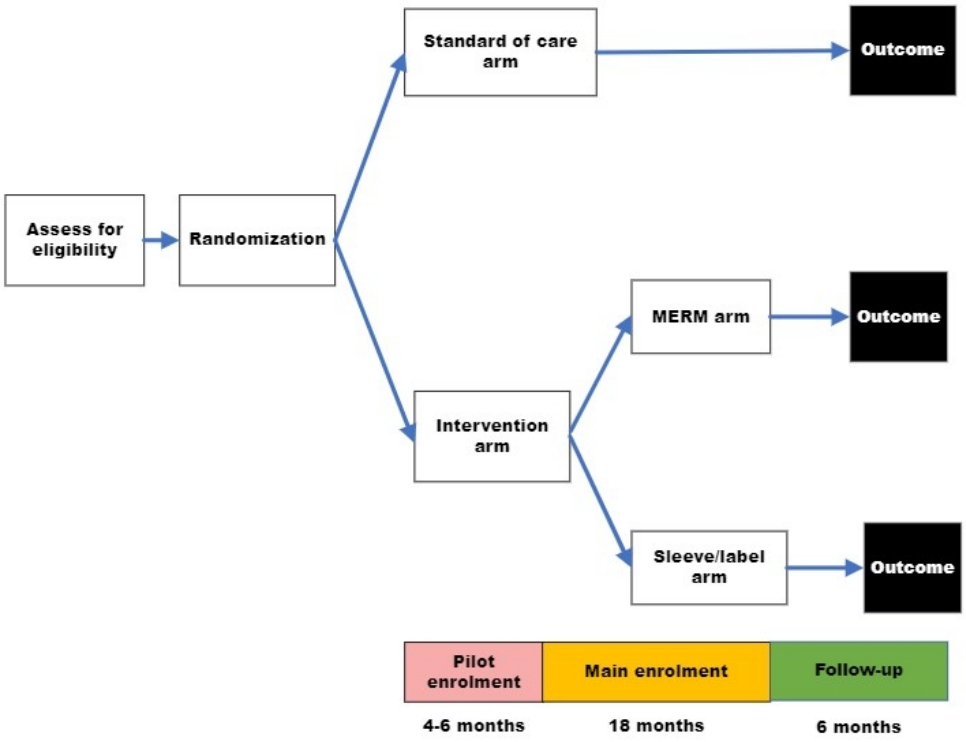

Overview of study design

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Effectiveness of digital adherence technologies in improving tuberculosis treatment outcomes in four countries: a pragmatic cluster randomized trial protocol

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Effectiveness of digital adherence technologies in improving tuberculosis treatment outcomes in four countries: a pragmatic cluster randomized trial protocol

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Abstract

Introduction

Successful treatment of tuberculosis (TB) depends to a large extent on good adherence to treatment regimens which relies on directly observed treatment (DOT). This in turn requires frequent visits to health facilities. High costs to patients, stigma, and burden to the health system challenged the DOT approach. Digital adherence technologies (DATs) have emerged as possibly more feasible alternatives to DOT but there is conflicting evidence on their effectiveness and feasibility. Our primary objective is to evaluate whether the implementation of DATs with daily monitoring and a differentiated response to patient adherence would reduce poor treatment outcomes compared with the standard of care (SOC). Our secondary objectives include: to evaluate the proportion of patients lost to follow-up; to compare effectiveness by DAT type; to evaluate the feasibility and acceptability of DATs; to describe factors affecting the longitudinal engagement of patients with the intervention; and to use a simple model to estimate the epidemiological impact and cost-effectiveness of the intervention from a health system perspective.

Methods and analysis

This is a pragmatic two-arm cluster-randomized trial in Philippines, South Africa, Tanzania and Ukraine, with health facilities as the unit of randomization. Facilities will first be randomized to either the DAT or SOC arm, and then the DAT arm will be further randomized into medication sleeve/labels or smart pill box in a 1:1:2 ratio for the smart pill box, medication sleeve/label or the SOC respectively. We will use data from the digital adherence platform and routine health facility records for analysis. In the main analysis, we will employ an intention-to-treat approach to evaluate treatment outcomes.

Ethics and dissemination

The study has been approved by the WHO Research Ethics Review Committee (0003296), and by country-specific committees. The results will be shared at national and international meetings and will be published in peer-reviewed journals.

Trial registration number: ISRCTN17706019

Strengths and limitations of this study

- This is a multi-country trial using rigorous methods to evaluate the effectiveness of DAT on treatment outcomes, going beyond measuring improvements in adherence to treatment
- The study will provide important evidence on patient and provider acceptability and feasibility necessary to provide country level guidance on decisions to adopt, implement and scale-up DATs across varying contexts
- Changes in the standard of care across countries due to the COVID-19 may have a confounding effect as some of the changes included the use of digital technologies

Introduction

About a quarter of the world population is infected with mycobacterium tuberculosis bacilli, and about 10 million people develop active tuberculosis (TB) each year.Of those with active TB, about a third are not detected by the health system. Furthermore, >10% of those detected are not successfully treated. (1) As a result, the global TB treatment success rate remained below the 20% reduction interim target between 2015 and 2020. (2)

To improve treatment outcomes, directly observed treatment (DOT) has been the standard recommendation since 1995. (3) However, DOT is no longer held as an adequate patient-centered model for TB care. (4) DOT by health care workers present challenges to patients owing to transportation costs, and lost income due to clinic appointments which can contribute to non-adherence. The evidence that DOT substantially improves treatment completion or cure relative to self-administration is mixed. (5, 6)

In recent years, digital adherence technologies (DATs) such as electronic medication monitors and text messaging, have emerged as alternatives to DOT. (7) Electronic medication boxes are medication monitoring devices that store TB medications, give audio-visual reminders to the patient, and record and transmits patients' dosing history. The medication sleeve is a type of electronic medication monitor that consists of medication blisters wrapped in special envelopes with printed codes. Patients use these codes when making a toll-free call/text to let their health care provider know when they have taken their medication. (7) In addition to reminding patients to take their TB medications, DATs provide mechanisms for compiling patient dosing histories that provide their health care providers with the ability to monitor adherence and to provide prioritized follow-up differentiated care. While the use of DATs is recommended, evidence that such technologies improve treatment outcomes is still limited.

Recent randomized studies in countries in Africa and Asia documented mixed results regarding effectiveness of medication monitoring to reduce poor medication adherence. (8-14) For the purposes of informing policy makers with information about when and where to use DATs, inference from Randomized Controlled Trials

(RCTs) is difficult because RCTs often do not reflect the real-life circumstances under which such tools would be employed in programmatic settings. Furthermore, the patient and health-care provider acceptability and uptake of these tools have been shown to be variable in different countries and settings. (15-17).

A more recent systematic review identified 16 RCTs that evaluated the effect of various digital health technology (DHT) interventions on TB treatment adherence and clinical outcomes. The DHT interventions evaluated included video directly observed therapy (VDOT), video-observed therapy (VOT), medication monitor boxes, short message text reminders, and ingestible sensors. (18). The interventions demonstrated variable effects in terms of both direction and extent, and those with personalized feedback component had a consistent and beneficial effect. Moreover, cultural or material circumstances may operate differently on the utility or acceptability of DATs to deliver the targeted treatment support. Data from individual randomized trials often do not provide country programs with the information needed to replicate their success in real-life settings and specific contexts. A pragmatic trial design implemented under real-life situation therefore is useful to provide the necessary evidence that can transform the way treatment support is provided in high TB burden settings.

The Adherence Support Coalition to End TB (ASCENT) study will evaluate effectiveness of medication sleeves/labels and smart pill boxes linked to a web-based adherence platform, to create a differentiated care response to patient adherence in relation to end of treatment outcomes. These DATs were selected based on several criteria including access to smartphones and broadband internet, type of ant-TB medication regimens in use, and stakeholder feedback as recommended in the WHO guidelines (7). Further, country-specific choice of DATs was decided based on experiences from the run-in phase of the study as described in the Methods section. A related study in Ethiopia will go further to provide effectiveness in relation to TB-free status within 6 months of end of treatment among patients with bacteriologically confirmed TB at baseline. (19). In addition to effectiveness, ASCENT will collect data on DAT engagement and fidelity to the adherence tools, costs, and projections of epidemiological impact and cost-effectiveness. Taken together, the ASCENT studies will provide valuable evidence of effectiveness as well as patient and provider

acceptability and feasibility necessary to provide country level guidance on decisions to adopt, implement and scale-up DATs across varying contexts around the world.

Objectives

Primary objective

The primary objective of this study is to evaluate whether the implementation of DAT with daily monitoring and differentiated response to patient adherence decreases the proportion of patients with poor treatment outcome compared to the standard of care in their respective countries. Poor treatment outcome is a composite of treatment outcomes that include death, treatment failure, or loss to follow-up (LTFU).

Secondary objectives

(i) To evaluate whether implementation of DAT with daily monitoring and a differentiated response to patient adherence decreases the proportion of adult drug-sensitive (DS-TB) patients lost to follow-up compared with the standard of care.

(ii) To explore the specific effect of standard of care versus (1) medication sleeve/label and (2) smart pill box with daily monitoring and a differentiated response to patient adherence on treatment outcomes among adult DS-TB patients

(iii) To describe longitudinal technology engagement of DS-TB and drug resistant TB (DR-TB) patients in the intervention arm

(iv) To describe the fidelity and characteristics associated with successful use of the intervention among DS-TB patients, including web-based platform usage statistics, technology failures or inability to engage with the DAT and mobile phone access

(v) To describe the longitudinal technology engagement of the smart pill box and video supported treatment and the (interim) treatment outcomes of patients

(vi) To project the epidemiological impact of scale-up of DAT with daily monitoring and a differentiated response to patient adherence compared with the standard of care as measured by the change in treatment outcome in the intervention relative to the standard of care among adult DS-TB patients

(vii) To explore the institutional feasibility and acceptability of implementing a DAT intervention and differentiated response to patient adherence in adult DS-TB and DR-TB patients.

Methods/ Design

Study design

Figure 1 shows an overview of the study design. These are pragmatic two-arm cluster-randomized trials, with health facilities as the unit of randomization, conducted in four countries. Facilities in each country were randomized (1:1) to either the intervention (DAT) or SOC arm. A second randomization among the intervention arm clusters (1:1) was conducted to determine which of two interventions to employ (medication sleeve/label or smart pill box). In each country facilities from multiple regions/districts were randomized using stratification and restriction. Since labels were not implemented in Ukraine, the randomization was 1:1. In Ukraine, all Rayons (analogous to facilities) randomized to the DAT intervention will employ the smart-pill box, because fixed dose combinations do not exist for DS TB and would not be suitable for medication sleeves/labels.

Study setting

The study is operating in four countries that are among the top 30 high-burden TB or MDR-TB countries: Ukraine, Tanzania, South Africa and the Philippines. See supplementary table for country TB profiles. These countries were selected based on epidemiological, socio- economic, geographic, infrastructural and health system factors. Facilities will include a mix of both large and small, urban and rural facilities. Eligible facilities needed to have previously notified TB patients and expressed willingness and capability to participate in study activities.

Study population

All adult DS-TB patients in the intervention and standard of care facilities contribute to the effectiveness evaluation using their treatment outcomes as reflected in the TB registries, typically after 6 months. Participation in using the DAT intervention is

extended to all adult DS-TB patients in the selected intervention facilities upon initiation of their therapy. In Ukraine where patients start treatment as inpatients, participants start the intervention at discharge. Those providing consent will be enrolled onto the ASCENT adherence platform and provided with the DAT.

Interventions

In three countries (South Africa, Tanzania, and Philippines) facilities will be randomized to one of two technologies (smart pill box or medication sleeve/label) to transmit to the ASCENT web-based digital adherence platform for treatment adherence monitoring. This allows the TB care provider to use the ASCENT adherence data platform to evaluate daily dosing and offer differentiated care specific to the country as appropriate.

The implementation starts with a run-in phase when in-country staff are trained, and the DAT adherence platform is integrated into the patient care pathway, followed by the main enrolment phase. After an introduction to the study and providing written consent, all adults (locally defined) diagnosed with DS-TB are offered the DAT technology and differentiated care intervention. By providing written informed consent, patients agree to use the DAT assigned to the facility during their TB treatment, and for researchers to (a) access their de-identified dosing history data on the ASCENT adherence platform to support the health facility staff to operationalize the DAT intervention and (b) use this de-identified data as well as accessing data on treatment outcomes to evaluate effectiveness and fidelity of the intervention.

Figure 1- overview of the study design

Intervention arm 1 – smart pill box (all countries)

Upon providing informed consent, participants receive a smart pill box ((also known as the Medication Event Reminder Monitor system or MERM). **We used evriMED1000C- (Wisepill Technologies https://www.wisepill.com/evrimed) in this study.** The TB drugs are placed in the smart pill box that is configured to routinely signal a reminder to the patient by either an audible signal (beep) and/or a blinking light once a day at a time based on the patient's preference. On a daily basis,

an electronic device embedded in the box sends a signal through a built-in mobile internet connection with all box openings of the patient to the Everwell Hub application platform. The Everwell Hub is an integrated platform for adherence and patient management where health care staff can log into a unified portal to register and follow up with patients, whose adherence reports from 99DOTS or evriMED devices. (20). If the internet connectivity is unavailable, the opening events are stored on the device to be uploaded upon resumption of connectivity.

Intervention arm 2 – medication sleeves/labels

Upon providing informed consent, participants with secure access to a mobile phone employ one of two analogous methods to send notification of their dosing to the ASCENT platform. These were based on 99DOTS medication sleeves (99DOTS A low-cost digital adherence engagement tool https://www.everwell.org/99dots**)**. Participants who do not have access to a mobile phone are given a smart pill box.

Participants have their Fixed Dose Combination (FDC) blister pack containing their medication placed in a custom card-stock medication sleeve with a series of unpredictable hidden codes that are revealed only upon removal of the daily pill. In countries where the FDC packaging was variable and therefore difficult to reliably supply custom cardstock, we employed a modified system called medication labels. Participants have a label, containing a code, placed on each of their fixed-dosed blister-packaged TB medication.

For both methods, when their daily dose is taken, participants message the code using a toll-free text, which automatically logs their daily dose to the Everwell Hub application. Box opened or short message service (SMS) sent by patient is assumed to be dose taken.

The Standard of Care arm

Patients in health facilities randomized to the control arm receive the current standard of care according to their country guidelines. In the Philippines and Tanzania, a treatment partner (TP) is identified by the patient and Public Health Nurse and

patients are either observed by the TP or self-administer "with trust". In South Africa patients employ self-administration, recording their taking medication on a TB card. Non-adherence according to this may prompt DOT (either at home or in the clinic). In Ukraine, outpatient adherence is monitored using either home-based or facility-based DOT.

Differentiated care delivery based on adherence to treatment

Patients utilizing the DAT at facilities randomized to the intervention arm have their adherence data recorded on the ASCENT adherence platform. These data are displayed in real-time in a single view via the mobile Android app to allow health care providers to visualize the data analytics and evaluate their medication taking behavior. Health care providers are then able to identify patients who have not taken their medication according to the patient calendar or by viewing Task Lists that contain patients with 1, 2 or 3 days of non-adherence. They then employ constructive measures to encourage timely medication adherence according to the differentiated response algorithm approved by the National TB Program (NTP). These measures include messaging educational reinforcements, reminders, phone calls and home visits progressively. Each country has a differentiated response algorithm that has been arrived at in consultation with the community advisory board, civil society stake holders, and approved by the country NTP.

Randomization

Randomization of clusters (treatment facilities or Rayons in Ukraine) to intervention or SOC arm were conducted by stratification and restriction in order to ensure balance between the intervention arms and SOC arm. Studies in the Philippines, Ukraine and Tanzania were stratified by poor treatment outcome and South Africa and the Philippines by province. Restriction varied by country based on evaluation of predictors of outcomes utilizing existing notification data. The stratification and restriction variables are shown in Table 1.

Table 1. Stratification and restriction variables per country

Country	Stratification variables	Restriction variables
Philippines	Province; poor treatment outcome*	Poor treatment outcome*; number of DS-TB notifications; facility type

Ukraine	Poor treatment outcome	Treatment failure*; number of DS-TB notifications; Oblast (district)
Tanzania	Poor treatment outcome	treatment failure*; number of DS-TB notifications; urban (vs rural); HIV co-infection rate; facility serving mining communities.
South Africa	Province (2 strata)	Treatment success*; urban/rural, number of DS-TB notifications; facility type

* Using data from a 12–18-month period abstracted from the TB register pre-implementation of the intervention

Trial outcomes

Primary outcome

The primary endpoint is a poor end of treatment outcome, a composite indicator that includes documented treatment failure, lost to follow-up or death.

Secondary outcomes

Secondary outcomes – effectiveness and feasibility

- The proportion of adult DS-TB patients who are lost to follow-up during treatment
- Time to treatment completion, among DS-TB patients
- The proportion of adult DS-TB patients with poor treatment outcomes for standard of care versus (1) medication sleeves/labels and (2) smart pill box
- Intervention arm only:
- Patterns of longitudinal technology engagement in the intensive- and continuation phase
- The proportion of patients who had a differentiated response due to non-adherence, among all patients and among non-adherent patients
- The proportion of patients who received phone calls, home visits, and motivational counselling due to non-adherence

Secondary outcomes - impact modelling

- The change in the incidence of TB arising from the impact that DATs may have on TB transmission compared to current standard of care if the intervention were to be scaled up
- A simplified cost-effectiveness of DAT compared to standard of care relative, considering changes in relevant cost drivers such as number of clinic visits, technology and training costs.

Secondary outcomes – DR-TB patients

- Patterns of longitudinal technology engagement in the intensive- and continuation phase
- The proportion of adult DR-TB patients with poor (interim) treatment outcomes

There are several secondary outcomes which will be assessed in sub studies described further below.

Sample size

For each country, we collected data from the TB registries in health facilities of the selected regions/districts to provide an estimate of the harmonic mean of the number of DS-TB registrations over an 18-month period and the percentage with poor treatment outcome (treatment failure, and death and lost to follow-up during treatment). We assumed a (conservative) coefficient of variation of poor outcome of 0.35 to arrive at the number of facilities in each of arm (DAT or Control) required to detect a reduction in the percentage with poor treatment outcome by 30% with 90% power and a type 1 error of 5%. Notable exceptions were applied to Ukraine, where health facilities are administered within rayons and randomization occurred at this level instead of the health facility level in other countries (Table 2). In Ukraine, due to the high proportion with poor outcomes, the study was powered to detect a reduction of 50%.

Table 2. Estimated cluster size and associated assumptions per country

Country	Harmonic Mean for the number of	Standard of care: poor treatment	Intervention: poor treatment	Clusters (facilities) per arm:

	DS-TB registrations over 18 months	outcomes (%)	outcomes (%)	90% power
Philippines	350	9%	6.3%	31
Tanzania	113	12%	8.4%	38
South Africa	253	25%	17.4%	29
Ukraine	176	31%	15.0%	8 (Rayons)

Study procedures

Study procedures in SOC and intervention facilities

The four countries followed the same basic study procedures. In the SOC facilities, the procedures imposed by the study are minimal in order to reflect the standard practices relevant as the counterfactual experience for the intervention facilities. Table 3 summarizes procedures in the SOC and intervention facilities.

Study procedures in the intervention facilities were similarly minimized to include the necessary informed consent. All patients at both intervention and SOC arms received the same anti-TB treatment regimens according to their country NTP guidelines. This included employing fixed-dose combinations in three countries (The Philippines, Tanzania, and South Africa) and loose doses in Ukraine. At treatment initiation, patients receive the same basic education based on NTP guidelines to ensure the same basic understanding of their tuberculosis and the importance of adherence to their treatment. TB focal persons and other health care staff underwent training for this in order to ensure a comparable baseline against which improvement from the DAT intervention.

Also, in both SOC and DAT facilities, the same information in the form of prominently displayed posters informing TB patients that the facility is participating in research and that information about their final de-identified treatment outcome will be collected. Patients were given the option to opt-out if they do not want that their data to be used for research purposes. Specifically, the poster states: "*If you are diagnosed with TB, information about the results of your treatment will be collected*

without using your name. If you would like the results of your treatment not to be used for this research, please inform the people giving you your TB care".

Table 3: Comparison of activities between intervention and standard of care facilities

Activities	Intervention facility	Standard of care facility
Counselling for TB adherence	Initial patient education on adherence counselling will be provided as per standard of care	Initial patient education on adherence counselling will be provided
Registration and informed consent	Adult patients in the intervention arm who agree to use of the DAT provide consent Patient will be registered on ASCENT adherence platform and upon registration receive confirmation verbally and/or by text message	-
Explain DAT	HCW explains how patient can use DAT (standardised script) and pictorial leaflet	-
Treatment provision	Self-administration of TB medication with support of DAT	As per standard of care (DOT at health facility or patient' home or self-administration) dependent on country
Provide TB medication	As per standard of care	As per standard of care
Daily dosing reminder	A reminder message to patient will be sent in case a dose was not recorded on the platform. Depending on patient preference, the smart pill box can also remind patients for medication intake using LED and/or sound	-
Follow-up visits for treatment	Patients will be provided a return date to visit the health facility for refill	As per standard of care
Follow-up visit for treatment reminders	Depending on the DAT-, patient- and health care worker preferences, patients can receive a reminder for follow-up visit via text message or via DAT.	-
Patient adherence data	Information on adherence will be collected via DAT and real-time available via ASCENT adherence platform for health staff	As per standard of care (pill counts, patient treatment cards etc). Only available when patient visits health facility
Follow up visit(s) during treatment	Health care workers have access to the ASCENT adherence platform and will use the patient' adherence calendar for counselling	Health care workers will review the patient's verbal report on adherence and counsel patients accordingly
Education and motivational messages	Patients can receive periodic educational and motivational messages	-
Patient access to adherence information	Patients can have access to their own adherence data	-

Study procedures in intervention facilities only

All TB patients at the participating facilities are screened by the TB care provider (TB focal person) for eligibility. All adults (as defined by national law, male and female) with DS-TB who are initiated on TB treatment at the health facility are eligible for inclusion in the study. We have made the inclusion criteria as inclusive as possible in order to reflect the real-world impact of the digital adherence technology. There are no specific exclusion criteria. Eligible patients are offered enrollment in the study followed by the process to obtain written informed consent. Consented participants are then registered onto the ASCENT adherence platform.

In facilities that are randomized to the smart pill box; consented participants are given their TB medication and instructional booklet inside the box. Upon each opening, the box sends a signal to the ASCENT platform that is recorded in a digital log for the patient. Participants are asked to bring the box with them at each visit for medication refill and to return the box at completion of therapy.

In facilities randomized to the medication sleeve/label, participants are provided their medication with packaging (either sleeve or label) that provides instructions, phone numbers and codes along with instructional booklet. Instructions direct participants upon taking their medication every day to send the code to the number using text messaging that records the dose on the ASCENT platform. Those patients who do not own a phone or who are uncomfortable using a shared phone are allowed to use a smart pill box. Patients in the intervention arm – either smart pill box or medication sleeve/label – can also receive reminder messages via SMS.

Adverse consequences of the trial include inadvertent disclosure of TB status due to the association of the DAT with TB treatment and/or receiving SMSs related to TB treatment. These events are collected by the health care workers in a "social harms register" at facility and monitored by study personnel either during phone calls or periodic visits to facilities.

Patients enrolled in the DAT employ self-administration of TB medication using the DAT and support according to the differentiated response according to the data logged to the ASCENT platform. Participants at SOC facilities and those at DAT

facilities who do not consent to use the DAT take their medication according to standard of care for the facility and under the NTP guidelines (See supplemental information). Adherence data and treatment follow-up is also according to the country specific NTP guidelines.

Data Management

Data from the DATs will be collected from the ASCENT adherence platform (patients on the intervention only) using the Everwell Hub, a cloud-based or in-country (Tanzania) hosted infrastructure according to country regulations. Patient data are collected on the ASCENT adherence platform, with permission from the participant provided in the informed consent. The ASCENT platform allows the TB health care providers to review patient medication adherence logged from the DAT and track SMS communications with patients. Data privacy is protected with access to the platform being password protected with defined data access that allows health care providers, but not researchers, to view personal identifying data.

Treatment outcome data are from the routine reporting to the NTP and are electronic in the Philippines and Ukraine and abstracted from paper TB registers in Tanzania and South Africa. These data are collected for all patients (excluding those who opt-out) and are imported/entered into the ASCENT research database hosted in-country using REDcap, a secure web database application. (21)

The routine data in the ASCENT research database are linked to deidentified individual patient data from the ASCENT platform using a corresponding electronic or paper record that has the TB registration number and ASCENT platform ID.

Trial Governance

A Technical Advisory Group (TAG) has been set up to provide oversight, monitor and oversee progress for this four-country study and its companion study in Ethiopia. The TAG meets every 6 months and is composed of representatives from the five countries and chaired by a senior researcher in Uganda.

Diverse in-country stakeholders provide input to the study through a Community Advisory Board (CAB) and/or other Civil Society Organizations (Tanzania). Consultation was sought in order to involve former TB patients and their care providers and various other stakeholders. The CABs were engaged beginning in the preparatory phase to provide input and advice into the facility selection and randomization procedures. They were further consulted after the preparatory phase in order to arrive at the specific country differentiated response algorithm.

Statistical Analysis Plan

Statistical analyses will employ appropriate methods for the cluster randomized trial design. We will conduct an intention-to-treat approach to evaluate treatment outcomes in the DAT arm relative to the SOC. Additionally, two separate analyses will be performed to evaluate the individual DAT - smart pill box or medication label/sleeve – in relation to the SOC. For South Africa, Tanzania and the Philippines we will employ a logistic regression model with random effects (to account for clustering at the facility-level) to estimate the respective intervention effect as an odds ratio and associated 95% confidence interval adjusted for variables employed in randomization strata. Adjustment for other patient level covariates will be employed where imbalance exists between the study arms. Sub-group analyses will be examined to examine heterogeneity of effect among patient characteristics including, urban/rural, gender and country specific health care delivery circumstances, and type of TB (pulmonary or extra-pulmonary). (22) A detailed statistical analysis plan will be finalized before the end of follow-up and data are unblinded.

Sub-studies

As part of the process evaluation of DAT interventions in each of the four countries, a series of sub-studies are administered by ASCENT research personnel to a sub-set of patients, health care workers and key stakeholders in a selection of facilities employed in the effectiveness evaluation. In sub-study 1, acceptability and feasibility data will be collected from TB patients. In sub-study 2, qualitative methods will explore the TB patient experience using the DAT and explore differences in the experience by gender. In sub-study 3, qualitative methods will explore the acceptability and

feasibility of implementing DAT and differentiated response among the health care workers providing TB care and relevant stakeholders.

Economic Evaluation and Impact Modelling

The decision to scale-up DATs in countries will need to consider the benefit to both the health system as well as to the individual. As TB is known to disproportionately affect the poor, the use of DATs may decrease the economic burden placed on TB patients and address the END TB Strategy milestone of eliminating families facing catastrophic health costs due to TB. We will use effectiveness data as well as estimates of costs incurred by patients (collected in sub-study 1) and the service level costs to estimate the cost-effectiveness of utilizing DATs relative to the standard of care.

To the extent that DATs may impact treatment outcomes, it will be useful to understand the result on TB epidemiology in the country. The change in the treatment outcome from DAT relative to the SOC will inform a simple cohort model, in order to project the epidemiological impact, in terms of cases, incidence and prevalence, of scaling up of DAT in the respective countries.

Ethical considerations and dissemination

The study has been approved by the WHO Ethical Review Committee (0003296) and London School of Hygiene & Tropical Medicine Ethics Committee, United Kingdom (19135) following external peer review. Individual protocols have been reviewed and approved by relevant country specific committees: Single Joint Research Ethics Board (Philippines SJREB 2019-57); Wits Human Research Ethics Committee (South Africa AUR2-1-268); Tanzania Medical Research Coordinating Committee (MRCC) at National Institute for Medical Research, Dar es Salaam (Tanzania NIMR/HQ/R.8a/Vol.IX/3431); and Ukraine Ethics Committee of Public Health Center of the MOH of Ukraine (Ukraine IRB 2019-33).

Written informed consents of TB patients for the main effectiveness study are collected from TB patients by the TB care providers at the intervention facilities. In

addition, a waiver of consent was obtained to access TB register data. Patients agree to use the DAT and consent to have researchers use anonymized data collected to the ASCENT Adherence platform. Informed consents for the sub-studies are collected by research associates prior to the interviews. The individual-level data sets visible to research staff to monitor the study and conduct analysis are de-identified. All databases are maintained in password-protected systems. Where paper records exist, they are stored in the participating facilities in locked cabinets with access permitted to only relevant facility health care providers and research team members.

The research findings will be presented first to national stakeholders, and disseminated to the Community Advisory Board, stakeholders and participants in each country at local meetings, and presented at national and international conferences. The primary results of the study will be written as country-specific articles for submission to suitable scientific journals along with deidentified research datasets for the sake of reproducibility. Exclusive use of the data for further publications will be given to the ASCENT consortium as well as the country's local research community. Major changes to the study are communicated to the CAB and TAG, updated to the protocol and trial registration, and reported to the ethics committee for approval.

Trial status

This is protocol version 2.1.1 dated 31 March 2021. Enrolled for the main trial has ended in August 2022 and follow up will continue through end of March 2023.

Funding

The study is funded by Unitaid (Grant Agreement Number: 2019-33-ASCENT).

Patient and public involvement

Patients and other members of the public were represented in the community advisory boards of the study, but they were not directly involved in the design and conception of the study. We will share key findings of the study with the study community through local TB program coordinators.

Contributorship statement

DJ contributed to designing the study, supervised implementation, wrote the first and subsequent drafts and approved the final version. JL led the designing of the study, coordinated ethical review processes, contributed to acquisition of resources, initiated the write up of the first draft of the manuscript, and approved the final version. KvK led acquisition of resources, contributed to study design, oversaw project implementation, reviewed the first and subsequent drafts, and approved the final draft. JvR contributed to resource acquisition and supervision of implementation and reviewed the draft manuscript. CFM and MQ designed the transmission modelling, contributed to supervising implementation, reviewed the draft manuscript, and approved the final version. SC and NM contributed to study design, supervised implementation in South Africa, and reviewed and approved the manuscript. KG, YT and AB supervised study implementation in Ukraine, and reviewed and approved the manuscript. AMCG and LM supervised study implementation in the Philippines and Tanzania respectively and reviewed and approved the manuscript. KF contributed to designing the study, developed statistical analysis plans, supervised implementation, and reviewed and approved the manuscript. The contents of the article are the responsibility of the authors alone and do not necessarily reflect the views of donors or employers of the authors.

Competing interests

We declare we have no competing interest.

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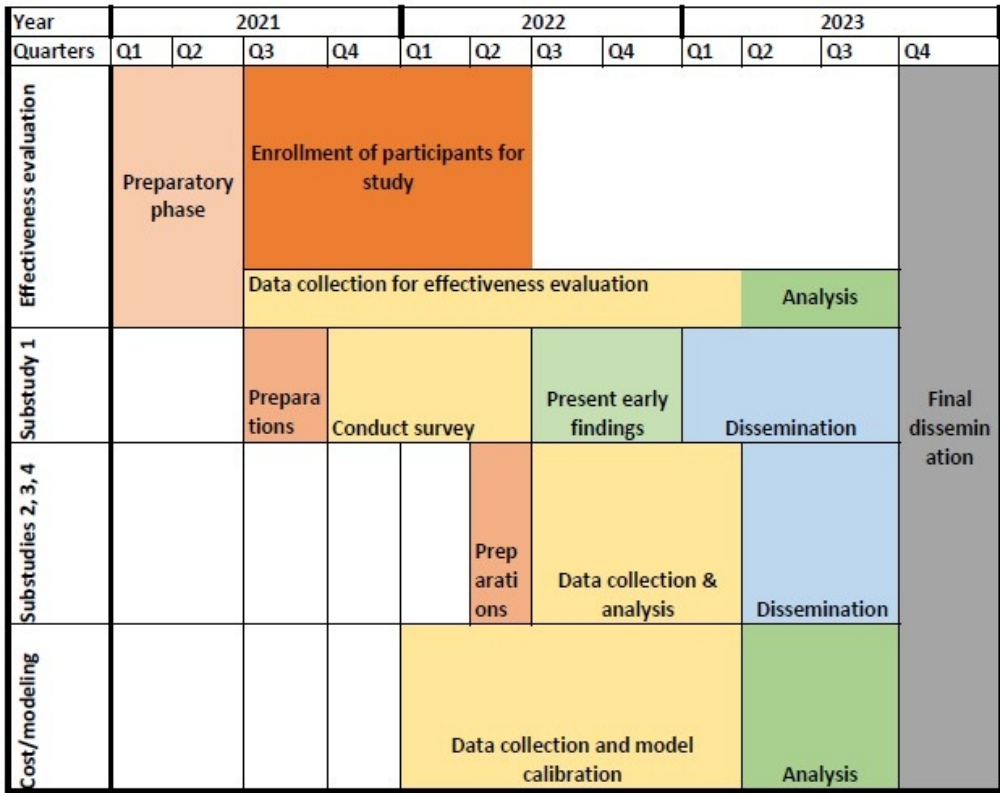

SPIRIT Figure showing study overview

130x103mm (120 x 120 DPI)

ASCENT study country TB profiles

Selected TB indicators (2021)	Philippines	South Africa	Tanzania	Ukraine
Total TB incidence, per 100,000	650	513	208	71
HIV-positive TB incidence, per 100,000	13	274	37	14
Total new and relapse cases notified	321 564	172 194	86,701	18,307
Estimated proportion of new TB cases with MDR/RR TB	1.5%	4.1%	1.3%	31%
TB treatment success rate, new and relapse 2020 cohort	76%	78%	96%	77%

ASCENT DATA USE AND SHARING

For the sake of transparency and reproducibility, all deidentified research datasets may be shared with the study sponsor overseeing research with permissions from countries

Data will be de-identified before release for sharing. Where there are indirect identifiers that could lead to deductive disclosure (e.g. name or location of health facility), these will be modified or removed from the dataset.

The ASCENT project is committed to protect the professional interests of the local co-investigators and to build scientific capacity among early career consortium investigators in participating countries. The project will therefore ensure that there will be a period of exclusive access to the data for researchers from the ASCENT consortium and local research community in each participating country.

Period of exclusive use

Researchers from the ASCENT consortium (referred to as *study team*) who collected data have a legitimate interest in benefiting from their investment of time and effort. The ASCENT consortium also has a commitment to supporting capacity building for early career consortium researchers and local research communities in participating countries. Therefore, in each participating country, the study team and the local research community will have a period of exclusive access to the data for a defined period.

1. Exclusive use will be for a fixed period of 2 (two) years after the data lock, during which time the primary results will be published.
2. De-identified analysis datasets for the primary publications will be released as required by the journal, for replication purposes ("minimal data set"). Analysis datasets supporting other manuscripts will be posted as required by journals at the time of publication.
3. This period of exclusive access will maximise publications from the ASCENT early career consortium researchers and will also be opened to the local research community in each participating country to exploit the data before the full dataset is released on open-access.

During the period of exclusive use, the ASCENT study team and local research community with approved publication concepts are provided access to ASCENT de-identified data by submission of a signed Data Access Agreement. Researchers agree that they will only use the data for the analyses in the approved publication concept.

During this period of exclusive use, requests made by the ASCENT study team will be reviewed by the ASCENT Trial Management Group. Requests made by the local research community, external to the ASCENT study team, are overseen by the ASCENT Technical Advisory Group (TAG). Access to and use of data will be restricted to projects approved by an ethics committee.

Local researchers, external to the ASCENT study team, who are granted access to the data are encouraged to engage with the ASCENT study team to ensure they have sufficient understanding of the study and the data elements.

After the period of exclusive use

After the period of exclusive use, de-identified data will be made available to users outside of the ASCENT team and the local research community via a publicly available data repository. Data access is restricted to non-commercial use only (creative commons non-commercial licensing) and for projects approved by an ethics committee.

Any publications arising from the shared data must acknowledge the investigators who collected the data, the institutions involved, and the funding sources. A standard acknowledgement statement will be provided.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	21
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21-22
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6

	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17-18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17-18
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20-21

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20-21
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	In the annex
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	Standard guidelines apply
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	In the annex
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	In the annex
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.