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

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ABSTRACT

Introduction Successful treatment of tuberculosis 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-randomised trial in the Philippines, South Africa, Tanzania and Ukraine, with health facilities as the unit of randomisation. Facilities will first be randomised to either the DAT or SOC arm, and then the DAT arm will be further randomised 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 pragmatic, multicountry trial using rigorous methods to evaluate the effectiveness of digital adherence technology (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* (TB) bacilli, and about 10 million people develop active TB each year.Of those with active TB, about one-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-centred model for TB care.[4] DOT by healthcare workers presents 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 healthcare 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 healthcare providers with the ability to monitor adherence and to provide prioritised follow-up differentiated care. While the use of DATs is recommended, evidence that such technologies improve treatment outcomes is still limited.

Recent randomised 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 randomised 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 healthcare 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, video-observed therapy, 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 personalised 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 randomised trials often do not provide country programmes 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 anti-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 with the standard of care (SOC) in their respective countries. Poor treatment outcome is a composite of treatment outcomes that include death, treatment failure or lost to follow-up.

Secondary objectives

1. To evaluate whether implementation of DAT with daily monitoring and a differentiated response to patient adherence decreases the proportion of adult drug-sensitive TB (DS-TB) patients lost to follow-up compared with the SOC.
2. To explore the specific effect of SOC 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.
3. To describe longitudinal technology engagement of DS-TB and drug resistant TB (DR-TB) patients in the intervention arm.
4. 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.
5. To describe the longitudinal technology engagement of the smart pill box and video supported treatment and the (interim) treatment outcomes of patients.
6. To project the epidemiological impact of scale-up of DAT with daily monitoring and a differentiated response to patient adherence compared with the SOC as measured by the change in treatment outcome in the intervention relative to the SOC among adult DS-TB patients.

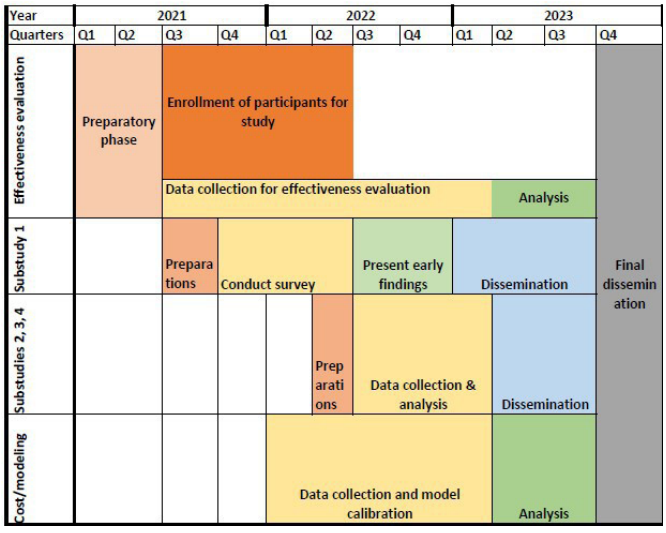

Figure 1 Overview of the study design.

7. 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-randomised trials, with health facilities as the unit of randomisation, conducted in four countries. Facilities in each country were randomised (1:1) to either the intervention (DAT) or SOC arm. A second randomisation 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 randomised using stratification and restriction. Since labels were not implemented in Ukraine, the randomisation was 1:1. In Ukraine, all Rayons (analogous to facilities) randomised to the DAT intervention will employ the smart-pill box, because fixed dose combinations (FDC) 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 online supplemental table for country TB profiles. These countries were selected based on epidemiological, socioeconomic, geographical, 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 SOC 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 on 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 randomised 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 deidentified dosing history data on the ASCENT adherence platform to support the health facility staff to operationalise the DAT intervention and (B) use this deidentified data as well as accessing data on treatment outcomes to evaluate effectiveness and fidelity of the intervention.

Intervention arm 1: smart pill box (all countries)

On 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 healthcare 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 on resumption of connectivity.

Intervention arm 2: medication sleeves/labels

On 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 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 on 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 SOC arm

Patients in health facilities randomised to the control arm receive the current SOC 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 using the DAT at facilities randomised 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 healthcare providers to visualise the data analytics and evaluate their medication taking behaviour. Healthcare 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 Programme (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 (CAB), civil society stake holders and approved by the country NTP.

Randomisation

Randomisation 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 using existing notification data. The stratification and restriction variables are shown in table 1.

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 SOC 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.

Table 1 Stratification and restriction variables per country

Country	Stratification variables	Restriction variables
Philippines	Province; poor treatment outcome*	Poor treatment outcome*; no of DS-TB notifications; facility type
Ukraine	Poor treatment outcome	Treatment failure*; no of DS-TB notifications; Oblast (district)
Tanzania	Poor treatment outcome	Treatment failure*; no of DS-TB notifications; urban (vs rural); HIV coinfection rate; facility serving mining communities
South Africa	Province (two strata)	Treatment success*; urban/rural, no of DS-TB notifications; facility type

*Using data from a period of 12–18 months abstracted from the TB register preimplementation of the intervention.
DS-TB, drug-sensitive tuberculosis.

- 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 with current SOC if the intervention were to be scaled up.
- A simplified cost-effectiveness of DAT compared with SOC 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 randomisation 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%.

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 summarises procedures in the SOC and intervention facilities.

Study procedures in the intervention facilities were similarly minimised 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 FDC 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 TB and the importance of adherence to their treatment. TB focal persons and other healthcare 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 deidentified 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*'.

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 DAT. There are no specific exclusion criteria. Eligible patients are offered enrolment 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 randomised to the smart pill box; consented participants are given their TB medication and

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)

DS-TB, drug-sensitive tuberculosis.

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 on 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 Light-Emitting Diode (LED) light 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 HCW 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	HCWs have access to the ASCENT adherence platform and will use the patient' adherence calendar for counselling	HCWs 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	–

ASCENT, Adherence Support Coalition to End TB; DAT, digital adherence technology; DOT, directly observed treatment; HCW, healthcare worker; TB, tuberculosis.

instructional booklet inside the box. On 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 randomised 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 on 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 healthcare 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 SOC for the facility and under the NTP guidelines (see online supplemental file 2). Adherence data and treatment follow-up are 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 healthcare 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 healthcare 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 CAB and/or other Civil Society Organisations (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 randomisation 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 randomised 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 OR and associated 95% CI adjusted for variables employed in randomisation strata. Adjustment for other patient level covariates will be employed where imbalance exists between the study arms. Subgroup analyses will be examined to examine heterogeneity of effect among patient characteristics including, urban/rural, gender and country-specific healthcare delivery circumstances, and type of TB (pulmonary or extra-pulmonary).[22] A detailed statistical analysis plan will be finalised before the end of follow-up and data are unblinded.

Substudies

As part of the process evaluation of DAT interventions in each of the four countries, a series of substudies are administered by ASCENT research personnel to a subset of patients, healthcare workers and key stakeholders in a selection of facilities employed in the effectiveness evaluation. In substudy 1, acceptability and feasibility data will be collected from TB patients. In substudy 2, qualitative methods will explore the TB patient experience using the DAT and explore differences in the experience by gender. In substudy 3, qualitative methods will explore the acceptability and feasibility of implementing DAT and differentiated response among the healthcare 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 and 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 substudy 1) and the service level costs to estimate the cost-effectiveness of using DATs relative to the SOC.

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, UK (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 anonymised data collected to the ASCENT Adherence platform. Informed consents for the substudies 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 deidentified. 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 healthcare providers and research team members.

The research findings will be presented first to national stakeholders, and disseminated to the CAB, 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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Contributors 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.

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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.