BMJ Open

Study protocol and implementation details for a pragmatic, stepped-wedge cluster randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039895
Article Type:	Protocol
Date Submitted by the Author:	29-Apr-2020

Complete List of Authors:	Crowder, Rebecca; University of California San Francisco, Curry International Tuberculosis Center and Division of Pulmonary and Critical Care Medicine, Zuckerberg San Francisco General Hospital Kityamuwesi, Alex; Uganda Tuberculosis Implementation Research Consortium, Kiwanuka, Noah; Makerere University College of Health Sciences, School of Public Heatlh Lamunu, Maureen; Uganda Tuberculosis Implementation Research Consortium, Namale, Catherine; Uganda Tuberculosis Implementation Research Consortium, Tinka, Lynn; Uganda Tuberculosis Implementation Research Consortium, Nakate, Agnes; Uganda Tuberculosis Implementation Research Consortium, Ggita, Joseph; Uganda Tuberculosis Implementation Research Consortium, Turimumahoro, Patricia; Uganda Tuberculosis Implementation Research Consortium, Babirye, Diana; Uganda Tuberculosis Implementation Research Consortium, Oyuku, Denis; Uganda Tuberculosis Implementation Research Consortium, Berger, Christopher; University of California San Francisco, Curry International Tuberculosis Center and Division of Pulmonary and Critical Care Medicine, Zuckerberg San Francisco General Hospital Tucker, Austin; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology Patel, Devika; University of California San Francisco, The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital Sammann, Amanda; University of California San Francisco, The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital Dowdy, DW; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology Stavia, Turyahabwe; Republic of Uganda Ministry of Health, National Tuberculosis and Leprosy Program Cattamanchi, A Katamba, Achilles; Makerere University College of Health Sciences,

	Clinical Epidemiology and Biostatistics Unit; Uganda Tuberculosis Implementation Research Consortium, Medicine
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Study protocol and implementation details for a pragmatic, stepped-wedge cluster randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion

Authors: Rebecca Crowder[1]*, Alex Kityamuwesi[2]*, Noah Kiwanuka[3], Maureen Lamunu[2], Catherine Namale[2], Lynn Kunihira Tinka[2], Agnes Sanyu Nakate[2], Joseph Ggita[2], Patricia Turimumahoro[2], Diana Babirye[2], Denis Oyuku[2], Christopher Berger[1], Austin Tucker[4], Devika Patel[5], Amanda Sammann[5], David Dowdy[2,4], Turyahabwe Stavia[6], Adithya Cattamanchi[1,2], Achilles Katamba[2,3]

* Authors contributed equally

Affiliations:

1. Curry International Tuberculosis Center and Division of Pulmonary and Critical Care Medicine, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
2. Uganda Tuberculosis Implementation Research Consortium, Kampala, Uganda
3. School of Public Health, Makerere University College of Health Sciences, Kampala, Uganda
4. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
5. The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
6. National Tuberculosis and Leprosy Program, Uganda Ministry of Health, Kampala, Uganda

Correspondence to:

Achilles Katamba
axk95@case.edu
Makerere University College of Health Sciences,
Clinical Epidemiology and Biostatistics Unit
Mulago Hill Road
Clinical Research Building Floor 3 Room 3.1
Kampala, Uganda 21696
+256-772-575-038

Abstract word count: 248

Manuscript word count (excluding tables and figures): 3,994

ABSTRACT

Introduction: Low-cost digital adherence technologies (DAT) such as 99DOTS have emerged as an alternative to directly observed therapy, (DOT), the current standard for TB treatment supervision. However, there are limited data to support DAT scale-up. The "DOT to DAT" trial aims to evaluate the effectiveness and implementation of a 99DOTS-based TB treatment supervision strategy.

Methods and analysis: This is a pragmatic, stepped-wedge cluster randomized trial, with hybrid type 1 effectiveness-implementation design. The trial will include all adults (estimated N=1890) treated for drug-susceptible pulmonary TB over an 8-month period at 18 TB treatment units in Uganda. Three sites per month will switch from routine care (DOT) to the intervention (99DOTS-based treatment supervision) beginning in Month 2, with the order determined randomly. 99DOTS enables patients to be monitored while self-administering TB medicines. Patients receive daily automated SMS dosing reminders and confirm dosing by calling toll-free numbers. The primary effectiveness outcome is the proportion of patients completing TB treatment. With 18 clusters randomized into 6 steps and an average cluster size of 15 patients per month, the study will have 89% power to detect a 10% or greater increase in treatment completion between the routine care and intervention periods. Secondary outcomes include more proximal effectiveness measures as well as quantitative and qualitative assessments of the reach, adoption and implementation of the intervention.

Ethics and dissemination: Ethics approval was granted by institutional review boards at Makerere University School of Public Health and the University of California San Francisco.

Trial registration number: PACTR201808609844917

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomized trial to evaluate a 99DOTS-based strategy for TB treatment supervision.
- The intervention was designed using the PRECEDE framework and adapted for local context in Uganda using human-centered design.
- Trial outcomes were selected using the RE-AIM framework.
- The intervention was implemented by health facility staff and will be assessed using routinely collected data to approximate the real-world impact of this intervention.

INTRODUCTION

Tuberculosis (TB) is the leading infectious cause of death worldwide despite being a preventable and curable disease.(1) Poor adherence to medication continues to be a major obstacle to TB elimination, resulting in prolonged infectiousness, emergence of multidrug resistance, and increased risk of poor treatment outcomes. The World Health Organization (WHO)-recommended strategy, directly observed therapy short-course (DOTS), has been the standard-of-care for TB treatment supervision since the 1990s. As part of this strategy, a health worker is expected to observe patients swallow each dose of anti-TB medication. However, directly observed therapy (DOT) is time-consuming, costly and inconvenient for both patients and providers, while its implementation is also difficult to monitor.(2, 3) Not surprisingly, TB treatment success rates remain below the 90% target in most high-burden countries, despite reported DOT coverage over 90%.(1)

With the increase in mobile phone penetration among patients and healthcare workers in high TB burden countries,(4) digital adherence technologies (DATs) could address some of the challenges associated with implementation of the DOTS strategy in a patient-centered manner. To date, such technologies have received only a conditional recommendation by the WHO due to very low quality of evidence.(5) The first randomized trial of a DAT found that SMS reminders alone did not improve medication adherence, but a medication event reminder monitor did.(6) However, treatment outcomes did not improve and both trials and programmatic research have shown variable uptake of DAT.(7-10)

The "DOT to DAT" trial aims to evaluate the effectiveness, implementation and cost-effectiveness of a culturally and contextually adapted version of 99DOTS in Uganda. 99DOTS is a low-cost DAT wherein patients self-report medication adherence by calling toll-free phone numbers hidden underneath pills in blister packs.(11) We present the research methods used for the first randomized trial to evaluate the effectiveness and implementation of a 99DOTS-based strategy for TB treatment supervision in routine care settings.

Conceptual basis for trial design

Numerous conceptual frameworks have emerged to improve the implementation and success of health interventions through theory-based design and evaluation. The PRECEDE framework guided the development of the 99DOTS-based intervention strategy, while the RE-AIM framework guided its comprehensive evaluation. Behavior change models including the Theoretical Domains Framework (TDF)(12, 13) and the Unified Theory of Acceptance and Use of Technology (UTAUT)(14, 15) guided the assessment and analysis of patient- and provider-level barriers to adoption and implementation of 99DOTS.

The PRECEDE framework emphasizes the need for multi-faceted health promotion interventions to address predisposing, enabling, and reinforcing factors in order to achieve behavior change.(16) The 99DOTS-based intervention was designed to address key predisposing (social isolation and the high direct and indirect cost of clinic visits), enabling (inability of health facility staff to focus limited time and resources on non-adherent patients), and reinforcing (a lack of real-time information on patient adherence to medications) factors related to TB treatment adherence identified through the literature and formative human factors research that preceded the trial.(11)

The RE-AIM framework was designed to ensure that trials not only assess the effect of interventions but also their translatability and public health impact.(17, 18) This hybrid type 1 trial therefore focuses on the effectiveness of the 99DOTS-based intervention in improving TB treatment outcomes, but concurrently examines its reach into the target population, adoption by target settings and staff, and implementation fidelity and costs.(19) The goal of assessing

translatability and public health impact is further enhanced through pragmatic design choices for each element of the trial in order to maximize applicability in real-world settings.(20)

METHODS AND ANALYSIS

Study aims

The primary aim of the trial is to determine whether a 99DOTS-based strategy increases the proportion of patients who complete TB treatment in comparison to routine care. Secondary aims include 1) comparing short-term treatment outcomes and loss to follow-up between the intervention and routine care arms; 2) assessing the reach, adoption and implementation of the 99DOTS-based strategy; and 3) evaluating the incremental costs and cost-effectiveness of the 99DOTS-based strategy as compared to routine care from the health system perspective. Our hypotheses are that the 99DOTS-based strategy will lead to higher treatment completion, have high uptake among patients and providers, and be cost-effective.

Study design

This is a pragmatic, stepped-wedge randomized trial, with a hybrid type 1 implementation-effectiveness design.(19) As depicted in **Figure 1**, the intervention strategy was sequentially introduced at 3 sites each in Months 2-6, with all sites under routine care in Month 1 and all sites using the intervention strategy in Month 8. The month of switch from control to intervention (buffer period) will be excluded from analysis. We chose the stepped-wedge trial design to maximize equity and acceptability (all sites will receive the intervention), minimize logistical constraints associated with introducing the intervention simultaneously at a large number of sites, account for secular outcome trends, and allow for iterative learning and changes in intervention roll-out as would occur during eventual scale-up. We chose a highly pragmatic approach to trial implementation, as described in sections below, to understand the real-world impact of the 99DOTS-based intervention strategy.

Study Setting

The trial is being conducted at 18 TB treatment units within hospitals and health centers across 15 districts of Uganda. The TB treatment units are affiliated with the Uganda National Tuberculosis and Leprosy Program (NTLP) and provide TB treatment free of charge using a mix of facility- and

community-based DOTS. Uganda was chosen as the trial setting due to its high TB burden (200 cases/100,000 in 2017) and low treatment success rate (72% in 2017).(1)

Study sites were selected after reviewing 2016 TB treatment outcomes and 2017 TB case finding data reported to the NTLP from all 1514 registered TB treatment units. We included treatment units that 1) diagnosed >10 pulmonary TB patients/month in 2017, 2) were not located within Kampala District (many active ongoing projects in this district), 3) were located within 225 km of Kampala City (for feasibility), and 4) had a pulmonary TB treatment success rate in 2016 <80% (to be able to show an impact).

Of the 1514 treatment units registered with the Uganda NTLP, 23 treatment units met our inclusion criteria (**Figure 2**). The majority (n=1435) diagnosed fewer than 10 TB patients/month in 2017, 17 are located within Kampala district, 31 are not within 225 km of Kampala district, and 9 had a treatment success rate >80% in 2016. Of the 23 remaining treatment units, we selected 18 located in 15 districts (10 in Central, 7 in Eastern and 1 in Western Uganda) in consultation with the NTLP. Project staff visited the Chief Administrative Officers, District Health Officers and Facility Directors for the 18 sites to discuss the study. All signed a memorandum of agreement for their site to participate in the study.

Study participants

All adult patients treated for drug-susceptible pulmonary TB at participating treatment units during the study period will be eligible for inclusion. Children, patients treated for drug-resistant or extrapulmonary TB, and patients transferred to another facility to complete treatment will be excluded. Surveys to assess 99DOTS implementation will be conducted in a random subset of eligible patients and all health workers involved in TB treatment supervision at each treatment unit. Time-and-motion studies to assess costs will also be conducted among health workers involved in TB treatment supervision at each treatment unit.

Routine care and intervention strategies

Routine care. The conventional approach to TB treatment supervision in Uganda is a mix of community- and facility-based DOT. At the time of treatment initiation, treatment unit staff record

patient demographic and clinical details in the NTLP register and are supposed to provide TB-focused counseling. Most TB patients are treated using community-based DOT, wherein they name a treatment supporter and are provided with a 2-week supply of medicines in the first two months (intensive phase) and a one-month supply of medicines in the next four months (continuation phase) of TB treatment. Patients take their medicines from home (with or without observation by a treatment supporter) and return to the health facility for medication refills. At each refill visit, health facility staff are supposed to assess adherence via patient self-report and provide additional counseling. Health facility staff are also supposed to call or visit patients who do not return for refills, but patient follow-up is limited across health facilities.

Intervention. The 99DOTS-based intervention strategy is comprised of four main components that address distinct barriers to successful TB treatment (**Table 1**):

1) Daily automated SMS dosing reminders
2) Daily dosing confirmation using toll-free phone calls
3) Weekly automated interactive voice response (IVR) check-in phone calls
4) Differential management protocol based on dosing history and response to IVR check-in

Table 1. Components of the "DOT to DAT" trial intervention and corresponding barriers addressed.

Component		Barrier addressed
1	Daily dosing reminders via automated SMS	Addresses high cost of clinic visits for patients and assists with memory and planning processes known to be importance to adherence.
2	Daily dosing confirmation via toll-free phone calls	Addresses high cost of clinic visits for patients, lack of real-time information for providers on patient adherence to medications.
3	Weekly check-in via interactive voice response phone calls	Addresses lack of social support and feeling of isolation during TB treatment; shown to be effective in other contexts at increasing connection with CHW and reducing social isolation.
4	Differential management protocol	Addresses limited time and resources among TB treatment unit staff and the need to focus on non-adherent patients.

Formative research using human-centered design was used to adapt the generic 99DOTS product to the local context, including changes to the envelope design and addition of a rotating series of educational/motivational audio messages heard when patients call in to report dosing (details of the formative research will be reported in a separate publication) (**Figure 3**).

TB treatment unit staff will be requested to offer 99DOTS-based treatment supervision to all eligible patients initiating TB treatment, and to register patients who accept 99DOTS-based treatment supervision on the 99DOTS platform via a mobile app. Given the pragmatic nature of the trial, the decision to offer and accept 99DOTS-based treatment supervision will be made by treatment unit staff and patients, respectively. Once registered, treatment unit staff will instruct patients on how to use the 99DOTS pill pack and make a call to the 99DOTS system using the toll-free number revealed when pills are pushed out of the medication blister pack (**Figure 3**). Staff will also help patients personalize their 99DOTS pill pack by choosing a decorative cover, educational or motivational sticker for the inside flap, writing in their health worker's contact information, and selecting a time of day to take their medication (**Figure 3**).

Each dose confirmed via phone call is logged by 99DOTS and reflected on the 99DOTS smartphone app dashboard, viewable by treatment unit staff. During routine drug refill visits (same schedule as described for routine care period), health facility staff are asked to review adherence data in the 99DOTS app before providing counseling. At the conclusion of the intensive phase of treatment, patients with adherence >90% are offered the option of returning back to the health facility after two months instead of the standard one month.

Health facilities using 99DOTS to manage TB patient treatment will be provided one smartphone per facility, minimal funds to cover cell phone data, and an average of 300,000 USh (approximately $82 USD) per month to facilitate patient follow-up. Treatment unit staff will not be provided any extra compensation to reflect future conditions under eventual scale-up.

Implementation considerations

99DOTS training will occur at each health facility during the month in which it is scheduled to switch to the intervention. Project staff and the District TB Officer will conduct a 2-3 day training

jointly at each health facility using standardized training materials. Treatment unit staff will be trained on how to register patients on the 99DOTS platform via a smartphone app, counsel patients regarding use of 99DOTS, use the 99DOTS application to review dosing history, and conduct differential management based on dosing history and response to weekly check-ins. Mentored patient enrollment on 99DOTS will be conducted as part of the training.

During the trial, treatment unit staff will make all decisions regarding management of TB patients in both the routine care and intervention periods. Research staff will not be onsite after training with the exception of 2-3 day quarterly site visits to resolve data cleaning queries and implement surveys and health economic sub-studies. Thus, the implementation is highly pragmatic and meant to approximate how 99DOTS would be used at treatment units in the absence of a research study.

Randomization

The 18 health facilities will be randomly assigned to one of the six groups (**Figure 1**) using a simple, unrestricted two-stage process. This process will occur by simple drawing during a public randomization ceremony held in Kampala, Uganda. A representative from each TB treatment unit, district health officers, and Uganda NTLP staff will be invited to attend the ceremony. First, health facilities will be randomly assigned into six groups of three by having health facility representatives each draw 1 of 18 balls (3 each labeled A-F) from an opaque bag; and second, each group will be randomly assigned into the sequence order in which they will switch from routine care to the intervention by drawing of 6 balls labeled 1-6 from an opaque bag.

Blinding

Blinding of the assigned intervention is not feasible given intervention implementation at the health facility level. Where possible, the investigators and study staff, with the exception of the statistician and data manager, are masked to step and intervention assignment.

Data collection and management

Patient-level data collection

Consistent with the pragmatic design, TB treatment outcomes will be assessed by extracting data on all eligible patients from routine Uganda NTLP TB treatment registers used at all treatment

units. Project staff will train two health workers at each site (one primary, one backup) identified by the health facility director to take photos of the register every 2-4 weeks for the duration of the project using a camera-enabled smartphone, and to upload the photos to a central secure server. Health workers will be trained to delete photos from the phone after upload confirmation. Completeness of TB treatment registers will be assessed, and at quarterly site visits, study staff will provide re-training as needed and resolve data cleaning queries. Study staff will extract data from photos of TB registers and enter data into a secure database use Research Electronic Data Capture software (REDCap).(21) Data queries for missing or nonsensical data will be reviewed with treatment unit staff at quarterly site visits.

99DOTS process metrics data collection

During the intervention period at each site, process metric data to assess the implementation of each component of the intervention strategy will be extracted from the 99DOTS server. The server logs all calls made by patients to confirm dosing and doses entered manually by providers, all SMS messages sent to patients, and all IVR calls sent to patients and their responses.

Qualitative data collection

Surveys will be conducted with 10 randomly selected eligible patients enrolled on 99DOTS (5 women and 5 men) and 1-2 eligible providers per site (180 total patients, 18-36 total providers) beginning in Month 10 of the trial to assess the acceptability of the 99DOTS-based intervention strategy. Research staff will contact selected patients by phone to review the verbal consent script, answer questions the patient may have, and administer the survey to consenting patients. Provider surveys and interviews will be conducted during quarterly site visits beginning in Month 13 of the trial to assess factors influencing the adoption and implementation of 99DOTS.

Health system cost data collection

Treatment unit staff at each site will be interviewed to gain a more complete understanding of the activities and staff involved in the operations of 99DOTS. Time-and-motion studies of health workers (anticipated to be 3-6 health workers per site, depending on the number of staff involved in delivering 99DOTS) will be carried out at six clinics, sampled to ensure good representation of clinic volume and geography. These time-and-motion studies will be performed on a quarterly

basis in conjunction with site visits and will consist of direct observation of all activities conducted by treatment unit staff over the corresponding 1-2 day evaluation period, for a total 6-12 days of observation every three months over the course of the 14-month study period. During these observation periods, the time and resources required to perform all activities related to TB treatment (e.g., medication preparation, contacting patients, observing medication doses, etc.) will be recorded. Additional costing data will be collected to assess the cost of implementing and maintaining 99DOTS technical assistance (budget records from Everwell Health Solutions, the creator of 99DOTS) and the cost at point of care (surveys of project staff to track resource use during trainings). Overhead costs will be estimated using an ingredients approach, incorporating the cost of supplies, building/space, vehicles, and human resources with incorporation of recurrent costs such as security, vehicle maintenance costs, and all supplies (medical and administrative).

Outcomes

Trial outcomes were selected in accordance with the RE-AIM evaluation framework (**Table 2**). The primary effectiveness outcome is the proportion of patients who complete TB treatment, defined as having an outcome of "cured" or "treatment completed" recorded in the unit TB treatment register. Secondary effectiveness outcomes include the proportion who persist on treatment through the intensive phase (*i.e.,* 56 days of treatment), the proportion lost to follow-up and estimated number of incremental disability-adjusted life years (DALYs) averted. Reach is defined as the proportion of eligible patients enrolled on 99DOTS. Adoption metrics include the proportion of scheduled doses confirmed by patient phone calls and the proportion of weekly IVR check-in calls to which patients send a response. Implementation outcomes include delivery of the intervention (proportions of daily SMS dosing reminders and weekly IVR check-in calls sent by the 99DOTS platform and received on patient handsets), acceptability (as assessed by patient and health worker surveys and interviews) and incremental costs of the 99DOTS-based intervention strategy.

Table 2. Outcome definitions and data source by RE-AIM dimension.

Outcome type	Outcome	Data Source
Reach		
Proportion enrolled on 99DOTS		99DOTS server, Treatment register
Effectiveness		
Primary	Proportion treated successfully	Treatment register
Secondary	Proportion with persistence	Treatment register
Secondary	Proportion lost to follow-up	Treatment register
Secondary	Incremental cost per patient treated successfully	Time and motion surveys; budgetary analysis
Adoption		
Proportion of scheduled doses confirmed by phone call		99DOTS server
Proportion of weekly IVR calls to which patients send a response		99DOTS server
Implementation		
Proportion of daily SMS sent by 99DOTS platform		99DOTS server
Proportion of daily SMS received on patient handset		99DOTS server
Proportion of weekly IVR calls sent by 99DOTS platform		99DOTS server
Proportion of weekly IVR calls received on patient handset		99DOTS server

Power and sample size

The trial aims to demonstrate the superiority of the 99DOTS-based strategy. The sample size was calculated for the primary effectiveness outcome, proportion of patients treated successfully, using formulae appropriate for stepped-wedge trials. A type I error of 5% and power of at least 90% is assumed. Based on 2017 data, the harmonic mean number of patients initiating treatment for drug-susceptible pulmonary TB per month across participating treatment units was 15. Thus, we anticipate that approximately 1890 patients will initiate treatment over the 8-month enrollment period (945 in the pre- and 945 in the post-implementation phases across treatment units). The trial will have 89% power to demonstrate that our strategy increases the proportion of patients treated successfully by 10% or more (assumptions: alpha=0.05; intraclass correlation coefficient, ICC = 0.001 calculated using 2017 NTLP data for the 18 treatment units; pre-implementation treatment

success = 51% based on 2017 NTLP data for the 18 treatment units; calculations performed using steppedwedge command in Stata 14).

Analysis

The primary effectiveness analysis will be conducted at the health facility level using multivariable mixed effect logit models. Analysis will be done for intention to treat and per protocol (excluding patients who are not enrolled on 99DOTS during the intervention period at each site) populations in Stata using melogit and meqrlogit commands. Models will adjust for the longitudinal design and clustering by site, nested within group. Patients initiating treatment during the month in which sites switch from routine treatment supervision to the intervention strategy will be excluded (buffer period). Confounders, selected *a priori,* will be included in the model as fixed effects. Secondary effectiveness outcomes (**Table 2**) will be analyzed in the same manner. Subgroup analyses will stratify by gender, HIV status, and health facility. Sensitivity analyses will be performed to assess the robustness of our findings with respect to treatment outcomes for patients lost to follow up, the staged intervention roll out, intervention timing and buffer period, and analysis method.

Quantitative reach, adoption and implementation outcomes will be summarized descriptively. Comparative analyses will identify factors independently associated with reach, adoption and implementation of intervention components. Health economic data will be used to calculate the incremental cost-effectiveness of the intervention strategy from a societal perspective, measured as the incremental cost per successfully completed treatment, comparing 99DOTS relative to routine care.

Ethics and dissemination

Patients can choose to use or not use 99DOTS at any time during the intervention period. 99DOTS enables closer patient monitoring than routine TB treatment supervision, but loss of patient privacy is a potential concern. Data on this are being collected through patient surveys. Because of the low-risk nature of the research, the Principal Investigators will be responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews on a quarterly basis. External monitoring is provided by a Stop TB Partnership project officer and Monitoring and Evaluation consultant. The Principal Investigator will submit regular progress reports, including

recommendations on whether the project should continue unchanged, require modification, or close to enrollment.

Ethics approval was granted by institutional review boards at Makerere University School of Public Health and the University of California San Francisco. To ensure that the study captures all eligible adults initiating treatment at study sites, a waiver of informed consent was granted to access routine TB treatment data recorded in standard NTLP registers. The protocol was registered with the Pan-African Clinical Trials Registry (PACTR201808609844917) on 31 August 2018, updated 11 July 2019 and complies with reporting guidelines outlined in the stepped-wedge trial extension of the Consolidated Standards of Reporting Trials.(22) Any major changes in protocol will be approved by the Stop TB Partnership project officer and both ethics committess and registered with the PACTR. The full protocol and statistical code will be made available upon request.

Findings will be disseminated through peer-reviewed publications, presentations at scientific conferences and presentations to key stakeholders. Drs. Cattamanchi, Katamba and Kiwanuka will have access to the final dataset; the participant-level dataset will be made available to other investigators who have IRB approval to analyze the data.

Patient and public involvement

Patients and members of the public were involved throughout the research process. The NTLP was involved in identifying health facilities to participate, selecting study design, and conducting research through partnership with District Health Officers and participating health facilities. Patients, health workers, and community members were involved in intervention design through a human-centered design process, which included several rounds of focus groups and interviews with stakeholders. Health workers at the 18 health facilities implemented 99DOTS without research staff present and assisted in data collection by completing routine TB treatment registers and sending photos of the register to the research team through secure means.

DISCUSSION

99DOTS is a low-cost DAT that has the potential to improve TB treatment outcomes and the patient experience of TB treatment in Uganda and other high-burden settings. Here, we describe the first randomized trial designed to evaluate the effectiveness of a 99DOTS-based TB treatment supervision strategy as part of routine care in a high burden setting. Other novel aspects of the trial include our use of human-centered design to adapt 99DOTS to the local context with the goal of increasing patient engagement with the technology, the use of theory and implementation science frameworks to guide intervention design and evaluation, and our focus on simultaneously assessing implementation and costs to guide scale-up decisions.

Many aspects of this trial are intentionally pragmatic to ensure the outcomes reflect what can be expected under non-research conditions.(23) The study population will include all patients with drug susceptible pulmonary TB, with the exception of children. A waiver of consent was obtained for patient-level data collection such that research staff will not be required to be onsite to enroll and consent patients. Primary and key secondary outcomes will be assessed using routine data available through NTLP registers and the 99DOTS platform, with focused additional data collection for implementation and cost outcomes. The intervention will be implemented by routine TB treatment unit staff, who also will make all decisions to offer 99DOTS-based treatment supervision to patients. At the same time, the stepped-wedge randomized trial design provides a rigorous assessment of intervention effect.

In summary, this pragmatic, hybrid type 1 effectiveness-implementation trial is well poised to assess both the effectiveness of an adapted 99DOTS-based intervention and potential barriers and facilitators to its scale-up if successful. The design and implementation of this trial intend to generate results to inform decisions on whether and how to implement 99DOTS in Uganda and other high burden countries.

References

1. World Health Organization. Global Tuberculosis Report Geneva: World Health Organization; 2017 [Available from: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf.
2. Izudi J, Tamwesigire IK, Bajunirwe F. Explaining the successes and failures of tuberculosis treatment programs; a tale of two regions in rural eastern Uganda. BMC Health Services Research. 2019;19(1):979.
3. Fiseha D, Demissie M. Assessment of Directly Observed Therapy (DOT) following tuberculosis regimen change in Addis Ababa, Ethiopia: a qualitative study. BMC Infect Dis. 2015;15:405.
4. GSMA Intelligence. The Mobile Economy - Africa London GSMA; 2016 [Available from: https://www.gsma.com/mobileeconomy/africa/.
5. World Health Organization. Treatment of tuberculosis: guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Geneva; 2017.
6. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS medicine. 2015;12(9):e1001876-e.
7. Subbaraman R, de Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMJ Glob Health. 2018;3(5):e001018.
8. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med. 2015;12(9):e1001876.
9. Liu X, Blaschke T, Thomas B, De Geest S, Jiang S, Gao Y, et al. Usability of a Medication Event Reminder Monitor System (MERM) by Providers and Patients to Improve Adherence in the Management of Tuberculosis. Int J Environ Res Public Health. 2017;14(10).
10. Thakkar D, Piparva KG, Lakkad SG. A pilot project: 99DOTS information communication technology-based approach for tuberculosis treatment in Rajkot district. Lung India. 2019;36(2):108-11.
11. Cross A, Gupta N, Liu B, Nair V, Kumar A, Kuttan R, et al. 99DOTS: A Low-Cost Approach to Monitoring and Improving Medication Adherence. Tenth International Conference on Information and Communication Technologies and Development. ICTD. 2019.
12. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77.
13. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. Implement Sci. 2012;7:38.
14. Sarfaraz J. Unified theory of acceptance and use of technology (Utaut) model-mobile banking. Journal of Internet Banking and Commerce. 2017;22(3):1-20.
15. Venkatesh V, Thong JY, Xu X. Consumer acceptance and use of information technology: extending the unified theory of acceptance and use of technology. MIS quarterly. 2012:157-78.
16. Green LW, Kreuter MW. Health promotion planning: An educational and ecological approach: McGraw-Hill; 1993.

17. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. American journal of public health. 1999;89(9):1322-7.
18. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. American journal of public health. 2013;103(6):e38-e46.
19. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.
20. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
21. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
22. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614.
23. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ : British Medical Journal. 2015;350:h2147.

Acknowledgements

We would like to thank the patients and health facility staff who make this research possible, as well as the Uganda NTLP, for their collaboration on this protocol.

Authors' contributions

AC and AKa conceived and designed the study. RC, AKi, ML, CN, LKT, ASN, JG, PT, DB, DO, CB, AT, DP, AM, DD, TS, AC and AKa participated in implementation of the study. RC, AKi, AC, and AKa drafted the manuscript. All authors reviewed and approved the manuscript.

Funding

This Project is supported by the Stop TB Partnership's TB REACH initiative, grant number STBP/TBREACH/GSA/W6-37, which is funded by the Government of Canada, the Bill & Melinda Gates Foundation, and the United States Agency for International Development. The study sponsor is not involved in data collection, analysis or interpretation.

Competing Interests

The authors have no conflicts of interest to report.

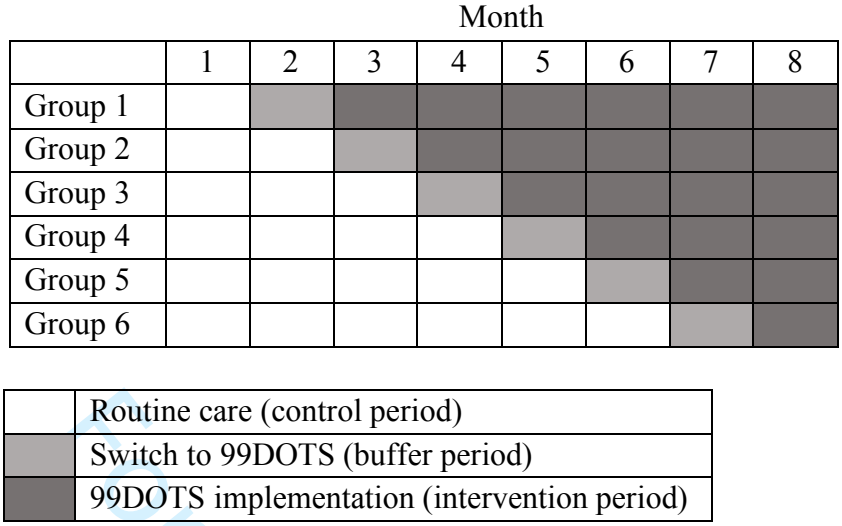


Figure 1. 99DOTS Randomization and Enrollment Schedule. The trial includes 18 health facilities divided into 6 equal size groups (3 health facilities per group). The health facilities all continue routine TB treatment supervision in Month 1, begin switching to the 99DOTS-based intervention strategy in Month 2 (one group per month in a random order), and all use the intervention strategy in Month 8.

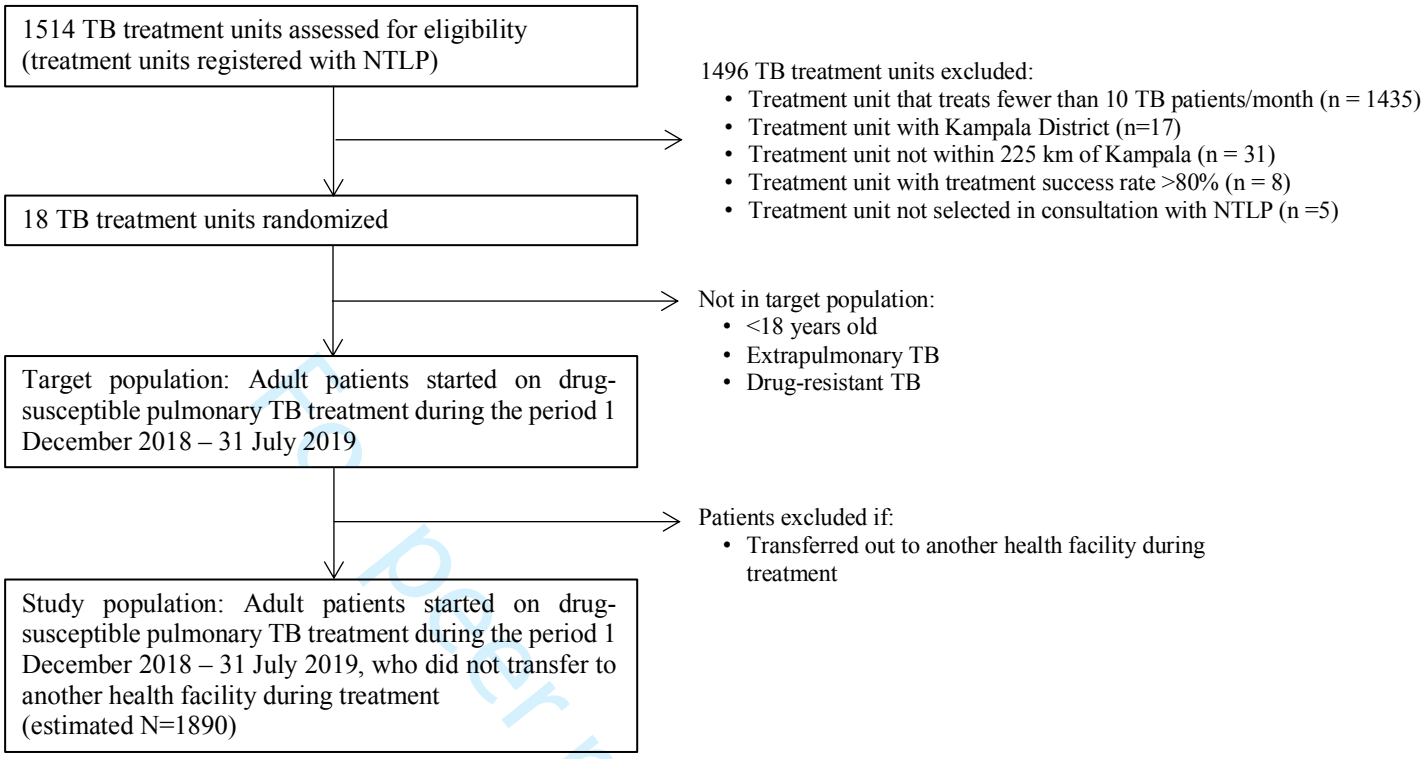
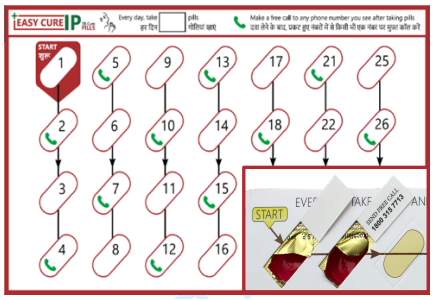


Figure 2. **Flow diagram of TB treatment units and patients included in the DOT to DAT trial**. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Original 99DOTS Envelope

Front of envelope

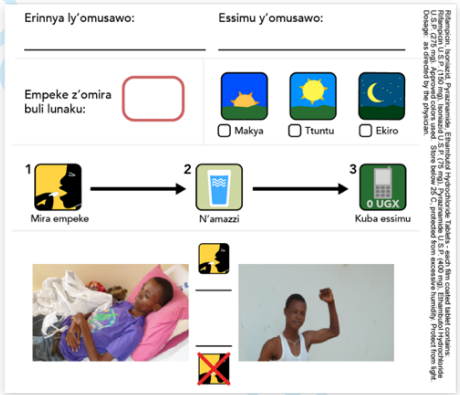


Back of envelope

Adapted 99DOTS envelope

Front cover

Inside cover



Back of envelope

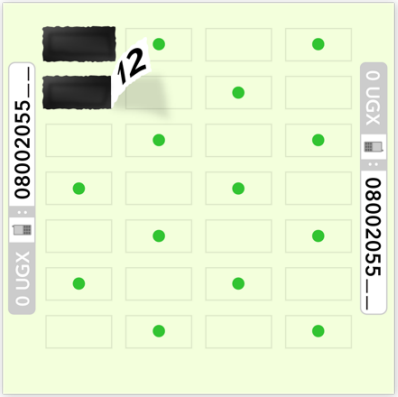


Figure 3. **Original and adapted versions of the 99DOTS envelope**. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space for writing in the health worker's name and phone number, simplified pictorial instructions for taking pills, and motivational imagery on the inside cover (bottom middle); and provide simplified guide to the order in which to take pills on the back cover (bottom right). In addition, the audio tone heard when patients make daily phone calls to report medication dosing was replaced with a rotating series of educational or motivational messages recorded by local health workers.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
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, 14
	2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,18
	5b	Name and contact information for the trial sponsor	18
	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	18
	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)	N/A

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	3-4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
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)	5
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	5-6
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)	6, Figure 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8, Figure 3
	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)	13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	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	11-12, Table 2
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)	5, Figure 1

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	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12

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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9

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	9-11
	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	11-12

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	9-11
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	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	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)	13
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	13-14
	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	13
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	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	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	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	14
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	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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.

BMJ Open

Study protocol and implementation details for a pragmatic, stepped-wedge cluster randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039895.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Sep-2020
Complete List of Authors:	Crowder, Rebecca; University of California San Francisco, Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital Kityamuwesi, Alex; Uganda Tuberculosis Implementation Research Consortium, Kiwanuka, Noah; Makerere University College of Health Sciences, School of Public Heatlh Lamunu, Maureen; Uganda Tuberculosis Implementation Research Consortium, Namale, Catherine; Uganda Tuberculosis Implementation Research Consortium, Tinka, Lynn; Uganda Tuberculosis Implementation Research Consortium, Nakate, Agnes; Uganda Tuberculosis Implementation Research Consortium, Ggita, Joseph; Uganda Tuberculosis Implementation Research Consortium, Turimumahoro, Patricia; Uganda Tuberculosis Implementation Research Consortium, Babirye, Diana; Uganda Tuberculosis Implementation Research Consortium, Oyuku, Denis; Uganda Tuberculosis Implementation Research Consortium, Berger, Christopher; University of California San Francisco, Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital Tucker, Austin; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology Patel, Devika; University of California San Francisco, The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital Sammann, Amanda; University of California San Francisco, The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital Dowdy, DW; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology Stavia, Turyahabwe; Republic of Uganda Ministry of Health, National Tuberculosis and Leprosy Program Cattamanchi, A; University of California San Francisco, Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, San

	Francisco General Hospital Katamba, Achilles; Makerere University College of Health Sciences, Clinical Epidemiology and Biostatistics Unit; Uganda Tuberculosis Implementation Research Consortium, Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Study protocol and implementation details for a pragmatic, stepped-wedge cluster randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion

Authors: Rebecca Crowder[1]*, Alex Kityamuwesi[2]*, Noah Kiwanuka[3], Maureen Lamunu[2], Catherine Namale[2], Lynn Kunihira Tinka[2], Agnes Sanyu Nakate[2], Joseph Ggita[2], Patricia Turimumahoro[2], Diana Babirye[2], Denis Oyuku[2], Christopher Berger[1], Austin Tucker[4], Devika Patel[5], Amanda Sammann[5], David Dowdy[2,4], Turyahabwe Stavia[6], Adithya Cattamanchi[1,2], Achilles Katamba[2,3]

* Authors contributed equally

Affiliations:

1. Curry International Tuberculosis Center and Division of Pulmonary and Critical Care Medicine, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
2. Uganda Tuberculosis Implementation Research Consortium, Kampala, Uganda
3. School of Public Health, Makerere University College of Health Sciences, Kampala, Uganda
4. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
5. The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
6. National Tuberculosis and Leprosy Program, Uganda Ministry of Health, Kampala, Uganda

Correspondence to:

Achilles Katamba
axk95@case.edu
Makerere University College of Health Sciences,
Clinical Epidemiology and Biostatistics Unit
Mulago Hill Road
Clinical Research Building Floor 3 Room 3.1
Kampala, Uganda 21696
+256-772-575-038

Abstract word count: 264

Manuscript word count (excluding tables and figures): 4,281

ABSTRACT

Introduction: Low-cost digital adherence technologies (DAT) such as 99DOTS have emerged as an alternative to directly observed therapy, (DOT), the current standard for TB treatment supervision. However, there are limited data to support DAT scale-up. The "DOT to DAT" trial aims to evaluate the effectiveness and implementation of a 99DOTS-based TB treatment supervision strategy.

Methods and analysis: This is a pragmatic, stepped-wedge cluster randomized trial, with hybrid type 2 effectiveness-implementation design. The trial will include all adults (estimated N=1890) treated for drug-susceptible pulmonary TB over an 8-month period at 18 TB treatment units in Uganda. Three sites per month will switch from routine care (DOT) to the intervention (99DOTS-based treatment supervision) beginning in Month 2, with the order determined randomly. 99DOTS enables patients to be monitored while self-administering TB medicines. Patients receive daily automated SMS dosing reminders and confirm dosing by calling toll-free numbers. The primary effectiveness outcome is the proportion of patients completing TB treatment. With 18 clusters randomized into 6 steps and an average cluster size of 15 patients per month, the study will have 89% power to detect a 10% or greater increase in treatment completion between the routine care and intervention periods. Secondary outcomes include more proximal effectiveness measures as well as quantitative and qualitative assessments of the reach, adoption and implementation of the intervention.

Ethics and dissemination: Ethics approval was granted by institutional review boards at Makerere University School of Public Health and the University of California San Francisco. Findings will be disseminated through peer-reviewed publications, presentations at scientific conferences and presentations to key stakeholders.

Trial registration number: PACTR201808609844917

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomized trial to evaluate a 99DOTS-based strategy for TB treatment supervision.
- The intervention was designed using the PRECEDE framework and adapted for local context in Uganda using human-centered design.
- Trial outcomes were selected using the RE-AIM framework.
- The intervention was implemented by health facility staff and will be assessed using routinely collected data to approximate the real-world impact of this intervention.

INTRODUCTION

Tuberculosis (TB) is the leading infectious cause of death worldwide despite being a preventable and curable disease.(1) Poor adherence to medication continues to be a major obstacle to TB elimination, resulting in prolonged infectiousness, emergence of multidrug resistance, and increased risk of poor treatment outcomes. The World Health Organization (WHO)-recommended strategy, directly observed therapy short-course (DOTS), has been the standard-of-care for TB treatment supervision since the 1990s. As part of this strategy, a health worker is expected to observe patients swallow each dose of anti-TB medication. However, directly observed therapy (DOT) is time-consuming, costly and inconvenient for both patients and providers, while its implementation is also difficult to monitor.(2, 3) Not surprisingly, TB treatment success rates remain below the 90% target in most high-burden countries, despite reported DOT coverage over 90%.(1)

With the increase in mobile phone penetration among patients and healthcare workers in high TB burden countries,(4) digital adherence technologies (DATs) could address some of the challenges associated with implementation of the DOTS strategy in a patient-centered manner. To date, such technologies have received only a conditional recommendation by the WHO due to very low quality of evidence.(5) The first randomized trial of a DAT found that SMS reminders alone did not improve medication adherence, but a medication event reminder monitor did.(6) However, treatment outcomes did not improve and both trials and programmatic research have shown variable uptake of DAT.(7-10)

The "DOT to DAT" trial aims to evaluate the effectiveness, implementation and cost-effectiveness of a culturally and contextually adapted version of 99DOTS in Uganda. 99DOTS is a low-cost DAT wherein patients self-report medication adherence by calling toll-free phone numbers hidden underneath pills in blister packs.(11) We present the research methods used for the first randomized trial to evaluate the effectiveness and implementation of a 99DOTS-based strategy for TB treatment supervision in routine care settings.

Conceptual basis for trial design

Numerous conceptual frameworks have emerged to improve the implementation and success of health interventions through theory-based design and evaluation. The PRECEDE framework(12) guided the development of the 99DOTS-based intervention strategy, while the RE-AIM framework guided its comprehensive evaluation. Behavior change models including the Theoretical Domains Framework (TDF)(13, 14) and the Unified Theory of Acceptance and Use of Technology (UTAUT)(15, 16) guided the assessment and analysis of patient- and provider-level barriers to adoption and implementation of 99DOTS.

The PRECEDE framework emphasizes the need for multi-faceted health promotion interventions to address predisposing, enabling, and reinforcing factors in order to achieve behavior change.(12) The 99DOTS-based intervention was designed to address key predisposing (social isolation and the high direct and indirect cost of clinic visits), enabling (inability of health facility staff to focus limited time and resources on non-adherent patients), and reinforcing (a lack of real-time information on patient adherence to medications) factors related to TB treatment adherence identified through the literature and formative human factors research that preceded the trial.(11)

The RE-AIM framework was designed to ensure that trials not only assess the effect of interventions but also their translatability and public health impact.(17, 18) This hybrid type 2 trial therefore focuses on the effectiveness of the 99DOTS-based intervention in improving TB treatment outcomes, but concurrently examines its reach into the target population, adoption by target settings and staff, and implementation fidelity and costs.(19) The goal of assessing

translatability and public health impact is further enhanced through pragmatic design choices for each element of the trial in order to maximize applicability in real-world settings.(20)

METHODS AND ANALYSIS

Study aims

The primary aim of the trial is to determine whether a 99DOTS-based strategy increases the proportion of patients who complete TB treatment in comparison to routine care. Secondary aims include 1) comparing short-term treatment outcomes and loss to follow-up between the intervention and routine care arms; 2) assessing the reach, adoption and implementation of the 99DOTS-based strategy; and 3) evaluating the incremental costs and cost-effectiveness of the 99DOTS-based strategy as compared to routine care from the health system perspective. Our primary hypothesis is that 99DOTS-based TB treatment supervision will improve TB treatment outcomes. Our secondary hypotheses are that the 99DOTS-based strategy will have high uptake among patients and providers, and be cost-effective.

Study design

This is a pragmatic, stepped-wedge randomized trial, with a hybrid type 2 implementation-effectiveness design.(19) We included repeated cross-sectional samples of eligible individuals initiating TB treatment at participating health facilities at 8 time points (months). Patient outcomes were assigned to the health facility and month in which they initiated treatment. As depicted in **Figure 1**, the intervention strategy was sequentially introduced at 3 sites each in Months 2-6, with all sites under routine care in Month 1 and all sites using the intervention strategy in Month 8. Following implementation of the intervention at each site, health facility staff were instructed to offer 99DOTS to all new eligible patients initiating treatment and to continue supervising patients already on treatment using routine care. The month of switch from control to intervention (buffer period) will be excluded from analysis. We chose the stepped-wedge trial design to maximize equity and acceptability (all sites will receive the intervention), minimize logistical constraints associated with introducing the intervention simultaneously at a large number of sites, account for secular outcome trends, and allow for iterative learning and changes in intervention roll-out as would occur during eventual scale-up. We chose a highly pragmatic approach to trial

implementation, as described in sections below, to understand the real-world impact of the 99DOTS-based intervention strategy.

Study Setting

The trial is being conducted at 18 TB treatment units within hospitals and health centers across 15 districts of Uganda. The TB treatment units are affiliated with the Uganda National Tuberculosis and Leprosy Program (NTLP) and provide TB treatment free of charge using a mix of facility- and community-based DOTS. Uganda was chosen as the trial setting due to its high TB burden (200 cases/100,000 in 2018) and low treatment success rate (72% in 2017).(1) Previous studies have found 69-75% of TB patients in Uganda have access to a phone.(21, 22)

Study sites were selected after reviewing 2016 TB treatment outcomes and 2017 TB case finding data reported to the NTLP from all 1514 registered TB treatment units. We included treatment units that 1) diagnosed >10 pulmonary TB patients/month in 2017, 2) were not located within Kampala District (many active ongoing projects in this district), 3) were located within 225 km of Kampala City (for feasibility), and 4) had a pulmonary TB treatment success rate in 2016 <80% (to be able to show an impact).

Of the 1514 treatment units registered with the Uganda NTLP, 23 treatment units met our inclusion criteria (**Figure 2**). The majority (n=1435) diagnosed fewer than 10 TB patients/month in 2017, 17 are located within Kampala district, 31 are not within 225 km of Kampala district, and 9 had a treatment success rate >80% in 2016. Of the 23 remaining treatment units, we selected 18 located in 15 districts (10 in Central, 7 in Eastern and 1 in Western Uganda) in consultation with the NTLP. Project staff visited the Chief Administrative Officers, District Health Officers and Facility Directors for the 18 sites to discuss the study. All signed a memorandum of agreement for their site to participate in the study.

Study participants

All adult patients treated for drug-susceptible pulmonary TB at participating treatment units during the study period will be eligible for inclusion. Children, patients treated for drug-resistant or extrapulmonary TB, and patients transferred to another facility to complete treatment will be

excluded. To be enrolled on 99DOTS, a patient must also have access to a phone. Surveys to assess 99DOTS implementation will be conducted in a random subset of eligible patients and all health workers involved in TB treatment supervision at each treatment unit. Time-and-motion studies to assess costs will also be conducted among health workers involved in TB treatment supervision at each treatment unit.

Routine care and intervention strategies

Routine care. The conventional approach to TB treatment supervision in Uganda is a mix of community- and facility-based DOT, as per NTLP guidelines. At the time of treatment initiation, treatment unit staff record patient demographic and clinical details in the NTLP register and are supposed to provide TB-focused counseling. Most TB patients are treated using community-based DOT, wherein they name a treatment supporter, a family member or non-family community member, and are provided with a 2-week supply of medicines in the first two months (intensive phase) and a one-month supply of medicines in the next four months (continuation phase) of TB treatment. Patients take their medicines from home (with or without observation by a treatment supporter) and return to the health facility for medication refills. At each refill visit, health facility staff are supposed to assess adherence via patient self-report and provide additional counseling. Health facility staff are also supposed to call or visit patients who do not return for refills, but patient follow-up is limited across health facilities.

Intervention. The 99DOTS-based intervention strategy is comprised of four main components that address distinct barriers to successful TB treatment (**Table 1**):

1) Daily automated SMS dosing reminders
2) Daily dosing confirmation using toll-free phone calls
3) Weekly automated interactive voice response (IVR) check-in phone calls
4) Differential management protocol based on dosing history and response to IVR check-in

Table 1. Components of the "DOT to DAT" trial intervention and corresponding barriers addressed.

Component	Barrier addressed

1	Daily dosing reminders via automated SMS	Addresses high cost of clinic visits for patients and assists with memory and planning processes known to be importance to adherence.
2	Daily dosing confirmation via toll-free phone calls	Addresses high cost of clinic visits for patients, lack of real-time information for providers on patient adherence to medications.
3	Weekly check-in via interactive voice response phone calls	Addresses lack of social support and feeling of isolation during TB treatment; shown to be effective in other contexts at increasing connection with CHW and reducing social isolation.
4	Differential management protocol	Addresses limited time and resources among TB treatment unit staff and the need to focus on non-adherent patients.

Formative research using human-centered design was used to adapt the generic 99DOTS product to the local context, including changes to the envelope design and addition of a rotating series of educational/motivational audio messages heard when patients call in to report dosing (details of the formative research will be reported in a separate publication) (**Figure 3**).

TB treatment unit staff will be requested to offer 99DOTS-based treatment supervision to all eligible patients initiating TB treatment, and to register patients who accept 99DOTS-based treatment supervision on the 99DOTS platform via a mobile app. Given the pragmatic nature of the trial, the decision to offer and accept 99DOTS-based treatment supervision will be made by treatment unit staff and patients, respectively. Once registered, treatment unit staff will instruct patients on how to use the 99DOTS pill pack and make a call to the 99DOTS system using the toll-free number revealed when pills are pushed out of the medication blister pack (**Figure 3**). Staff will also help patients personalize their 99DOTS pill pack by choosing a decorative cover, educational or motivational sticker for the inside flap, writing in their health worker's contact information, and selecting a time of day to take their medication (**Figure 3**).

When patients call to confirm dosing, they hear a recorded educational or motivational message about continuing and completing TB treatment. Each dose confirmed via phone call is logged by 99DOTS and reflected on the 99DOTS smartphone app dashboard, viewable by treatment unit staff. During routine drug refill visits (same schedule as described for routine care period), health

facility staff are asked to review adherence data in the 99DOTS app before providing counseling. At the conclusion of the intensive phase of treatment, patients with adherence >90% are offered the option of returning back to the health facility after two months instead of the standard one month.

Health facilities using 99DOTS to manage TB patient treatment will be provided one smartphone per facility, minimal funds to cover cell phone data, and an average of 300,000 USh (approximately $82 USD) per month to facilitate patient follow-up. Treatment unit staff will not be provided any extra compensation to reflect future conditions under eventual scale-up.

Implementation considerations

99DOTS training will occur at each health facility during the month in which it is scheduled to switch to the intervention. Project staff and the District TB Officer will conduct a 2-3 day training jointly at each health facility using standardized training materials. Treatment unit staff will be trained on how to register patients on the 99DOTS platform via a smartphone app, counsel patients regarding use of 99DOTS, use the 99DOTS application to review dosing history, and conduct differential management based on dosing history and response to weekly check-ins. Mentored patient enrollment on 99DOTS will be conducted as part of the training.

During the trial, treatment unit staff will make all decisions regarding management of TB patients in both the routine care and intervention periods. Research staff will not be onsite after training with the exception of 2-3 day quarterly site visits to resolve data cleaning queries and implement surveys and health economic sub-studies. Thus, the implementation is highly pragmatic and meant to approximate how 99DOTS would be used at treatment units in the absence of a research study.

Randomization

The 18 health facilities will be randomly assigned to one of the six allocation sequences (**Figure 1**) using a simple, unrestricted two-stage process. This process will occur by simple drawing during a public randomization ceremony held in Kampala, Uganda. A representative from each TB treatment unit, district health officers, and Uganda NTLP staff will be invited to attend the ceremony. First, health facilities (*i.e.,* clusters) will be randomly assigned into six blocks of three

by having health facility representatives each draw 1 of 18 balls (3 each labeled A-F) from an opaque bag. Blocks will then be randomly assigned to an intervention initiation time, which will occur at equally spaced one-month intervals during the trial, by drawing of 6 balls labeled 1-6 from an opaque bag.

Blinding

Blinding of the assigned intervention is not feasible given intervention implementation at the health facility level. Where possible, the investigators and study staff, with the exception of the statistician and data manager, will be blinded to aggregate TB outcomes by study period.

Data collection and management

Patient-level data collection

Consistent with the pragmatic design, TB treatment outcomes will be assessed by extracting data on all eligible patients from routine Uganda NTLP TB treatment registers used at all treatment units. Project staff will train two health workers at each site (one primary, one backup) identified by the health facility director to take photos of the register every 2-4 weeks for the duration of the project using a camera-enabled smartphone, and to upload the photos to a central secure, password-protected server, only accessible to staff. Health workers will be trained to delete photos from the phone after upload confirmation. Completeness of TB treatment registers will be assessed, and at quarterly site visits, study staff will provide re-training as needed and resolve data cleaning queries. Study staff will extract data from photos of TB registers and enter data into a secure database use Research Electronic Data Capture software (REDCap).(23) Data queries for missing or nonsensical data will be reviewed with treatment unit staff at quarterly site visits.

99DOTS process metrics data collection

During the intervention period at each site, process metric data to assess the implementation of each component of the intervention strategy will be extracted from the 99DOTS server. The server logs all calls made by patients to confirm dosing and doses entered manually by providers, all SMS messages sent to patients, and all IVR calls sent to patients and their responses.

Qualitative data collection

Surveys will be conducted with 10 randomly selected eligible patients enrolled on 99DOTS (5 women and 5 men) and 1-2 eligible providers per site (180 total patients, 18-36 total providers) beginning in Month 10 of the trial to assess the acceptability of the 99DOTS-based intervention strategy. Research staff will contact selected patients by phone to review the verbal consent script, answer questions the patient may have, and administer the survey to consenting patients. Provider surveys and interviews will be conducted during quarterly site visits beginning in Month 13 of the trial to assess factors influencing the adoption and implementation of 99DOTS.

Health system cost data collection

Costing and cost-effectiveness analyses will focus on the health system perspective. Treatment unit staff at each site will be interviewed to gain a more complete understanding of the activities and staff involved in the operations of 99DOTS. Time-and-motion studies of health workers (anticipated to be 3-6 health workers per site, depending on the number of staff involved in delivering 99DOTS) will be carried out at six clinics, sampled to ensure good representation of clinic volume and geography. These time-and-motion studies will be performed on a quarterly basis in conjunction with site visits and will consist of direct observation of all activities conducted by treatment unit staff over the corresponding 1-2 day evaluation period, for a total 6-12 days of observation every three months over the course of the 14-month study period. During these observation periods, the time and resources required to perform all activities related to TB treatment (e.g., medication preparation, contacting patients, observing medication doses, etc.) will be recorded. Additional costing data will be collected to assess the cost of implementing and maintaining 99DOTS technical assistance (budget records from Everwell Health Solutions, the creator of 99DOTS) and the cost at point of care (surveys of project staff to track resource use during trainings). Overhead costs will be estimated using an ingredients approach, incorporating the cost of supplies, building/space, vehicles, and human resources with incorporation of recurrent costs such as security, vehicle maintenance costs, and all supplies (medical and administrative).

Outcomes

Trial outcomes were selected in accordance with the RE-AIM evaluation framework (**Table 2**). The primary effectiveness outcome is the proportion of patients who complete TB treatment, defined as having an outcome of "cured" or "treatment completed" recorded in the unit TB

treatment register. Secondary effectiveness outcomes include the proportion who persist on treatment through the intensive phase (*i.e.,* 56 days of treatment), the proportion lost to follow-up and estimated number of incremental disability-adjusted life years (DALYs) averted. Reach is defined as the proportion of eligible patients enrolled on 99DOTS. Adoption metrics include the proportion of scheduled doses confirmed by patient phone calls and the proportion of weekly IVR check-in calls to which patients send a response. Implementation outcomes include delivery of the intervention (proportions of daily SMS dosing reminders and weekly IVR check-in calls sent by the 99DOTS platform and received on patient handsets), acceptability (as assessed by patient and health worker surveys and interviews) and incremental costs of the 99DOTS-based intervention strategy.

Table 2. Outcome definitions and data source by RE-AIM dimension.

Outcome type	Outcome	Data Source
Reach		
Proportion enrolled on 99DOTS		99DOTS server, Treatment register
Effectiveness		
Primary	Proportion treated successfully	Treatment register
Secondary	Proportion with persistence	Treatment register
Secondary	Proportion lost to follow-up	Treatment register
Secondary	Incremental cost per patient treated successfully	Time and motion surveys; budgetary analysis
Adoption		
Proportion of scheduled doses confirmed by phone call		99DOTS server
Proportion of weekly IVR calls to which patients send a response		99DOTS server
Implementation		
Proportion of daily SMS sent by 99DOTS platform		99DOTS server
Proportion of daily SMS received on patient handset		99DOTS server
Proportion of weekly IVR calls sent by 99DOTS platform		99DOTS server
Proportion of weekly IVR calls received on patient handset		99DOTS server

Power and sample size

The trial aims to demonstrate the superiority of the 99DOTS-based strategy. The sample size was calculated for the primary effectiveness outcome, proportion of patients treated successfully, using formulae appropriate for stepped-wedge trials. A type I error of 5% and power of at least 90% is assumed. Based on 2017 data, the harmonic mean number of patients initiating treatment for drug-susceptible pulmonary TB per month across participating treatment units was 15. Thus, we anticipate that approximately 1890 patients will initiate treatment over the 8-month enrollment period (945 in the pre- and 945 in the post-implementation phases across treatment units). The trial will have 89% power to demonstrate that our strategy increases the proportion of patients treated successfully by 10% or more (assumptions: alpha=0.05; intraclass correlation coefficient, ICC = 0.001 calculated using 2017 NTLP data for the 18 treatment units; pre-implementation treatment success = 51% based on 2017 NTLP data for the 18 treatment units; calculations performed using steppedwedge command in Stata 14).

Analysis

The primary effectiveness analysis will be conducted at the health facility level using multivariable mixed effect logit models with random effects for site and fixed effects for trial period, time, and confounders (using Stata's melogit and meqrlogit commands). Analysis will be done for intention to treat and per protocol (excluding patients who are not enrolled on 99DOTS during the intervention period at each site) populations. Models will adjust for the longitudinal design (indicator variable for each trial month) and clustering by site (random effect for health facility). Patients initiating treatment during the month in which sites switch from routine treatment supervision to the intervention strategy will be excluded (buffer period). Potential confounders, selected *a priori,* including sex, HIV status, disease class (bacteriologically confirmed vs. clinically diagnosed), and TB type (new vs. retreatment), will be included in the model as fixed effects. Secondary effectiveness outcomes (**Table 2**) will be analyzed in the same manner. Subgroup analyses will stratify by gender, HIV status, and health facility. Sensitivity analyses will be performed to assess the robustness of our findings with respect to treatment outcomes for patients lost to follow up, the staged intervention roll out, intervention timing and buffer period, and analysis method.

Quantitative reach, adoption and implementation outcomes will be summarized descriptively. Comparative analyses will identify factors independently associated with reach, adoption and implementation of intervention components. Health economic data will be used to calculate the incremental cost-effectiveness of the intervention strategy from a health system perspective, measured as the incremental cost per successfully completed treatment, comparing 99DOTS relative to routine care.

Ethics and dissemination

Patients can choose to use or not use 99DOTS at any time during the intervention period. 99DOTS enables closer patient monitoring than routine TB treatment supervision, but loss of patient privacy is a potential concern. Data on this are being collected through patient surveys. Because of the low-risk nature of the research, the Principal Investigators will be responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews on a quarterly basis. External monitoring is provided by a Stop TB Partnership project officer and Monitoring and Evaluation consultant. The Principal Investigator will submit regular progress reports, including recommendations on whether the project should continue unchanged, require modification, or close to enrollment.

Ethics approval was granted by institutional review boards at Makerere University School of Public Health and the University of California San Francisco. To ensure that the study captures all eligible adults initiating treatment at study sites, a waiver of informed consent was granted to access routine TB treatment data recorded in standard NTLP registers, such that research staff will not be required to be onsite to enroll and consent patients. The protocol was registered with the Pan-African Clinical Trials Registry (PACTR201808609844917) on 31 August 2018, updated 7 November 2019 and complies with reporting guidelines outlined in the stepped-wedge trial extension of the Consolidated Standards of Reporting Trials.(24) Any major changes in protocol will be approved by the Stop TB Partnership project officer and both ethics committess and registered with the PACTR. The full protocol and statistical code will be made available upon request.

Findings will be disseminated through peer-reviewed publications, presentations at scientific conferences and presentations to key stakeholders. Drs. Cattamanchi, Katamba and Kiwanuka will have access to the final dataset; the participant-level dataset will be made available to other investigators who have IRB approval to analyze the data.

Patient and public involvement

Patients and members of the public were involved throughout the research process. The NTLP was involved in identifying health facilities to participate, selecting study design, and conducting research through partnership with District Health Officers and participating health facilities. Patients, health workers, and community members were involved in intervention design through a human-centered design process, which included several rounds of focus groups and interviews with stakeholders. Health workers at the 18 health facilities implemented 99DOTS without research staff present and assisted in data collection by completing routine TB treatment registers and sending photos of the register to the research team through secure means.

DISCUSSION

99DOTS is a low-cost DAT that has the potential to improve TB treatment outcomes and the patient experience of TB treatment in Uganda and other high-burden settings. Here, we describe the first randomized trial designed to evaluate the effectiveness of a 99DOTS-based TB treatment supervision strategy as part of routine care in a high burden setting. Other novel aspects of the trial include our use of human-centered design to adapt 99DOTS to the local context with the goal of increasing patient engagement with the technology, the use of theory and implementation science frameworks to guide intervention design and evaluation, and our focus on simultaneously assessing implementation and costs to guide scale-up decisions.

Many aspects of this trial are intentionally pragmatic to ensure the outcomes reflect what can be expected under non-research conditions.(25) The study population will include all patients with drug susceptible pulmonary TB, with the exception of children. A waiver of consent was obtained for patient-level data collection such that research staff will not be required to be onsite to enroll and consent patients. Primary and key secondary outcomes will be assessed using routine data available through NTLP registers and the 99DOTS platform, with focused additional data

collection for implementation and cost outcomes. The intervention will be implemented by routine TB treatment unit staff, who also will make all decisions to offer 99DOTS-based treatment supervision to patients. At the same time, the stepped-wedge randomized trial design provides a rigorous assessment of intervention effect. Limitations of such a pragmatic trial design include less control over intervention delivery and potential limited uptake of the intervention given the wide inclusion criteria (all adults initiating treatment for drug-suceptible pulmonary TB). In order to enroll enough patients to assess the effectiveness of the 99DOTS-based intervention, we selected facilities that treat larger numbers of TB patients. Uptake and effectiveness of 99DOTS may be different at lower volume health centers.

In summary, this pragmatic, hybrid type 2 effectiveness-implementation trial is well poised to assess both the effectiveness of an adapted 99DOTS-based intervention and potential barriers and facilitators to its scale-up if successful. The design and implementation of this trial intend to generate results to inform decisions on whether and how to implement 99DOTS in Uganda and other high burden countries.

References

1. World Health Organization. Global Tuberculosis Report. 2019.
2. Izudi J, Tamwesigire IK, Bajunirwe F. Explaining the successes and failures of tuberculosis treatment programs; a tale of two regions in rural eastern Uganda. BMC Health Services Research. 2019;19(1):979.
3. Fiseha D, Demissie M. Assessment of Directly Observed Therapy (DOT) following tuberculosis regimen change in Addis Ababa, Ethiopia: a qualitative study. BMC Infect Dis. 2015;15:405.
4. GSMA Intelligence. The Mobile Economy - Africa London: GSMA; 2016 [Available from: https://www.gsma.com/mobileeconomy/africa/.
5. World Health Organization. Treatment of tuberculosis: guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Geneva; 2017.
6. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS medicine. 2015;12(9):e1001876-e.
7. Subbaraman R, de Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMJ Glob Health. 2018;3(5):e001018.
8. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med. 2015;12(9):e1001876.
9. Liu X, Blaschke T, Thomas B, De Geest S, Jiang S, Gao Y, et al. Usability of a Medication Event Reminder Monitor System (MERM) by Providers and Patients to Improve Adherence in the Management of Tuberculosis. Int J Environ Res Public Health. 2017;14(10).
10. Thakkar D, Piparva KG, Lakkad SG. A pilot project: 99DOTS information communication technology-based approach for tuberculosis treatment in Rajkot district. Lung India. 2019;36(2):108-11.
11. Cross A, Gupta N, Liu B, Nair V, Kumar A, Kuttan R, et al. 99DOTS: A Low-Cost Approach to Monitoring and Improving Medication Adherence. Tenth International Conference on Information and Communication Technologies and Development. ICTD. 2019.
12. Green LW, Kreuter MW. Health promotion planning: An educational and ecological approach: McGraw-Hill; 1993.
13. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77.
14. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. Implement Sci. 2012;7:38.
15. Sarfaraz J. Unified theory of acceptance and use of technology (Utaut) model-mobile banking. Journal of Internet Banking and Commerce. 2017;22(3):1-20.
16. Venkatesh V, Thong JY, Xu X. Consumer acceptance and use of information technology: extending the unified theory of acceptance and use of technology. MIS quarterly. 2012:157-78.

17. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. American journal of public health. 1999;89(9):1322-7.
18. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. American journal of public health. 2013;103(6):e38-e46.
19. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.
20. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
21. Ggita JM, Ojok C, Meyer AJ, Farr K, Shete PB, Ochom E, et al. Patterns of usage and preferences of users for tuberculosis-related text messages and voice calls in Uganda. Int J Tuberc Lung Dis. 2018;22(5):530-6.
22. Babirye D, Shete PB, Farr K, Nalugwa T, Ojok C, Nantale M, et al. Feasibility of a short message service (SMS) intervention to deliver tuberculosis testing results in peri-urban and rural Uganda. J Clin Tuberc Other Mycobact Dis. 2019;16:100110.
23. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
24. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614.
25. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ : British Medical Journal. 2015;350:h2147.

Acknowledgements

We would like to thank the patients and health facility staff who make this research possible, as well as the Uganda NTLP, for their collaboration on this protocol.

Authors' contributions

AC, AKa, and NK conceived and designed the study. RC, AKi, ML, CN, LKT, ASN, JG, PT, DB, DO, CB, AT, DP, AM, DD, TS, AC and AKa participated in implementation of the study. RC, AKi, AC, and AKa drafted the manuscript. All authors reviewed and approved the manuscript.

Funding

This Project is supported by the Stop TB Partnership's TB REACH initiative, grant number STBP/TBREACH/GSA/W6-37, which is funded by the Government of Canada, the Bill & Melinda Gates Foundation, and the United States Agency for International Development. The study sponsor is not involved in data collection, analysis or interpretation.

Competing Interests

The authors have no conflicts of interest to report.

Figure 1. 99DOTS Randomization and Enrollment Schedule. The trial includes 18 health facilities divided into 6 equal size blocks (3 health facilities per block). The health facilities all continue routine TB treatment supervision in Month 1, begin switching to the 99DOTS-based intervention strategy in Month 2 (one block per month in a random order), and all use the intervention strategy in Month 8.

Figure 2. **Flow diagram of TB treatment units and patients included in the DOT to DAT trial**. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Figure 3. **Original and adapted versions of the 99DOTS envelope**. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space for writing in the health worker's name and phone number, simplified pictorial instructions for taking pills, and motivational imagery on the inside cover (bottom middle); and provide simplified guide to the order in which to take pills on the back cover (bottom

right). In addition, the audio tone heard when patients make daily phone calls to report medication dosing was replaced with a rotating series of educational or motivational messages recorded by local health workers.

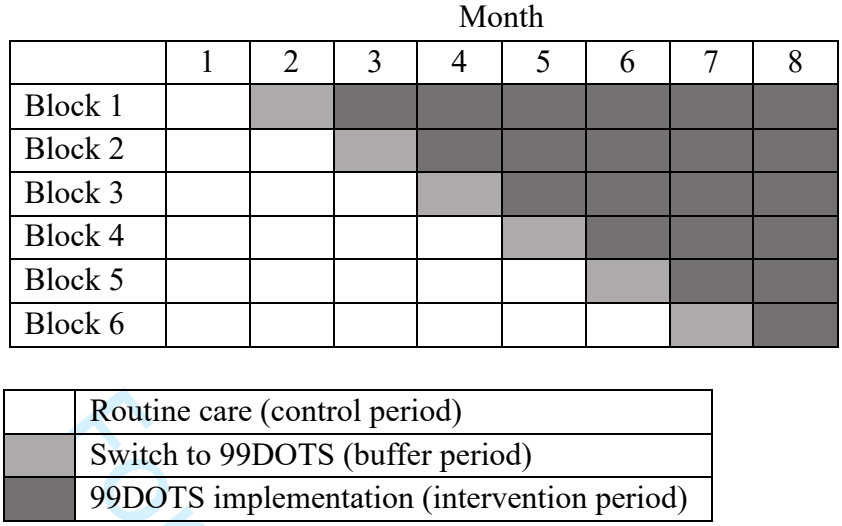


Figure 1. 99DOTS Randomization and Enrollment Schedule. The trial includes 18 health facilities divided into 6 equal size blocks (3 health facilities per block), each block representing an allocation sequence. The health facilities all continue routine TB treatment supervision in Month 1, begin switching to the 99DOTS-based intervention strategy in Month 2 (one block per month in a random order), and all use the intervention strategy in Month 8.

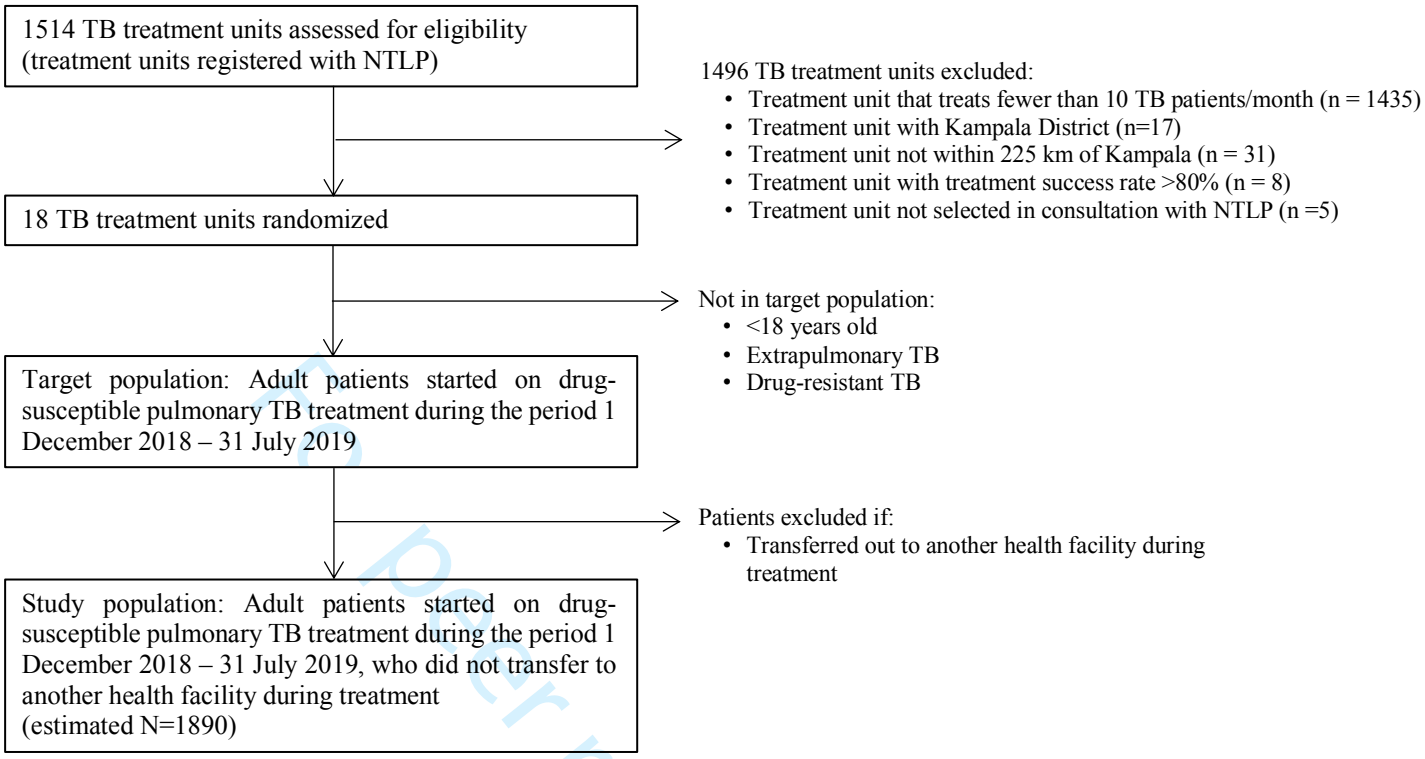
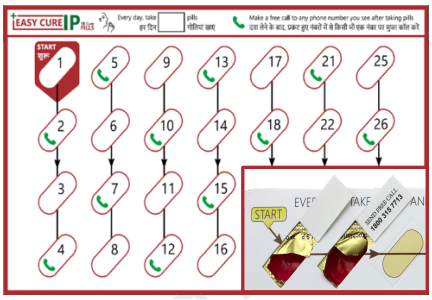


Figure 2. **Flow diagram of TB treatment units and patients included in the DOT to DAT trial**. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Original 99DOTS Envelope

Front of envelope

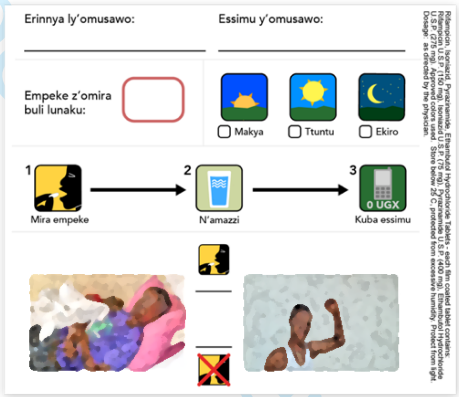


Back of envelope

Adapted 99DOTS envelope

Front cover

Inside cover



Back of envelope

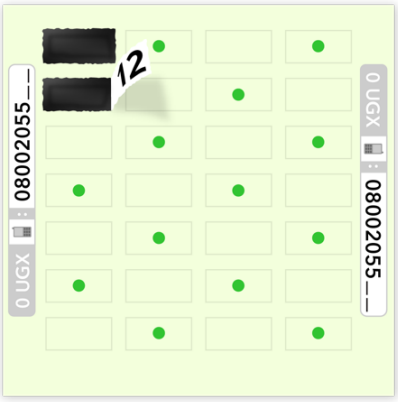


Figure 3. **Original and adapted versions of the 99DOTS envelope**. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space for writing in the health worker's name and phone number, simplified pictorial instructions for taking pills, and motivational imagery on the inside cover (bottom middle); and provide simplified guide to the order in which to take pills on the back cover (bottom right). In addition, the audio tone heard when patients make daily phone calls to report medication dosing was replaced with a rotating series of educational or motivational messages recorded by local health workers.

Supplementary materials 3: Checklist of information to include when reporting a stepped wedge cluster randomised trial (SW-CRT)

Topic	Item no	Checklist item	Page no
Title and abstract			
	1a	Identification as a SW-CRT in the title.	1
	1b	Structured summary of trial design, methods, results, and conclusions (see separate SW-CRT checklist for abstracts).	2
Introduction			
Background and objectives	2a	Scientific background. Rationale for using a cluster design and rationale for using a stepped wedge design.	5
	2b	Specific objectives or hypotheses.	5
Methods			
Trial design	3a	Description and diagram of trial design including definition of cluster, number of sequences, number of clusters randomised to each sequence, number of periods, duration of time between each step, and whether the participants assessed in different periods are the same people, different people, or a mixture.	5, Figure
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.	N/A
Participants	4a	Eligibility criteria for clusters and participants.	6
	4b	Settings and locations where the data were collected.	6
Interventions	5	The intervention and control conditions with sufficient details to allow replication, including whether the intervention was maintained or repeated, and whether it was delivered at the cluster level, the individual participant level, or both.	7-9
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.	11-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons.	N/A
Sample size	7a	How sample size was determined. Method of calculation and relevant parameters with sufficient detail so the calculation can be replicated. Assumptions made about correlations between outcomes of participants from the same cluster. (see separate checklist for SW-CRT sample size items).	12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines.	N/A
Randomisation			
Sequence generation	8a	Method used to generate the random allocation to the sequences of treatments.	9-10
	8b	Type of randomisation; details of any constrained randomisation or stratification, if used.	9-10
Allocation concealment mechanism	9	Specification that allocation was based on clusters; description of any methods used to conceal the allocation from the clusters until after recruitment.	9-10
Implementation	10a	Who generated the randomisation schedule, who enrolled clusters, and who assigned clusters to sequences.	9-10
	10b	Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling; continuous recruitment or ascertainment; or recruitment at a fixed point in time), including who recruited or identified participants.	6
	10c	Whether, from whom and when consent was sought and for what; whether this differed between treatment conditions.	14
Blinding	11a	If done, who was blinded after assignment to sequences (eg, cluster level participants, individual level participants, those assessing outcomes) and how.	10
	11b	If relevant, description of the similarity of treatments.	7-9
Statistical methods	12a	Statistical methods used to compare treatment conditions for primary and secondary outcomes including how time effects, clustering and repeated measures were taken into account.	13
	12b	Methods for additional analyses, such as subgroup analyses, sensitivity analyses, and adjusted analyses.	13-14

(*Continued*)

Supplementary materials 3 (*Continued*)

Topic	Item no	Checklist item	Page no
Results			
Participant flow (a diagram is strongly recommended)	13a	For each treatment condition or allocated sequence, the numbers of clusters and participants who were assessed for eligibility, were randomly assigned, received intended treatments, and were analysed for the primary outcome (see separate SW-CRT flow chart).	6, Figure
	13b	For each treatment condition or allocated sequence, losses and exclusions for both clusters and participants with reasons.	6, Figure
Recruitment	14a	Dates defining the steps, initiation of intervention, and deviations from planned dates. Dates defining recruitment and follow-up for participants.	6
	14b	Why the trial ended or was stopped.	N/A
Baseline data	15	Baseline characteristics for the individual and cluster levels as applicable for each treatment condition or allocated sequence.	N/A
Numbers analysed	16	The number of observations and clusters included in each analysis for each treatment condition and whether the analysis was according to the allocated schedule.	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each treatment condition, and the estimated effect size and its precision (such as 95% confidence interval); any correlations (or covariances) and time effects estimated in the analysis.	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended.	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.	N/A
Harms	19	Important harms or unintended effects in each treatment condition (for specific guidance see CONSORT for harms).	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses.	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings. Generalisability to clusters or individual participants, or both (as relevant).	15-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.	N/A
Other information			
Registration	23	Registration number and name of trial registry.	14
Protocol	24	Where the full trial protocol can be accessed, if available.	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), and the role of funders.	19
Research ethics review	26	Whether the study was approved by a research ethics committee, with identification of the review committee(s). Justification for any waiver or modification of informed consent requirements.	14

This checklist has been taken from table 3 in *BMJ* 2018;363:k1614, as a standalone document for readers to print out or fill in electronically.

BMJ Open

Study protocol and implementation details for a pragmatic, stepped-wedge cluster randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039895.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Nov-2020
Complete List of Authors:	Crowder, Rebecca; University of California San Francisco, Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital Kityamuwesi, Alex; Uganda Tuberculosis Implementation Research Consortium, Kiwanuka, Noah; Makerere University College of Health Sciences, School of Public Heatlh Lamunu, Maureen; Uganda Tuberculosis Implementation Research Consortium, Namale, Catherine; Uganda Tuberculosis Implementation Research Consortium, Tinka, Lynn; Uganda Tuberculosis Implementation Research Consortium, Nakate, Agnes; Uganda Tuberculosis Implementation Research Consortium, Ggita, Joseph; Uganda Tuberculosis Implementation Research Consortium, Turimumahoro, Patricia; Uganda Tuberculosis Implementation Research Consortium, Babirye, Diana; Uganda Tuberculosis Implementation Research Consortium, Oyuku, Denis; Uganda Tuberculosis Implementation Research Consortium, Berger, Christopher; University of California San Francisco, Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital Tucker, Austin; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology Patel, Devika; University of California San Francisco, The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital Sammann, Amanda; University of California San Francisco, The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital Dowdy, DW; Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology Stavia, Turyahabwe; Republic of Uganda Ministry of Health, National Tuberculosis and Leprosy Program Cattamanchi, A; University of California San Francisco, Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, San

	Francisco General Hospital Katamba, Achilles; Makerere University College of Health Sciences, Clinical Epidemiology and Biostatistics Unit; Uganda Tuberculosis Implementation Research Consortium, Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Study protocol and implementation details for a pragmatic, stepped-wedge cluster randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion

Authors: Rebecca Crowder[1]*, Alex Kityamuwesi[2]*, Noah Kiwanuka[3], Maureen Lamunu[2], Catherine Namale[2], Lynn Kunihira Tinka[2], Agnes Sanyu Nakate[2], Joseph Ggita[2], Patricia Turimumahoro[2], Diana Babirye[2], Denis Oyuku[2], Christopher Berger[1], Austin Tucker[4], Devika Patel[5], Amanda Sammann[5], David Dowdy[2,4], Turyahabwe Stavia[6], Adithya Cattamanchi[1,2], Achilles Katamba[2,3]

* Authors contributed equally

Affiliations:

1. Curry International Tuberculosis Center and Division of Pulmonary and Critical Care Medicine, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
2. Uganda Tuberculosis Implementation Research Consortium, Kampala, Uganda
3. School of Public Health, Makerere University College of Health Sciences, Kampala, Uganda
4. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
5. The Better Lab, Department of Surgery, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
6. National Tuberculosis and Leprosy Program, Uganda Ministry of Health, Kampala, Uganda

Correspondence to:

Achilles Katamba
axk95@case.edu
Makerere University College of Health Sciences,
Clinical Epidemiology and Biostatistics Unit
Mulago Hill Road
Clinical Research Building Floor 3 Room 3.1
Kampala, Uganda 21696
+256-772-575-038

Abstract word count: 264

Manuscript word count (excluding tables and figures): 4,307

ABSTRACT

Introduction: Low-cost digital adherence technologies (DAT) such as 99DOTS have emerged as an alternative to directly observed therapy, (DOT), the current standard for TB treatment supervision. However, there are limited data to support DAT scale-up. The "DOT to DAT" trial aims to evaluate the effectiveness and implementation of a 99DOTS-based TB treatment supervision strategy.

Methods and analysis: This is a pragmatic, stepped-wedge cluster randomized trial, with hybrid type 2 effectiveness-implementation design. The trial will include all adults (estimated N=1890) treated for drug-susceptible pulmonary TB over an 8-month period at 18 TB treatment units in Uganda. Three sites per month will switch from routine care (DOT) to the intervention (99DOTS-based treatment supervision) beginning in Month 2, with the order determined randomly. 99DOTS enables patients to be monitored while self-administering TB medicines. Patients receive daily automated SMS dosing reminders and confirm dosing by calling toll-free numbers. The primary effectiveness outcome is the proportion of patients completing TB treatment. With 18 clusters randomized into 6 steps and an average cluster size of 15 patients per month, the study will have 89% power to detect a 10% or greater increase in treatment completion between the routine care and intervention periods. Secondary outcomes include more proximal effectiveness measures as well as quantitative and qualitative assessments of the reach, adoption and implementation of the intervention.

Ethics and dissemination: Ethics approval was granted by institutional review boards at Makerere University School of Public Health and the University of California San Francisco. Findings will be disseminated through peer-reviewed publications, presentations at scientific conferences and presentations to key stakeholders.

Trial registration number: PACTR201808609844917

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomized trial to evaluate a 99DOTS-based strategy for TB treatment supervision.
- The intervention was designed using the PRECEDE framework and adapted for local context in Uganda using human-centered design.
- Trial outcomes were selected using the RE-AIM framework.
- The intervention was implemented by health facility staff and will be assessed using routinely collected data to approximate the real-world impact of this intervention.
- Adherence is not a primary outcome of this trial.

INTRODUCTION

Tuberculosis (TB) is the leading infectious cause of death worldwide despite being a preventable and curable disease.(1) Poor adherence to medication continues to be a major obstacle to TB elimination, resulting in prolonged infectiousness, emergence of multidrug resistance, and increased risk of poor treatment outcomes. The World Health Organization (WHO)-recommended strategy, directly observed therapy short-course (DOTS), has been the standard-of-care for TB treatment supervision since the 1990s. As part of this strategy, a health worker is expected to observe patients swallow each dose of anti-TB medication. However, directly observed therapy (DOT) is time-consuming, costly and inconvenient for both patients and providers, while its implementation is also difficult to monitor.(2, 3) Not surprisingly, TB treatment success rates remain below the 90% target in most high-burden countries, despite reported DOT coverage over 90%.(1)

With the increase in mobile phone penetration among patients and healthcare workers in high TB burden countries,(4) digital adherence technologies (DATs) could address some of the challenges associated with implementation of the DOTS strategy in a patient-centered manner. To date, such technologies have received only a conditional recommendation by the WHO due to very low quality of evidence.(5) The first randomized trial of a DAT found that SMS reminders alone did not improve medication adherence, but a medication event reminder monitor did.(6) However, treatment outcomes did not improve and both trials and programmatic research have shown variable uptake of DAT.(7-10)

The "DOT to DAT" trial aims to evaluate the effectiveness, implementation and cost-effectiveness of a culturally and contextually adapted version of 99DOTS in Uganda. 99DOTS is a low-cost DAT wherein patients self-report medication adherence by calling toll-free phone numbers hidden underneath pills in blister packs.(11) We present the research methods used for the first randomized trial to evaluate the effectiveness and implementation of a 99DOTS-based strategy for TB treatment supervision in routine care settings.

Conceptual basis for trial design

Numerous conceptual frameworks have emerged to improve the implementation and success of health interventions through theory-based design and evaluation. The PRECEDE framework(12) guided the development of the 99DOTS-based intervention strategy, while the RE-AIM framework guided its comprehensive evaluation. Behavior change models including the Theoretical Domains Framework (TDF)(13, 14) and the Unified Theory of Acceptance and Use of Technology (UTAUT)(15, 16) guided the assessment and analysis of patient- and provider-level barriers to adoption and implementation of 99DOTS.

The PRECEDE framework emphasizes the need for multi-faceted health promotion interventions to address predisposing, enabling, and reinforcing factors in order to achieve behavior change.(12) The 99DOTS-based intervention was designed to address key predisposing (social isolation and the high direct and indirect cost of clinic visits), enabling (inability of health facility staff to focus limited time and resources on non-adherent patients), and reinforcing (a lack of real-time information on patient adherence to medications) factors related to TB treatment adherence identified through the literature and formative human factors research that preceded the trial.(11)

The RE-AIM framework was designed to ensure that trials not only assess the effect of interventions but also their translatability and public health impact.(17, 18) This hybrid type 2 trial therefore focuses on the effectiveness of the 99DOTS-based intervention in improving TB treatment outcomes, but concurrently examines its reach into the target population, adoption by target settings and staff, and implementation fidelity and costs.(19) The goal of assessing

translatability and public health impact is further enhanced through pragmatic design choices for each element of the trial in order to maximize applicability in real-world settings.(20)

METHODS AND ANALYSIS

Study aims

The primary aim of the trial is to determine whether a 99DOTS-based strategy increases the proportion of patients who complete TB treatment in comparison to routine care. Secondary aims include 1) comparing short-term treatment outcomes and loss to follow-up between the intervention and routine care arms; 2) assessing the reach, adoption and implementation of the 99DOTS-based strategy; and 3) evaluating the incremental costs and cost-effectiveness of the 99DOTS-based strategy as compared to routine care from the health system perspective. Our primary hypothesis is that 99DOTS-based TB treatment supervision will improve TB treatment outcomes. Our secondary hypotheses are that the 99DOTS-based strategy will have high uptake among patients and providers, and be cost-effective.

Study design

This is a pragmatic, stepped-wedge randomized trial, with a hybrid type 2 implementation-effectiveness design.(19) We included repeated cross-sectional samples of eligible individuals initiating TB treatment at participating health facilities at 8 time points (months). Patient outcomes were assigned to the health facility and month in which they initiated treatment. As depicted in **Figure 1**, the intervention strategy was sequentially introduced at 3 sites each in Months 2-6, with all sites under routine care in Month 1 and all sites using the intervention strategy in Month 8. Following implementation of the intervention at each site, health facility staff were instructed to offer 99DOTS to all new eligible patients initiating treatment and to continue supervising patients already on treatment using routine care. The month of switch from control to intervention (buffer period) will be excluded from analysis. We chose the stepped-wedge trial design to maximize equity and acceptability (all sites will receive the intervention), minimize logistical constraints associated with introducing the intervention simultaneously at a large number of sites, account for secular outcome trends, and allow for iterative learning and changes in intervention roll-out as would occur during eventual scale-up. We chose a highly pragmatic approach to trial

implementation, as described in sections below, to understand the real-world impact of the 99DOTS-based intervention strategy.

Study Setting

The trial is being conducted at 18 TB treatment units within hospitals and health centers across 15 districts of Uganda. The TB treatment units are affiliated with the Uganda National Tuberculosis and Leprosy Program (NTLP) and provide TB treatment free of charge using a mix of facility- and community-based DOTS. Uganda was chosen as the trial setting due to its high TB burden (200 cases/100,000 in 2018) and low treatment success rate (72% in 2017).(1) Previous studies have found 69-75% of TB patients in Uganda have access to a phone.(21, 22)

Study sites were selected after reviewing 2016 TB treatment outcomes and 2017 TB case finding data reported to the NTLP from all 1514 registered TB treatment units. We included treatment units that 1) diagnosed >10 pulmonary TB patients/month in 2017, 2) were not located within Kampala District (many active ongoing projects in this district), 3) were located within 225 km of Kampala City (for feasibility), and 4) had a pulmonary TB treatment success rate in 2016 <80% (to be able to show an impact).

Of the 1514 treatment units registered with the Uganda NTLP, 23 treatment units met our inclusion criteria (**Figure 2**). The majority (n=1435) diagnosed fewer than 10 TB patients/month in 2017, 17 are located within Kampala district, 31 are not within 225 km of Kampala district, and 9 had a treatment success rate >80% in 2016. Of the 23 remaining treatment units, we selected 18 located in 15 districts (10 in Central, 7 in Eastern and 1 in Western Uganda) in consultation with the NTLP. Project staff visited the Chief Administrative Officers, District Health Officers and Facility Directors for the 18 sites to discuss the study. All signed a memorandum of agreement for their site to participate in the study.

Study participants

All adult patients treated for drug-susceptible pulmonary TB at participating treatment units during the study period will be eligible for inclusion. Children, patients treated for drug-resistant or extrapulmonary TB, and patients transferred to another facility to complete treatment will be

excluded. To be enrolled on 99DOTS, a patient must also have access to a phone. Surveys to assess 99DOTS implementation will be conducted in a random subset of eligible patients and all health workers involved in TB treatment supervision at each treatment unit. Time-and-motion studies to assess costs will also be conducted among health workers involved in TB treatment supervision at each treatment unit.

Routine care and intervention strategies

Routine care. The conventional approach to TB treatment supervision in Uganda is a mix of community- and facility-based DOT, as per NTLP guidelines. At the time of treatment initiation, treatment unit staff record patient demographic and clinical details in the NTLP register and are supposed to provide TB-focused counseling. Most TB patients are treated using community-based DOT, wherein they name a treatment supporter, a family member or non-family community member, and are provided with a 2-week supply of medicines in the first two months (intensive phase) and a one-month supply of medicines in the next four months (continuation phase) of TB treatment. Patients take their medicines from home (with or without observation by a treatment supporter) and return to the health facility for medication refills. At each refill visit, health facility staff are supposed to assess adherence via patient self-report and provide additional counseling. Health facility staff are also supposed to call or visit patients who do not return for refills, but patient follow-up is limited across health facilities.

Intervention. The 99DOTS-based intervention strategy is comprised of four main components that address distinct barriers to successful TB treatment (**Table 1**):

1) Daily automated SMS dosing reminders
2) Daily dosing confirmation using toll-free phone calls
3) Weekly automated interactive voice response (IVR) check-in phone calls
4) Differential management protocol based on dosing history and response to IVR check-in

Table 1. Components of the "DOT to DAT" trial intervention and corresponding barriers addressed.

Component	Barrier addressed

1	Daily dosing reminders via automated SMS	Addresses high cost of clinic visits for patients and assists with memory and planning processes known to be importance to adherence.
2	Daily dosing confirmation via toll-free phone calls	Addresses high cost of clinic visits for patients, lack of real-time information for providers on patient adherence to medications.
3	Weekly check-in via interactive voice response phone calls	Addresses lack of social support and feeling of isolation during TB treatment; shown to be effective in other contexts at increasing connection with CHW and reducing social isolation.
4	Differential management protocol	Addresses limited time and resources among TB treatment unit staff and the need to focus on non-adherent patients.

Formative research using human-centered design was used to adapt the generic 99DOTS product to the local context, including changes to the envelope design and addition of a rotating series of educational/motivational audio messages heard when patients call in to report dosing (details of the formative research will be reported in a separate publication) (**Figure 3**).

TB treatment unit staff will be requested to offer 99DOTS-based treatment supervision to all eligible patients initiating TB treatment, and to register patients who accept 99DOTS-based treatment supervision on the 99DOTS platform via a mobile app. Given the pragmatic nature of the trial, the decision to offer and accept 99DOTS-based treatment supervision will be made by treatment unit staff and patients, respectively. Once registered, treatment unit staff will instruct patients on how to use the 99DOTS pill pack and make a call to the 99DOTS system using the toll-free number revealed when pills are pushed out of the medication blister pack (**Figure 3**). Staff will also help patients personalize their 99DOTS pill pack by choosing a decorative cover, educational or motivational sticker for the inside flap, writing in their health worker's contact information, and selecting a time of day to take their medication (**Figure 3**).

When patients call to confirm dosing, they hear a recorded educational or motivational message about continuing and completing TB treatment. Each dose confirmed via phone call is logged by 99DOTS and reflected on the 99DOTS smartphone app dashboard, viewable by treatment unit staff. During routine drug refill visits (same schedule as described for routine care period), health

facility staff are asked to review adherence data in the 99DOTS app before providing counseling. At the conclusion of the intensive phase of treatment, patients with adherence >90% are offered the option of returning back to the health facility after two months instead of the standard one month.

Health facilities using 99DOTS to manage TB patient treatment will be provided one smartphone per facility, minimal funds to cover cell phone data, and an average of 300,000 USh (approximately $82 USD) per month to facilitate patient follow-up. Treatment unit staff will not be provided any extra compensation to reflect future conditions under eventual scale-up.

Implementation considerations

99DOTS training will occur at each health facility during the month in which it is scheduled to switch to the intervention. Project staff and the District TB Officer will conduct a 2-3 day training jointly at each health facility using standardized training materials. Treatment unit staff will be trained on how to register patients on the 99DOTS platform via a smartphone app, counsel patients regarding use of 99DOTS, use the 99DOTS application to review dosing history, and conduct differential management based on dosing history and response to weekly check-ins. Mentored patient enrollment on 99DOTS will be conducted as part of the training.

During the trial, treatment unit staff will make all decisions regarding management of TB patients in both the routine care and intervention periods. Research staff will not be onsite after training with the exception of 2-3 day quarterly site visits to resolve data cleaning queries and implement surveys and health economic sub-studies. Thus, the implementation is highly pragmatic and meant to approximate how 99DOTS would be used at treatment units in the absence of a research study.

Randomization

The 18 health facilities will be randomly assigned to one of the six allocation sequences (**Figure 1**) using a simple, unrestricted two-stage process. This process will occur by simple drawing during a public randomization ceremony held in Kampala, Uganda. A representative from each TB treatment unit, district health officers, and Uganda NTLP staff will be invited to attend the ceremony. First, health facilities (*i.e.,* clusters) will be randomly assigned into six blocks of three

by having health facility representatives each draw 1 of 18 balls (3 each labeled A-F) from an opaque bag. Blocks will then be randomly assigned to an intervention initiation time, which will occur at equally spaced one-month intervals during the trial, by drawing of 6 balls labeled 1-6 from an opaque bag.

Blinding

Blinding of the assigned intervention is not feasible given intervention implementation at the health facility level. Where possible, the investigators and study staff, with the exception of the statistician and data manager, will be blinded to aggregate TB outcomes by study period.

Data collection and management

Patient-level data collection

Consistent with the pragmatic design, TB treatment outcomes will be assessed by extracting data on all eligible patients from routine Uganda NTLP TB treatment registers used at all treatment units. Project staff will train two health workers at each site (one primary, one backup) identified by the health facility director to take photos of the register every 2-4 weeks for the duration of the project using a camera-enabled smartphone, and to upload the photos to a central secure, password-protected server, only accessible to staff. Health workers will be trained to delete photos from the phone after upload confirmation. Completeness of TB treatment registers will be assessed, and at quarterly site visits, study staff will provide re-training as needed and resolve data cleaning queries. Study staff will extract data from photos of TB registers and enter data into a secure database use Research Electronic Data Capture software (REDCap).(23) Data queries for missing or nonsensical data will be reviewed with treatment unit staff at quarterly site visits.

99DOTS process metrics data collection

During the intervention period at each site, process metric data to assess the implementation of each component of the intervention strategy will be extracted from the 99DOTS server. The server logs all calls made by patients to confirm dosing and doses entered manually by providers, all SMS messages sent to patients, and all IVR calls sent to patients and their responses.

Qualitative data collection

Surveys will be conducted with 10 randomly selected eligible patients enrolled on 99DOTS (5 women and 5 men) and 1-2 eligible providers per site (180 total patients, 18-36 total providers) beginning in Month 10 of the trial to assess the acceptability of the 99DOTS-based intervention strategy. Research staff will contact selected patients by phone to review the verbal consent script, answer questions the patient may have, and administer the survey to consenting patients. Provider surveys and interviews will be conducted during quarterly site visits beginning in Month 13 of the trial to assess factors influencing the adoption and implementation of 99DOTS.

Health system cost data collection

Costing and cost-effectiveness analyses will focus on the health system perspective. Treatment unit staff at each site will be interviewed to gain a more complete understanding of the activities and staff involved in the operations of 99DOTS. Time-and-motion studies of health workers (anticipated to be 3-6 health workers per site, depending on the number of staff involved in delivering 99DOTS) will be carried out at six clinics, sampled to ensure good representation of clinic volume and geography. These time-and-motion studies will be performed on a quarterly basis in conjunction with site visits and will consist of direct observation of all activities conducted by treatment unit staff over the corresponding 1-2 day evaluation period, for a total 6-12 days of observation every three months over the course of the 14-month study period. During these observation periods, the time and resources required to perform all activities related to TB treatment (e.g., medication preparation, contacting patients, observing medication doses, etc.) will be recorded. Additional costing data will be collected to assess the cost of implementing and maintaining 99DOTS technical assistance (budget records from Everwell Health Solutions, the creator of 99DOTS) and the cost at point of care (surveys of project staff to track resource use during trainings). Overhead costs will be estimated using an ingredients approach, incorporating the cost of supplies, building/space, vehicles, and human resources with incorporation of recurrent costs such as security, vehicle maintenance costs, and all supplies (medical and administrative).

Outcomes

Trial outcomes were selected in accordance with the RE-AIM evaluation framework (**Table 2**). The primary effectiveness outcome is the proportion of patients who complete TB treatment, defined as having an outcome of "cured" or "treatment completed" recorded in the unit TB

treatment register. Secondary effectiveness outcomes include the proportion who persist on treatment through the intensive phase (*i.e.,* 56 days of treatment), the proportion lost to follow-up and estimated number of incremental disability-adjusted life years (DALYs) averted. Reach is defined as the proportion of eligible patients enrolled on 99DOTS. Adoption metrics include the proportion of scheduled doses confirmed by patient phone calls and the proportion of weekly IVR check-in calls to which patients send a response. Implementation outcomes include delivery of the intervention (proportions of daily SMS dosing reminders and weekly IVR check-in calls sent by the 99DOTS platform and received on patient handsets), acceptability (as assessed by patient and health worker surveys and interviews) and incremental costs of the 99DOTS-based intervention strategy.

Table 2. Outcome definitions and data source by RE-AIM dimension.

Outcome type	Outcome	Data Source
Reach		
Proportion enrolled on 99DOTS		99DOTS server, Treatment register
Effectiveness		
Primary	Proportion treated successfully	Treatment register
Secondary	Proportion with persistence	Treatment register
Secondary	Proportion lost to follow-up	Treatment register
Secondary	Incremental cost per patient treated successfully	Time and motion surveys; budgetary analysis
Adoption		
Proportion of scheduled doses confirmed by phone call		99DOTS server
Proportion of weekly IVR calls to which patients send a response		99DOTS server
Implementation		
Proportion of daily SMS sent by 99DOTS platform		99DOTS server
Proportion of daily SMS received on patient handset		99DOTS server
Proportion of weekly IVR calls sent by 99DOTS platform		99DOTS server
Proportion of weekly IVR calls received on patient handset		99DOTS server

Power and sample size

The trial aims to demonstrate the superiority of the 99DOTS-based strategy. The sample size was calculated for the primary effectiveness outcome, proportion of patients treated successfully, using formulae appropriate for stepped-wedge trials. A type I error of 5% and power of at least 90% is assumed. Based on 2017 data, the harmonic mean number of patients initiating treatment for drug-susceptible pulmonary TB per month across participating treatment units was 15. Thus, we anticipate that approximately 1890 patients will initiate treatment over the 8-month enrollment period (945 in the pre- and 945 in the post-implementation phases across treatment units). The trial will have 89% power to demonstrate that our strategy increases the proportion of patients treated successfully by 10% or more (assumptions: alpha=0.05; intraclass correlation coefficient, ICC = 0.001 calculated using 2017 NTLP data for the 18 treatment units; pre-implementation treatment success = 51% based on 2017 NTLP data for the 18 treatment units; calculations performed using steppedwedge command in Stata 14).

Analysis

The primary effectiveness analysis will be conducted at the health facility level using multivariable mixed effect logit models with random effects for site and fixed effects for trial period, time, and confounders (using Stata's melogit and meqrlogit commands). Analysis will be done for intention to treat (all eligible patients) and per protocol (excluding patients who are not enrolled on 99DOTS during the intervention period at each site) populations. Models will adjust for the longitudinal design (indicator variable for each trial month) and clustering by site (random effect for health facility). Patients initiating treatment during the month in which sites switch from routine treatment supervision to the intervention strategy will be excluded (buffer period). Potential confounders, selected *a priori,* including sex, HIV status, disease class (bacteriologically confirmed vs. clinically diagnosed), and TB type (new vs. retreatment), will be included in the model as fixed effects. Secondary effectiveness outcomes (**Table 2**) will be analyzed in the same manner. Subgroup analyses will stratify by gender, HIV status, and health facility. To further assess the robustness of our findings, we will conduct sensitivity analyses that include patients who initiated treatment during the buffer period, impute outcomes for patients lost to follow up and compare treatment outcomes using permutation tests.(24)

Quantitative reach, adoption and implementation outcomes will be summarized descriptively. Comparative analyses will identify factors independently associated with reach, adoption and implementation of intervention components. Health economic data will be used to calculate the incremental cost-effectiveness of the intervention strategy from a health system perspective, measured as the incremental cost per successfully completed treatment, comparing 99DOTS relative to routine care.

Ethics and dissemination

Patients can choose to use or not use 99DOTS at any time during the intervention period. 99DOTS enables closer patient monitoring than routine TB treatment supervision, but loss of patient privacy is a potential concern. Data on this are being collected through patient surveys. Because of the low-risk nature of the research, the Principal Investigators will be responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews on a quarterly basis. External monitoring is provided by a Stop TB Partnership project officer and Monitoring and Evaluation consultant. The Principal Investigator will submit regular progress reports, including recommendations on whether the project should continue unchanged, require modification, or close to enrollment.

Ethics approval was granted by institutional review boards at Makerere University School of Public Health and the University of California San Francisco. To ensure that the study captures all eligible adults initiating treatment at study sites, a waiver of informed consent was granted to access routine TB treatment data recorded in standard NTLP registers, such that research staff will not be required to be onsite to enroll and consent patients. The protocol was registered with the Pan-African Clinical Trials Registry (PACTR201808609844917) on 31 August 2018, updated 7 November 2019 and complies with reporting guidelines outlined in the stepped-wedge trial extension of the Consolidated Standards of Reporting Trials.(25) Any major changes in protocol will be approved by the Stop TB Partnership project officer and both ethics committess and registered with the PACTR. The full protocol and statistical code will be made available upon request.

Findings will be disseminated through peer-reviewed publications, presentations at scientific conferences and presentations to key stakeholders. Drs. Cattamanchi, Katamba and Kiwanuka will have access to the final dataset; the participant-level dataset will be made available to other investigators who have IRB approval to analyze the data.

Patient and public involvement

Patients and members of the public were involved throughout the research process. The NTLP was involved in identifying health facilities to participate, selecting study design, and conducting research through partnership with District Health Officers and participating health facilities. Patients, health workers, and community members were involved in intervention design through a human-centered design process, which included several rounds of focus groups and interviews with stakeholders. Health workers at the 18 health facilities implemented 99DOTS without research staff present and assisted in data collection by completing routine TB treatment registers and sending photos of the register to the research team through secure means.

DISCUSSION

99DOTS is a low-cost DAT that has the potential to improve TB treatment outcomes and the patient experience of TB treatment in Uganda and other high-burden settings. Here, we describe the first randomized trial designed to evaluate the effectiveness of a 99DOTS-based TB treatment supervision strategy as part of routine care in a high burden setting. Other novel aspects of the trial include our use of human-centered design to adapt 99DOTS to the local context with the goal of increasing patient engagement with the technology, the use of theory and implementation science frameworks to guide intervention design and evaluation, and our focus on simultaneously assessing implementation and costs to guide scale-up decisions.

Many aspects of this trial are intentionally pragmatic to ensure the outcomes reflect what can be expected under non-research conditions.(26) The study population will include all patients with drug susceptible pulmonary TB, with the exception of children. A waiver of consent was obtained for patient-level data collection such that research staff will not be required to be onsite to enroll and consent patients. Primary and key secondary outcomes will be assessed using routine data available through NTLP registers and the 99DOTS platform, with focused additional data

collection for implementation and cost outcomes. The intervention will be implemented by routine TB treatment unit staff, who also will make all decisions to offer 99DOTS-based treatment supervision to patients. At the same time, the stepped-wedge randomized trial design provides a rigorous assessment of intervention effect. Limitations of such a pragmatic trial design include less control over intervention delivery, potential limited uptake of the intervention given the wide inclusion criteria (all adults initiating treatment for drug-susceptible pulmonary TB) and inability to rigorously verify medication adherence during the control and intervention periods. In order to enroll enough patients to assess the effectiveness of the 99DOTS-based intervention, we selected facilities that treat larger numbers of TB patients. Uptake and effectiveness of 99DOTS may be different at lower volume health centers.

In summary, this pragmatic, hybrid type 2 effectiveness-implementation trial is well poised to assess both the effectiveness of an adapted 99DOTS-based intervention and potential barriers and facilitators to its scale-up if successful. The design and implementation of this trial intend to generate results to inform decisions on whether and how to implement 99DOTS in Uganda and other high burden countries.

References

1. World Health Organization. Global Tuberculosis Report. 2019.
2. Izudi J, Tamwesigire IK, Bajunirwe F. Explaining the successes and failures of tuberculosis treatment programs; a tale of two regions in rural eastern Uganda. BMC Health Services Research. 2019;19(1):979.
3. Fiseha D, Demissie M. Assessment of Directly Observed Therapy (DOT) following tuberculosis regimen change in Addis Ababa, Ethiopia: a qualitative study. BMC Infect Dis. 2015;15:405.
4. GSMA Intelligence. The Mobile Economy - Africa London: GSMA; 2016 [Available from: https://www.gsma.com/mobileeconomy/africa/.
5. World Health Organization. Treatment of tuberculosis: guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Geneva; 2017.
6. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS medicine. 2015;12(9):e1001876-e.
7. Subbaraman R, de Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMJ Glob Health. 2018;3(5):e001018.
8. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med. 2015;12(9):e1001876.
9. Liu X, Blaschke T, Thomas B, De Geest S, Jiang S, Gao Y, et al. Usability of a Medication Event Reminder Monitor System (MERM) by Providers and Patients to Improve Adherence in the Management of Tuberculosis. Int J Environ Res Public Health. 2017;14(10).
10. Thakkar D, Piparva KG, Lakkad SG. A pilot project: 99DOTS information communication technology-based approach for tuberculosis treatment in Rajkot district. Lung India. 2019;36(2):108-11.
11. Cross A, Gupta N, Liu B, Nair V, Kumar A, Kuttan R, et al. 99DOTS: A Low-Cost Approach to Monitoring and Improving Medication Adherence. Tenth International Conference on Information and Communication Technologies and Development. ICTD. 2019.
12. Green LW, Kreuter MW. Health promotion planning: An educational and ecological approach: McGraw-Hill; 1993.
13. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77.
14. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. Implement Sci. 2012;7:38.
15. Sarfaraz J. Unified theory of acceptance and use of technology (Utaut) model-mobile banking. Journal of Internet Banking and Commerce. 2017;22(3):1-20.
16. Venkatesh V, Thong JY, Xu X. Consumer acceptance and use of information technology: extending the unified theory of acceptance and use of technology. MIS quarterly. 2012:157-78.

17. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. American journal of public health. 1999;89(9):1322-7.
18. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. American journal of public health. 2013;103(6):e38-e46.
19. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.
20. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
21. Ggita JM, Ojok C, Meyer AJ, Farr K, Shete PB, Ochom E, et al. Patterns of usage and preferences of users for tuberculosis-related text messages and voice calls in Uganda. Int J Tuberc Lung Dis. 2018;22(5):530-6.
22. Babirye D, Shete PB, Farr K, Nalugwa T, Ojok C, Nantale M, et al. Feasibility of a short message service (SMS) intervention to deliver tuberculosis testing results in peri-urban and rural Uganda. J Clin Tuberc Other Mycobact Dis. 2019;16:100110.
23. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
24. Thompson J, Davey C, Hayes R, Hargreaves J, Fielding K. swpermute: Permutation tests for Stepped-Wedge Cluster-Randomised Trials. The Stata journal. 2019;19(4):803-19.
25. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614.
26. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ : British Medical Journal. 2015;350:h2147.

Acknowledgements

We would like to thank the patients and health facility staff who make this research possible, as well as the Uganda NTLP, for their collaboration on this protocol.

Authors' contributions

AC, AKa, and NK conceived and designed the study. RC, AKi, ML, CN, LKT, ASN, JG, PT, DB, DO, CB, AT, DP, AM, DD, TS, AC and AKa participated in implementation of the study. RC, AKi, AC, and AKa drafted the manuscript. All authors reviewed and approved the manuscript.

Funding

This Project is supported by the Stop TB Partnership's TB REACH initiative, grant number STBP/TBREACH/GSA/W6-37, which is funded by the Government of Canada, the Bill & Melinda Gates Foundation, and the United States Agency for International Development. The study sponsor is not involved in data collection, analysis or interpretation.

Competing Interests

The authors have no conflicts of interest to report.

Figure 1. 99DOTS Randomization and Enrollment Schedule. The trial includes 18 health facilities divided into 6 equal size blocks (3 health facilities per block). The health facilities all continue routine TB treatment supervision in Month 1, begin switching to the 99DOTS-based intervention strategy in Month 2 (one block per month in a random order), and all use the intervention strategy in Month 8.

Figure 2. **Flow diagram of TB treatment units and patients included in the DOT to DAT trial**. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Figure 3. **Original and adapted versions of the 99DOTS envelope**. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space for writing in the health worker's name and phone number, simplified pictorial instructions for taking pills, and motivational imagery on the inside cover (bottom middle); and provide simplified guide to the order in which to take pills on the back cover (bottom

right). In addition, the audio tone heard when patients make daily phone calls to report medication dosing was replaced with a rotating series of educational or motivational messages recorded by local health workers.

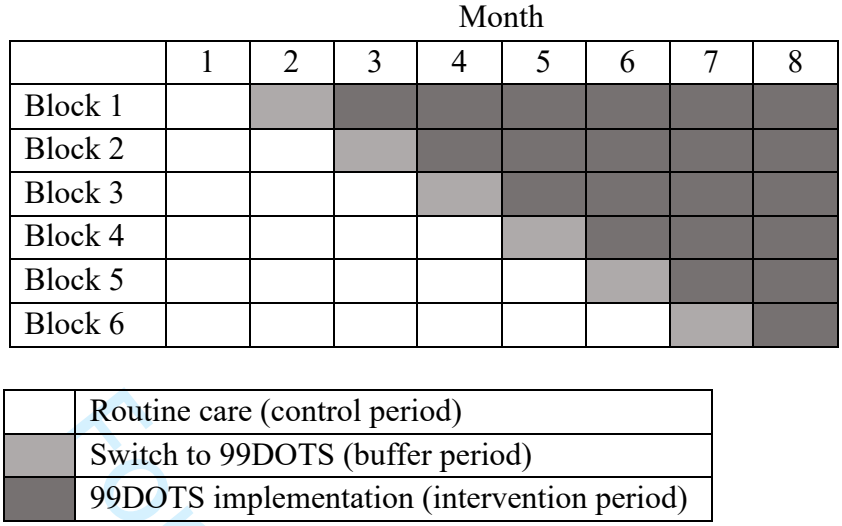


Figure 1. 99DOTS Randomization and Enrollment Schedule. The trial includes 18 health facilities divided into 6 equal size blocks (3 health facilities per block), each block representing an allocation sequence. The health facilities all continue routine TB treatment supervision in Month 1, begin switching to the 99DOTS-based intervention strategy in Month 2 (one block per month in a random order), and all use the intervention strategy in Month 8.

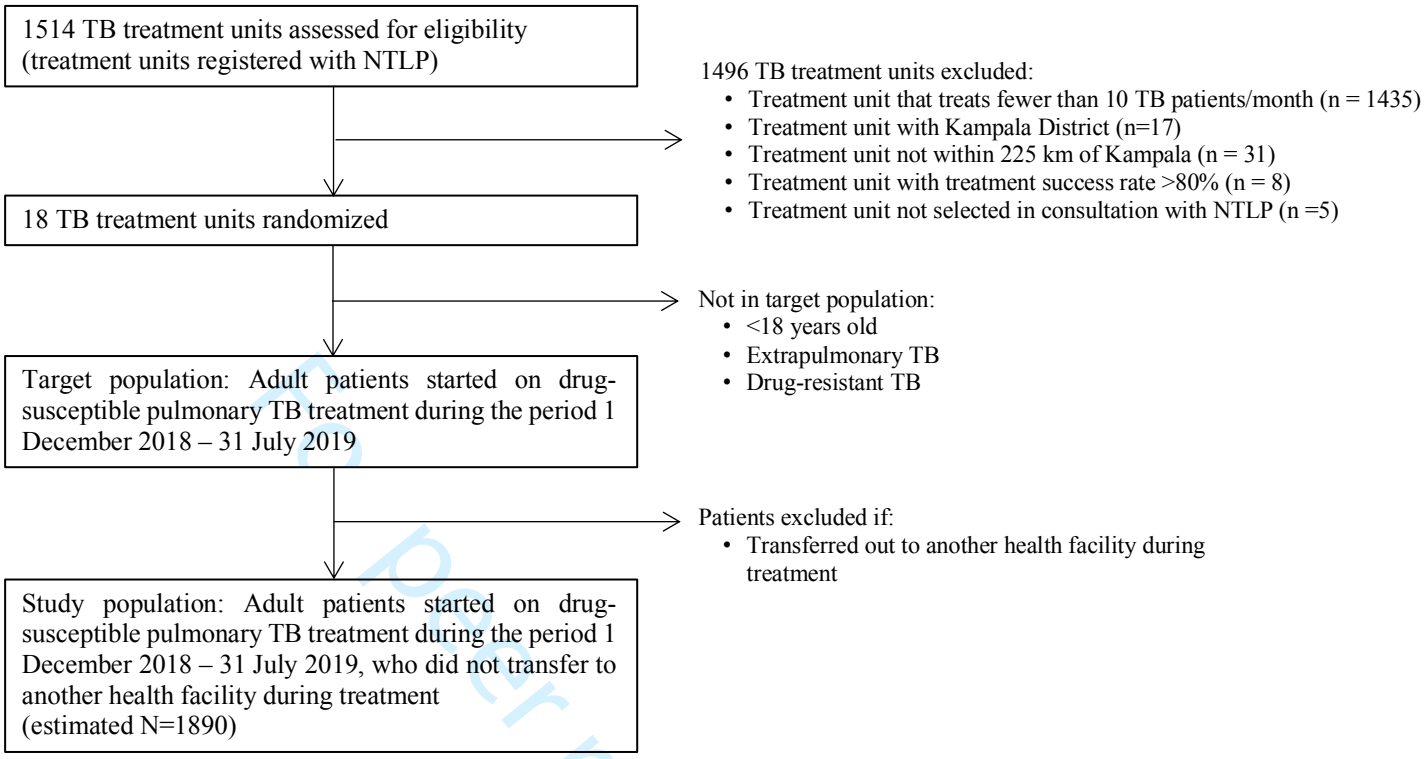
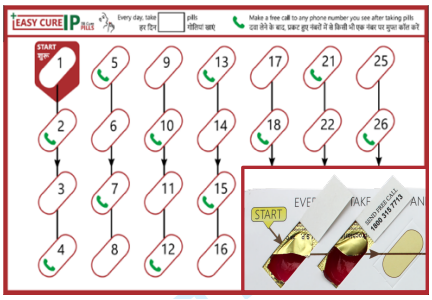


Figure 2. **Flow diagram of TB treatment units and patients included in the DOT to DAT trial**. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Original 99DOTS Envelope

Front of envelope

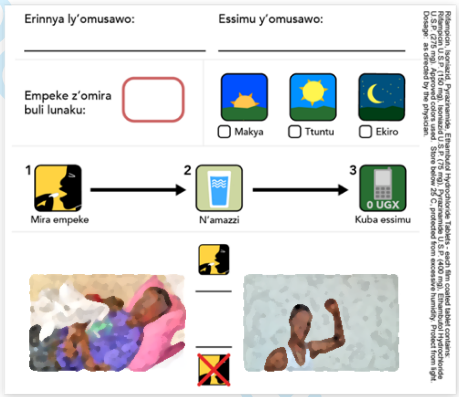


Back of envelope

Adapted 99DOTS envelope

Front cover

Inside cover



Back of envelope

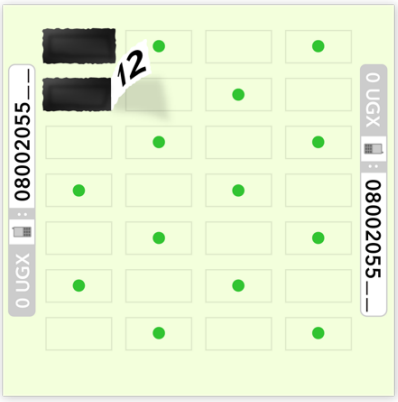


Figure 3. **Original and adapted versions of the 99DOTS envelope**. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space for writing in the health worker's name and phone number, simplified pictorial instructions for taking pills, and motivational imagery on the inside cover (bottom middle); and provide simplified guide to the order in which to take pills on the back cover (bottom right). In addition, the audio tone heard when patients make daily phone calls to report medication dosing was replaced with a rotating series of educational or motivational messages recorded by local health workers.

Supplementary materials 3: Checklist of information to include when reporting a stepped wedge cluster randomised trial (SW-CRT)

Topic	Item no	Checklist item	Page no
Title and abstract			
	1a	Identification as a SW-CRT in the title.	1
	1b	Structured summary of trial design, methods, results, and conclusions (see separate SW-CRT checklist for abstracts).	2
Introduction			
Background and objectives	2a	Scientific background. Rationale for using a cluster design and rationale for using a stepped wedge design.	5
	2b	Specific objectives or hypotheses.	5
Methods			
Trial design	3a	Description and diagram of trial design including definition of cluster, number of sequences, number of clusters randomised to each sequence, number of periods, duration of time between each step, and whether the participants assessed in different periods are the same people, different people, or a mixture.	5, Figure
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.	N/A
Participants	4a	Eligibility criteria for clusters and participants.	6
	4b	Settings and locations where the data were collected.	6
Interventions	5	The intervention and control conditions with sufficient details to allow replication, including whether the intervention was maintained or repeated, and whether it was delivered at the cluster level, the individual participant level, or both.	7-9
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.	11-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons.	N/A
Sample size	7a	How sample size was determined. Method of calculation and relevant parameters with sufficient detail so the calculation can be replicated. Assumptions made about correlations between outcomes of participants from the same cluster. (see separate checklist for SW-CRT sample size items).	12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines.	N/A
Randomisation			
Sequence generation	8a	Method used to generate the random allocation to the sequences of treatments.	9-10
	8b	Type of randomisation; details of any constrained randomisation or stratification, if used.	9-10
Allocation concealment mechanism	9	Specification that allocation was based on clusters; description of any methods used to conceal the allocation from the clusters until after recruitment.	9-10
Implementation	10a	Who generated the randomisation schedule, who enrolled clusters, and who assigned clusters to sequences.	9-10
	10b	Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling; continuous recruitment or ascertainment; or recruitment at a fixed point in time), including who recruited or identified participants.	6
	10c	Whether, from whom and when consent was sought and for what; whether this differed between treatment conditions.	14
Blinding	11a	If done, who was blinded after assignment to sequences (eg, cluster level participants, individual level participants, those assessing outcomes) and how.	10
	11b	If relevant, description of the similarity of treatments.	7-9
Statistical methods	12a	Statistical methods used to compare treatment conditions for primary and secondary outcomes including how time effects, clustering and repeated measures were taken into account.	13
	12b	Methods for additional analyses, such as subgroup analyses, sensitivity analyses, and adjusted analyses.	13-14

(*Continued*)

Supplementary materials 3 (*Continued*)

Topic	Item no	Checklist item	Page no
Results			
Participant flow (a diagram is strongly recommended)	13a	For each treatment condition or allocated sequence, the numbers of clusters and participants who were assessed for eligibility, were randomly assigned, received intended treatments, and were analysed for the primary outcome (see separate SW-CRT flow chart).	6, Figure
	13b	For each treatment condition or allocated sequence, losses and exclusions for both clusters and participants with reasons.	6, Figure
Recruitment	14a	Dates defining the steps, initiation of intervention, and deviations from planned dates. Dates defining recruitment and follow-up for participants.	6
	14b	Why the trial ended or was stopped.	N/A
Baseline data	15	Baseline characteristics for the individual and cluster levels as applicable for each treatment condition or allocated sequence.	N/A
Numbers analysed	16	The number of observations and clusters included in each analysis for each treatment condition and whether the analysis was according to the allocated schedule.	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each treatment condition, and the estimated effect size and its precision (such as 95% confidence interval); any correlations (or covariances) and time effects estimated in the analysis.	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended.	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.	N/A
Harms	19	Important harms or unintended effects in each treatment condition (for specific guidance see CONSORT for harms).	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses.	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings. Generalisability to clusters or individual participants, or both (as relevant).	15-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.	N/A
Other information			
Registration	23	Registration number and name of trial registry.	14
Protocol	24	Where the full trial protocol can be accessed, if available.	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), and the role of funders.	19
Research ethics review	26	Whether the study was approved by a research ethics committee, with identification of the review committee(s). Justification for any waiver or modification of informed consent requirements.	14

This checklist has been taken from table 3 in *BMJ* 2018;363:k1614, as a standalone document for readers to print out or fill in electronically.