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

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

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3 37 **ABSTRACT**
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5
6 38 **Introduction:** Low-cost digital adherence technologies (DAT) such as 99DOTS have emerged as
7
8 39 an alternative to directly observed therapy, (DOT), the current standard for TB treatment
9
10 40 supervision. However, there are limited data to support DAT scale-up. The “DOT to DAT” trial
11
12 41 aims to evaluate the effectiveness and implementation of a 99DOTS-based TB treatment
13
14 42 supervision strategy.

15 43 **Methods and analysis:** This is a pragmatic, stepped-wedge cluster randomized trial, with hybrid
16
17 44 type 1 effectiveness-implementation design. The trial will include all adults (estimated N=1890)
18
19 45 treated for drug-susceptible pulmonary TB over an 8-month period at 18 TB treatment units in
20
21 46 Uganda. Three sites per month will switch from routine care (DOT) to the intervention (99DOTS-
22
23 47 based treatment supervision) beginning in Month 2, with the order determined randomly. 99DOTS
24
25 48 enables patients to be monitored while self-administering TB medicines. Patients receive daily
26
27 49 automated SMS dosing reminders and confirm dosing by calling toll-free numbers. The primary
28
29 50 effectiveness outcome is the proportion of patients completing TB treatment. With 18 clusters
30
31 51 randomized into 6 steps and an average cluster size of 15 patients per month, the study will have
32
33 52 89% power to detect a 10% or greater increase in treatment completion between the routine care
34
35 53 and intervention periods. Secondary outcomes include more proximal effectiveness measures as
36
37 54 well as quantitative and qualitative assessments of the reach, adoption and implementation of the
38
39 55 intervention.

40 56 **Ethics and dissemination:** Ethics approval was granted by institutional review boards at
41
42 57 Makerere University School of Public Health and the University of California San Francisco.

43 58
44 59 **Trial registration number:** PACTR201808609844917
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60 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

69 INTRODUCTION

70 Tuberculosis (TB) is the leading infectious cause of death worldwide despite being a preventable
71 and curable disease.(1) Poor adherence to medication continues to be a major obstacle to TB
72 elimination, resulting in prolonged infectiousness, emergence of multidrug resistance, and
73 increased risk of poor treatment outcomes. The World Health Organization (WHO)-recommended
74 strategy, directly observed therapy short-course (DOTS), has been the standard-of-care for TB
75 treatment supervision since the 1990s. As part of this strategy, a health worker is expected to
76 observe patients swallow each dose of anti-TB medication. However, directly observed therapy
77 (DOT) is time-consuming, costly and inconvenient for both patients and providers, while its
78 implementation is also difficult to monitor.(2, 3) Not surprisingly, TB treatment success rates
79 remain below the 90% target in most high-burden countries, despite reported DOT coverage over
80 90%.(1)

81
82 With the increase in mobile phone penetration among patients and healthcare workers in high TB
83 burden countries,(4) digital adherence technologies (DATs) could address some of the challenges
84 associated with implementation of the DOTS strategy in a patient-centered manner. To date, such
85 technologies have received only a conditional recommendation by the WHO due to very low
86 quality of evidence.(5) The first randomized trial of a DAT found that SMS reminders alone did
87 not improve medication adherence, but a medication event reminder monitor did.(6) However,
88 treatment outcomes did not improve and both trials and programmatic research have shown
89 variable uptake of DAT.(7-10)

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6 91 The “DOT to DAT” trial aims to evaluate the effectiveness, implementation and cost-effectiveness
7 92 of a culturally and contextually adapted version of 99DOTS in Uganda. 99DOTS is a low-cost
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9 93 DAT wherein patients self-report medication adherence by calling toll-free phone numbers hidden
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11 94 underneath pills in blister packs.(11) We present the research methods used for the first
12
13 95 randomized trial to evaluate the effectiveness and implementation of a 99DOTS-based strategy for
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15 96 TB treatment supervision in routine care settings.

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18 98 **Conceptual basis for trial design**
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20 99 Numerous conceptual frameworks have emerged to improve the implementation and success of
21
22 100 health interventions through theory-based design and evaluation. The PRECEDE framework
23
24 101 guided the development of the 99DOTS-based intervention strategy, while the RE-AIM
25
26 102 framework guided its comprehensive evaluation. Behavior change models including the
27
28 103 Theoretical Domains Framework (TDF)(12, 13) and the Unified Theory of Acceptance and Use
29
30 104 of Technology (UTAUT)(14, 15) guided the assessment and analysis of patient- and provider-level
31
32 105 barriers to adoption and implementation of 99DOTS.

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34 107 The PRECEDE framework emphasizes the need for multi-faceted health promotion interventions
35
36 108 to address predisposing, enabling, and reinforcing factors in order to achieve behavior change.(16)
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38 109 The 99DOTS-based intervention was designed to address key predisposing (social isolation and
39
40 110 the high direct and indirect cost of clinic visits), enabling (inability of health facility staff to focus
41
42 111 limited time and resources on non-adherent patients), and reinforcing (a lack of real-time
43
44 112 information on patient adherence to medications) factors related to TB treatment adherence
45
46 113 identified through the literature and formative human factors research that preceded the trial.(11)

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48 115 The RE-AIM framework was designed to ensure that trials not only assess the effect of
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50 116 interventions but also their translatability and public health impact.(17, 18) This hybrid type 1 trial
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52 117 therefore focuses on the effectiveness of the 99DOTS-based intervention in improving TB
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54 118 treatment outcomes, but concurrently examines its reach into the target population, adoption by
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56 119 target settings and staff, and implementation fidelity and costs.(19) The goal of assessing

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3 120 translatability and public health impact is further enhanced through pragmatic design choices for
4
5 121 each element of the trial in order to maximize applicability in real-world settings.(20)

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8 123 **METHODS AND ANALYSIS**

9 124 **Study aims**

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11 125 The primary aim of the trial is to determine whether a 99DOTS-based strategy increases the
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13 126 proportion of patients who complete TB treatment in comparison to routine care. Secondary aims
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15 127 include 1) comparing short-term treatment outcomes and loss to follow-up between the
16
17 128 intervention and routine care arms; 2) assessing the reach, adoption and implementation of the
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19 129 99DOTS-based strategy; and 3) evaluating the incremental costs and cost-effectiveness of the
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21 130 99DOTS-based strategy as compared to routine care from the health system perspective. Our
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23 131 hypotheses are that the 99DOTS-based strategy will lead to higher treatment completion, have
24
25 132 high uptake among patients and providers, and be cost-effective.

26 133

27 134 **Study design**

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29 135 This is a pragmatic, stepped-wedge randomized trial, with a hybrid type 1 implementation-
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31 136 effectiveness design.(19) As depicted in **Figure 1**, the intervention strategy was sequentially
32
33 137 introduced at 3 sites each in Months 2-6, with all sites under routine care in Month 1 and all sites
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35 138 using the intervention strategy in Month 8. The month of switch from control to intervention
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37 139 (buffer period) will be excluded from analysis. We chose the stepped-wedge trial design to
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39 140 maximize equity and acceptability (all sites will receive the intervention), minimize logistical
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41 141 constraints associated with introducing the intervention simultaneously at a large number of sites,
42
43 142 account for secular outcome trends, and allow for iterative learning and changes in intervention
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45 143 roll-out as would occur during eventual scale-up. We chose a highly pragmatic approach to trial
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47 144 implementation, as described in sections below, to understand the real-world impact of the
48
49 145 99DOTS-based intervention strategy.

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51 147 **Study Setting**

52 148 The trial is being conducted at 18 TB treatment units within hospitals and health centers across 15
53
54 149 districts of Uganda. The TB treatment units are affiliated with the Uganda National Tuberculosis
55
56 150 and Leprosy Program (NTLP) and provide TB treatment free of charge using a mix of facility- and

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3 151 community-based DOTS. Uganda was chosen as the trial setting due to its high TB burden (200
4 cases/100,000 in 2017) and low treatment success rate (72% in 2017).(1)
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7 153
8 154 Study sites were selected after reviewing 2016 TB treatment outcomes and 2017 TB case finding
9 data reported to the NTLP from all 1514 registered TB treatment units. We included treatment
10 155 units that 1) diagnosed >10 pulmonary TB patients/month in 2017, 2) were not located within
11 156 Kampala District (many active ongoing projects in this district), 3) were located within 225 km of
12 157 Kampala City (for feasibility), and 4) had a pulmonary TB treatment success rate in 2016 <80%
13 158 (to be able to show an impact).
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19 160
20 161 Of the 1514 treatment units registered with the Uganda NTLP, 23 treatment units met our inclusion
21 162 criteria (**Figure 2**). The majority (n=1435) diagnosed fewer than 10 TB patients/month in 2017,
22 163 17 are located within Kampala district, 31 are not within 225 km of Kampala district, and 9 had a
23 164 treatment success rate >80% in 2016. Of the 23 remaining treatment units, we selected 18 located
24 165 in 15 districts (10 in Central, 7 in Eastern and 1 in Western Uganda) in consultation with the NTLP.
25 166 Project staff visited the Chief Administrative Officers, District Health Officers and Facility
26 167 Directors for the 18 sites to discuss the study. All signed a memorandum of agreement for their
27 168 site to participate in the study.
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36 170 **Study participants**
37 171 All adult patients treated for drug-susceptible pulmonary TB at participating treatment units during
38 172 the study period will be eligible for inclusion. Children, patients treated for drug-resistant or
39 173 extrapulmonary TB, and patients transferred to another facility to complete treatment will be
40 174 excluded. Surveys to assess 99DOTS implementation will be conducted in a random subset of
41 175 eligible patients and all health workers involved in TB treatment supervision at each treatment
42 176 unit. Time-and-motion studies to assess costs will also be conducted among health workers
43 177 involved in TB treatment supervision at each treatment unit.
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51 179 **Routine care and intervention strategies**
52 180 *Routine care.* The conventional approach to TB treatment supervision in Uganda is a mix of
53 181 community- and facility-based DOT. At the time of treatment initiation, treatment unit staff record
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182 patient demographic and clinical details in the NTLP register and are supposed to provide TB-
 183 focused counseling. Most TB patients are treated using community-based DOT, wherein they
 184 name a treatment supporter and are provided with a 2-week supply of medicines in the first two
 185 months (intensive phase) and a one-month supply of medicines in the next four months
 186 (continuation phase) of TB treatment. Patients take their medicines from home (with or without
 187 observation by a treatment supporter) and return to the health facility for medication refills. At
 188 each refill visit, health facility staff are supposed to assess adherence via patient self-report and
 189 provide additional counseling. Health facility staff are also supposed to call or visit patients who
 190 do not return for refills, but patient follow-up is limited across health facilities.

191
 192 *Intervention.* The 99DOTS-based intervention strategy is comprised of four main components that
 193 address distinct barriers to successful TB treatment (**Table 1**):

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

199 **Table 1. Components of the “DOT to DAT” trial intervention and corresponding barriers**
 200 **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.

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3 203 Formative research using human-centered design was used to adapt the generic 99DOTS product
4 204 to the local context, including changes to the envelope design and addition of a rotating series of
5 205 educational/motivational audio messages heard when patients call in to report dosing (details of
6 206 the formative research will be reported in a separate publication) (**Figure 3**).

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11 208 TB treatment unit staff will be requested to offer 99DOTS-based treatment supervision to all
12 209 eligible patients initiating TB treatment, and to register patients who accept 99DOTS-based
13 210 treatment supervision on the 99DOTS platform via a mobile app. Given the pragmatic nature of
14 211 the trial, the decision to offer and accept 99DOTS-based treatment supervision will be made by
15 212 treatment unit staff and patients, respectively. Once registered, treatment unit staff will instruct
16 213 patients on how to use the 99DOTS pill pack and make a call to the 99DOTS system using the
17 214 toll-free number revealed when pills are pushed out of the medication blister pack (**Figure 3**). Staff
18 215 will also help patients personalize their 99DOTS pill pack by choosing a decorative cover,
19 216 educational or motivational sticker for the inside flap, writing in their health worker's contact
20 217 information, and selecting a time of day to take their medication (**Figure 3**).

21 218
22 219 Each dose confirmed via phone call is logged by 99DOTS and reflected on the 99DOTS
23 220 smartphone app dashboard, viewable by treatment unit staff. During routine drug refill visits (same
24 221 schedule as described for routine care period), health facility staff are asked to review adherence
25 222 data in the 99DOTS app before providing counseling. At the conclusion of the intensive phase of
26 223 treatment, patients with adherence >90% are offered the option of returning back to the health
27 224 facility after two months instead of the standard one month.

28 225
29 226 Health facilities using 99DOTS to manage TB patient treatment will be provided one smartphone
30 227 per facility, minimal funds to cover cell phone data, and an average of 300,000 US\$ (approximately
31 228 \$82 USD) per month to facilitate patient follow-up. Treatment unit staff will not be provided any
32 229 extra compensation to reflect future conditions under eventual scale-up.

33 230 34 231 **Implementation considerations**

35 232 99DOTS training will occur at each health facility during the month in which it is scheduled to
36 233 switch to the intervention. Project staff and the District TB Officer will conduct a 2-3 day training

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

239

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

245

246 **Randomization**

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

255

256 **Blinding**

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

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261 **Data collection and management**

262 *Patient-level data collection*

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

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3 265 units. Project staff will train two health workers at each site (one primary, one backup) identified
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5 266 by the health facility director to take photos of the register every 2-4 weeks for the duration of the
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7 267 project using a camera-enabled smartphone, and to upload the photos to a central secure server.
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9 268 Health workers will be trained to delete photos from the phone after upload confirmation.
10
11 269 Completeness of TB treatment registers will be assessed, and at quarterly site visits, study staff
12
13 270 will provide re-training as needed and resolve data cleaning queries. Study staff will extract data
14
15 271 from photos of TB registers and enter data into a secure database use Research Electronic Data
16
17 272 Capture software (REDCap).(21) Data queries for missing or nonsensical data will be reviewed
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19 273 with treatment unit staff at quarterly site visits.

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274 275 *99DOTS process metrics data collection*

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

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281 *Qualitative data collection*

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

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290 *Health system cost data collection*

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

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3 296 basis in conjunction with site visits and will consist of direct observation of all activities conducted
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5 297 by treatment unit staff over the corresponding 1-2 day evaluation period, for a total 6-12 days of
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7 298 observation every three months over the course of the 14-month study period. During these
8
9 299 observation periods, the time and resources required to perform all activities related to TB
10
11 300 treatment (e.g., medication preparation, contacting patients, observing medication doses, etc.) will
12
13 301 be recorded. Additional costing data will be collected to assess the cost of implementing and
14
15 302 maintaining 99DOTS technical assistance (budget records from Everwell Health Solutions, the
16
17 303 creator of 99DOTS) and the cost at point of care (surveys of project staff to track resource use
18
19 304 during trainings). Overhead costs will be estimated using an ingredients approach, incorporating
20
21 305 the cost of supplies, building/space, vehicles, and human resources with incorporation of recurrent
22
23 306 costs such as security, vehicle maintenance costs, and all supplies (medical and administrative).

307

308 **Outcomes**

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

322

323 **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

324

325 *Power and sample size*

326 The trial aims to demonstrate the superiority of the 99DOTS-based strategy. The sample size was
327 calculated for the primary effectiveness outcome, proportion of patients treated successfully, using
328 formulae appropriate for stepped-wedge trials. A type I error of 5% and power of at least 90% is
329 assumed. Based on 2017 data, the harmonic mean number of patients initiating treatment for drug-
330 susceptible pulmonary TB per month across participating treatment units was 15. Thus, we
331 anticipate that approximately 1890 patients will initiate treatment over the 8-month enrollment
332 period (945 in the pre- and 945 in the post-implementation phases across treatment units). The trial
333 will have 89% power to demonstrate that our strategy increases the proportion of patients treated
334 successfully by 10% or more (assumptions: alpha=0.05; intraclass correlation coefficient, ICC =
335 0.001 calculated using 2017 NTLTP data for the 18 treatment units; pre-implementation treatment

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3 336 success = 51% based on 2017 NTLP data for the 18 treatment units; calculations performed using
4
5 337 steppedwedge command in Stata 14).

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8 339 **Analysis**

9
10 340 The primary effectiveness analysis will be conducted at the health facility level using multivariable
11
12 341 mixed effect logit models. Analysis will be done for intention to treat and per protocol (excluding
13
14 342 patients who are not enrolled on 99DOTS during the intervention period at each site) populations
15
16 343 in Stata using melogit and meqrlogit commands. Models will adjust for the longitudinal design
17
18 344 and clustering by site, nested within group. Patients initiating treatment during the month in which
19
20 345 sites switch from routine treatment supervision to the intervention strategy will be excluded (buffer
21
22 346 period). Confounders, selected *a priori*, will be included in the model as fixed effects. Secondary
23
24 347 effectiveness outcomes (**Table 2**) will be analyzed in the same manner. Subgroup analyses will
25
26 348 stratify by gender, HIV status, and health facility. Sensitivity analyses will be performed to assess
27
28 349 the robustness of our findings with respect to treatment outcomes for patients lost to follow up, the
30
31 350 staged intervention roll out, intervention timing and buffer period, and analysis method.

29 351
30
31 352 Quantitative reach, adoption and implementation outcomes will be summarized descriptively.
32
33 353 Comparative analyses will identify factors independently associated with reach, adoption and
34
35 354 implementation of intervention components. Health economic data will be used to calculate the
36
37 355 incremental cost-effectiveness of the intervention strategy from a societal perspective, measured
38
39 356 as the incremental cost per successfully completed treatment, comparing 99DOTS relative to
40
41 357 routine care.

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43 358

43 359 **Ethics and dissemination**

44
45 360 Patients can choose to use or not use 99DOTS at any time during the intervention period. 99DOTS
46
47 361 enables closer patient monitoring than routine TB treatment supervision, but loss of patient privacy
48
49 362 is a potential concern. Data on this are being collected through patient surveys. Because of the
50
51 363 low-risk nature of the research, the Principal Investigators will be responsible for monitoring the
52
53 364 data, assuring protocol compliance, and conducting safety reviews on a quarterly basis. External
54
55 365 monitoring is provided by a Stop TB Partnership project officer and Monitoring and Evaluation
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57 366 consultant. The Principal Investigator will submit regular progress reports, including

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3 367 recommendations on whether the project should continue unchanged, require modification, or
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5 368 close to enrollment.

6 369
7
8 370 Ethics approval was granted by institutional review boards at Makerere University School of
9
10 371 Public Health and the University of California San Francisco. To ensure that the study captures all
11
12 372 eligible adults initiating treatment at study sites, a waiver of informed consent was granted to
13
14 373 access routine TB treatment data recorded in standard NTLP registers. The protocol was registered
15
16 374 with the Pan-African Clinical Trials Registry (PACTR201808609844917) on 31 August 2018,
17
18 375 updated 11 July 2019 and complies with reporting guidelines outlined in the stepped-wedge trial
19
20 376 extension of the Consolidated Standards of Reporting Trials.(22) Any major changes in protocol
21
22 377 will be approved by the Stop TB Partnership project officer and both ethics committess and
23
24 378 registered with the PACTR. The full protocol and statistical code will be made available upon
25
26 379 request.

27 380
28 381 Findings will be disseminated through peer-reviewed publications, presentations at scientific
29
30 382 conferences and presentations to key stakeholders. Drs. Cattamanchi, Katamba and Kiwanuka will
31
32 383 have access to the final dataset; the participant-level dataset will be made available to other
33
34 384 investigators who have IRB approval to analyze the data.

35 385

36 386 **Patient and public involvement**

37 387 Patients and members of the public were involved throughout the research process. The NTLP was
38
39 388 involved in identifying health facilities to participate, selecting study design, and conducting
40
41 389 research through partnership with District Health Officers and participating health facilities.
42
43 390 Patients, health workers, and community members were involved in intervention design through a
44
45 391 human-centered design process, which included several rounds of focus groups and interviews
46
47 392 with stakeholders. Health workers at the 18 health facilities implemented 99DOTS without
48
49 393 research staff present and assisted in data collection by completing routine TB treatment registers
50
51 394 and sending photos of the register to the research team through secure means.

52 395

53 396 **DISCUSSION**

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2
3 397 99DOTS is a low-cost DAT that has the potential to improve TB treatment outcomes and the
4
5 398 patient experience of TB treatment in Uganda and other high-burden settings. Here, we describe
6
7 399 the first randomized trial designed to evaluate the effectiveness of a 99DOTS-based TB treatment
8
9 400 supervision strategy as part of routine care in a high burden setting. Other novel aspects of the trial
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11 401 include our use of human-centered design to adapt 99DOTS to the local context with the goal of
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13 402 increasing patient engagement with the technology, the use of theory and implementation science
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15 403 frameworks to guide intervention design and evaluation, and our focus on simultaneously
16
17 404 assessing implementation and costs to guide scale-up decisions.
18

19 406 Many aspects of this trial are intentionally pragmatic to ensure the outcomes reflect what can be
20
21 407 expected under non-research conditions.(23) The study population will include all patients with
22
23 408 drug susceptible pulmonary TB, with the exception of children. A waiver of consent was obtained
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25 409 for patient-level data collection such that research staff will not be required to be onsite to enroll
26
27 410 and consent patients. Primary and key secondary outcomes will be assessed using routine data
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29 411 available through NTLP registers and the 99DOTS platform, with focused additional data
30
31 412 collection for implementation and cost outcomes. The intervention will be implemented by routine
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33 413 TB treatment unit staff, who also will make all decisions to offer 99DOTS-based treatment
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35 414 supervision to patients. At the same time, the stepped-wedge randomized trial design provides a
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37 415 rigorous assessment of intervention effect.
38

39 417 In summary, this pragmatic, hybrid type 1 effectiveness-implementation trial is well poised to
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41 418 assess both the effectiveness of an adapted 99DOTS-based intervention and potential barriers and
42
43 419 facilitators to its scale-up if successful. The design and implementation of this trial intend to
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45 420 generate results to inform decisions on whether and how to implement 99DOTS in Uganda and
46
47 421 other high burden countries.
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3 489 **Acknowledgements**
4

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6
7 491 well as the Uganda NTLP, for their collaboration on this protocol.
8

9 492

10 493 **Authors' contributions**
11

12 494 AC and AKa conceived and designed the study. RC, AKi, ML, CN, LKT, ASN, JG, PT, DB, DO,
13
14 495 CB, AT, DP, AM, DD, TS, AC and AKa participated in implementation of the study. RC, AKi,
15
16 496 AC, and AKa drafted the manuscript. All authors reviewed and approved the manuscript.
17

18 497

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21
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23
24 501 Melinda Gates Foundation, and the United States Agency for International Development. The
25
26 502 study sponsor is not involved in data collection, analysis or interpretation.
27

28 503

29 504 **Competing Interests**
30

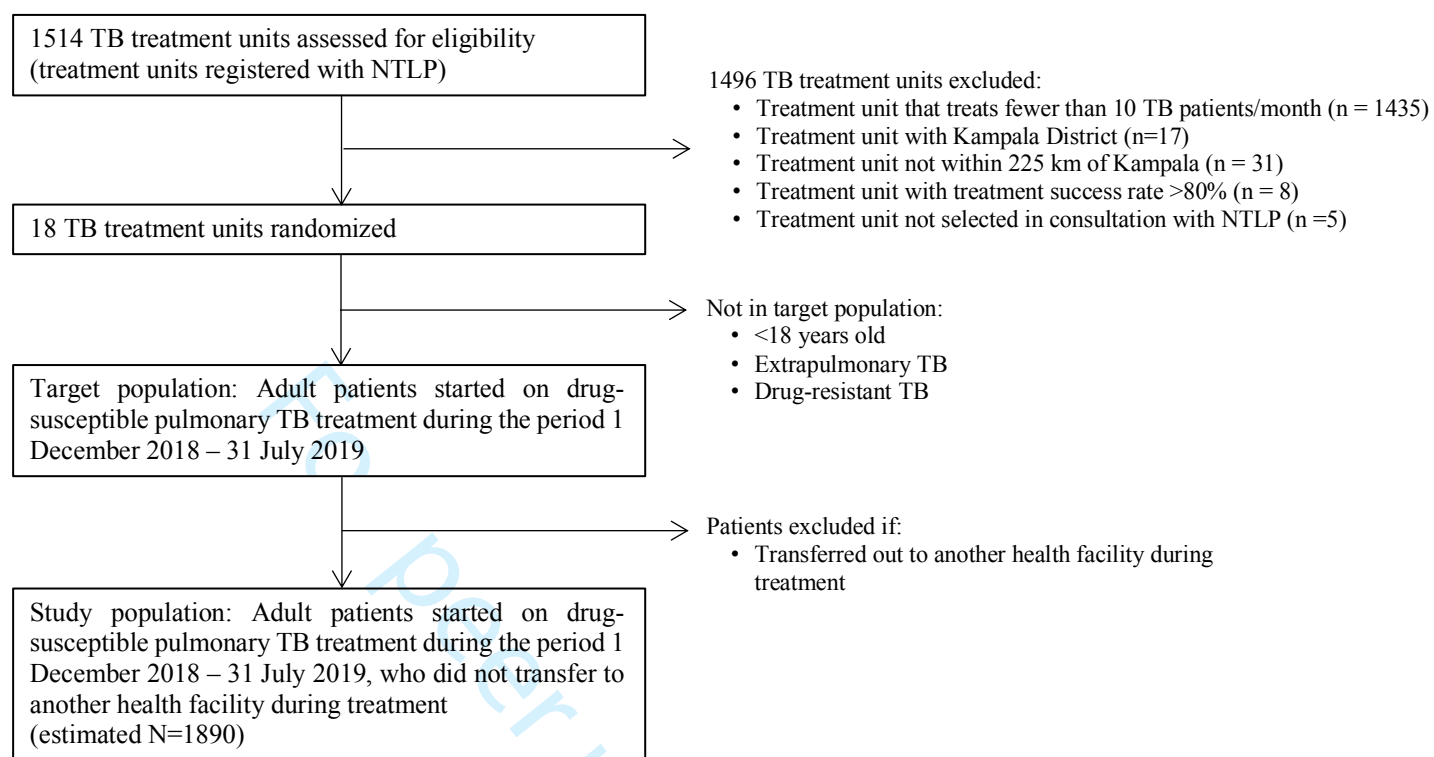
31 505 The authors have no conflicts of interest to report.
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	Month							
	1	2	3	4	5	6	7	8
Group 1								
Group 2								
Group 3								
Group 4								
Group 5								
Group 6								

	Routine care (control period)
	Switch to 99DOTS (buffer period)
	99DOTS implementation (intervention period)

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.

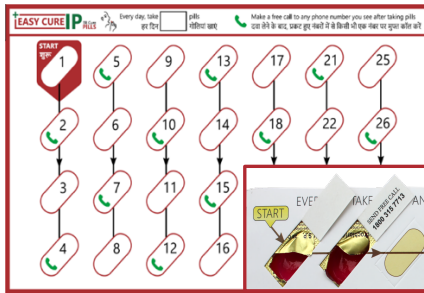


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Figure 2. Flow diagram of TB treatment units and patients included in the DOT to DAT trial. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Original 99DOTS Envelope

Front of envelope



Back of envelope

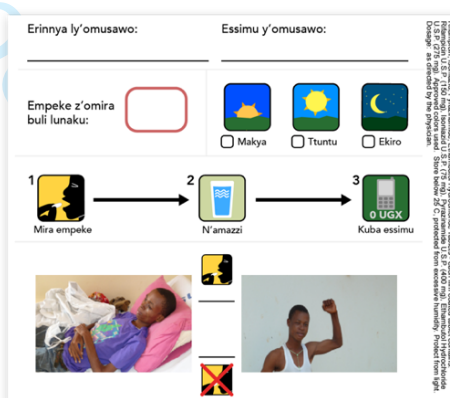


Adapted 99DOTS envelope

Front cover



Inside cover



Back of envelope

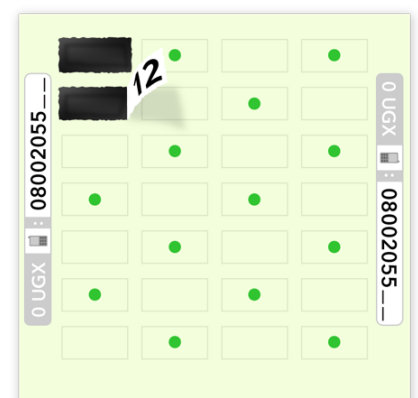


Figure 3. Original and adapted versions of the 99DOTS envelope. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space 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 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	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>2, 14</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>14</u>
Protocol version	3	Date and version identifier	<u>14</u>
Funding	4	Sources and types of financial, material, and other support	<u>18</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>1,18</u>
	5b	Name and contact information for the trial sponsor	<u>18</u>
	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	<u>18</u>
	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)	<u>N/A</u>

1	Introduction			
2				
3	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	<u>3-4</u>
4				
5				
6		6b	Explanation for choice of comparators	<u>5</u>
7				
8	Objectives	7	Specific objectives or hypotheses	<u>5</u>
9				
10	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)	<u>5</u>
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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	<u>5-6</u>
17				
18				
19	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)	<u>6, Figure 2</u>
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>6-8, Figure 3</u>
23				
24		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)	<u>13-14</u>
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>9</u>
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>N/A</u>
29				
30	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	<u>11-12, Table 2</u>
31				
32				
33	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)	<u>5, Figure 1</u>
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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	<u>12-13</u>
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>12</u>
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10				
11	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	<u>9</u>
12				
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16	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	<u>9</u>
17				
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>9</u>
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>9</u>
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>9</u>
28				
29				
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31	Methods: Data collection, management, and analysis			
32				
33	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	<u>9-11</u>
34				
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39		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	<u>11-12</u>
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1	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	<u>9-11</u>
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4				
5	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	<u>13</u>
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>13-14</u>
9				
10		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)	<u>13</u>
11				
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14	Methods: Monitoring			
15				
16	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	<u>13-14</u>
17				
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22		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	<u>13</u>
23				
24				
25	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	<u>13</u>
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>13</u>
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>14</u>
35				
36				
37	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)	<u>14</u>
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>14</u>
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
5				
6				
7	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	<u>14</u>
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>18</u>
11				
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13	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	<u>14</u>
14				
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17	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	<u>N/A</u>
18				
19				
20	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	<u>14</u>
21				
22				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>18</u>
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>14</u>
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>N/A</u>
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33				
34	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	<u>N/A</u>
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36				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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

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Manuscript ID	bmjopen-2020-039895.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Sep-2020
Complete List of Authors:	<p>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 Health Lamunu, Maureen; Uganda Tuberculosis Implementation Research Consortium, Namale, Catherine; Uganda Tuberculosis Implementation Research Consortium, Tinka, Lynn; Uganda Tuberculosis Implementation Research Consortium,</p> <p>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</p>

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	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
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3 1 **Title:** Study protocol and implementation details for a pragmatic, stepped-wedge cluster
4 2 randomized trial of a digital adherence technology to facilitate tuberculosis treatment completion
5 3

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2
3 **37 ABSTRACT**
4

5 **38 Introduction:** Low-cost digital adherence technologies (DAT) such as 99DOTS have emerged as
6
7 **39** an alternative to directly observed therapy, (DOT), the current standard for TB treatment
8
9 **40** supervision. However, there are limited data to support DAT scale-up. The “DOT to DAT” trial
10
11 **41** aims to evaluate the effectiveness and implementation of a 99DOTS-based TB treatment
12
13 **42** supervision strategy.

14
15 **43 Methods and analysis:** This is a pragmatic, stepped-wedge cluster randomized trial, with hybrid
16
17 **44** type 2 effectiveness-implementation design. The trial will include all adults (estimated N=1890)
18
19 **45** treated for drug-susceptible pulmonary TB over an 8-month period at 18 TB treatment units in
20
21 **46** Uganda. Three sites per month will switch from routine care (DOT) to the intervention (99DOTS-
22
23 **47** based treatment supervision) beginning in Month 2, with the order determined randomly. 99DOTS
24
25 **48** enables patients to be monitored while self-administering TB medicines. Patients receive daily
26
27 **49** automated SMS dosing reminders and confirm dosing by calling toll-free numbers. The primary
28
29 **50** effectiveness outcome is the proportion of patients completing TB treatment. With 18 clusters
30
31 **51** randomized into 6 steps and an average cluster size of 15 patients per month, the study will have
32
33 **52** 89% power to detect a 10% or greater increase in treatment completion between the routine care
34
35 **53** and intervention periods. Secondary outcomes include more proximal effectiveness measures as
36
37 **54** well as quantitative and qualitative assessments of the reach, adoption and implementation of the
38
39 **55** intervention.

40
41 **56 Ethics and dissemination:** Ethics approval was granted by institutional review boards at
42
43 **57** Makerere University School of Public Health and the University of California San Francisco.
44
45 **58** Findings will be disseminated through peer-reviewed publications, presentations at scientific
46
47 **59** conferences and presentations to key stakeholders.
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51 **60**
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53 **61 Trial registration number:** PACTR201808609844917
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62 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

71 INTRODUCTION

72 Tuberculosis (TB) is the leading infectious cause of death worldwide despite being a preventable
73 and curable disease.(1) Poor adherence to medication continues to be a major obstacle to TB
74 elimination, resulting in prolonged infectiousness, emergence of multidrug resistance, and
75 increased risk of poor treatment outcomes. The World Health Organization (WHO)-recommended
76 strategy, directly observed therapy short-course (DOTS), has been the standard-of-care for TB
77 treatment supervision since the 1990s. As part of this strategy, a health worker is expected to
78 observe patients swallow each dose of anti-TB medication. However, directly observed therapy
79 (DOT) is time-consuming, costly and inconvenient for both patients and providers, while its
80 implementation is also difficult to monitor.(2, 3) Not surprisingly, TB treatment success rates
81 remain below the 90% target in most high-burden countries, despite reported DOT coverage over
82 90%.(1)

83
84 With the increase in mobile phone penetration among patients and healthcare workers in high TB
85 burden countries,(4) digital adherence technologies (DATs) could address some of the challenges
86 associated with implementation of the DOTS strategy in a patient-centered manner. To date, such
87 technologies have received only a conditional recommendation by the WHO due to very low
88 quality of evidence.(5) The first randomized trial of a DAT found that SMS reminders alone did
89 not improve medication adherence, but a medication event reminder monitor did.(6) However,
90 treatment outcomes did not improve and both trials and programmatic research have shown
91 variable uptake of DAT.(7-10)

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6 93 The “DOT to DAT” trial aims to evaluate the effectiveness, implementation and cost-effectiveness
7 94 of a culturally and contextually adapted version of 99DOTS in Uganda. 99DOTS is a low-cost
8
9 95 DAT wherein patients self-report medication adherence by calling toll-free phone numbers hidden
10
11 96 underneath pills in blister packs.(11) We present the research methods used for the first
12
13 97 randomized trial to evaluate the effectiveness and implementation of a 99DOTS-based strategy for
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15 98 TB treatment supervision in routine care settings.

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17
18 100 **Conceptual basis for trial design**
19
20 101 Numerous conceptual frameworks have emerged to improve the implementation and success of
21
22 102 health interventions through theory-based design and evaluation. The PRECEDE framework(12)
23
24 103 guided the development of the 99DOTS-based intervention strategy, while the RE-AIM
25
26 104 framework guided its comprehensive evaluation. Behavior change models including the
27
28 105 Theoretical Domains Framework (TDF)(13, 14) and the Unified Theory of Acceptance and Use
29
30 106 of Technology (UTAUT)(15, 16) guided the assessment and analysis of patient- and provider-level
31
32 107 barriers to adoption and implementation of 99DOTS.

33
34 109 The PRECEDE framework emphasizes the need for multi-faceted health promotion interventions
35
36 110 to address predisposing, enabling, and reinforcing factors in order to achieve behavior change.(12)
37
38 111 The 99DOTS-based intervention was designed to address key predisposing (social isolation and
39
40 112 the high direct and indirect cost of clinic visits), enabling (inability of health facility staff to focus
41
42 113 limited time and resources on non-adherent patients), and reinforcing (a lack of real-time
43
44 114 information on patient adherence to medications) factors related to TB treatment adherence
45
46 115 identified through the literature and formative human factors research that preceded the trial.(11)

47
48 117 The RE-AIM framework was designed to ensure that trials not only assess the effect of
49
50 118 interventions but also their translatability and public health impact.(17, 18) This hybrid type 2 trial
51
52 119 therefore focuses on the effectiveness of the 99DOTS-based intervention in improving TB
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54 120 treatment outcomes, but concurrently examines its reach into the target population, adoption by
55
56 121 target settings and staff, and implementation fidelity and costs.(19) The goal of assessing

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3 122 translatability and public health impact is further enhanced through pragmatic design choices for
4 123 each element of the trial in order to maximize applicability in real-world settings.(20)
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8 125 **METHODS AND ANALYSIS**

9 126 **Study aims**

10 127 The primary aim of the trial is to determine whether a 99DOTS-based strategy increases the
11
12 128 proportion of patients who complete TB treatment in comparison to routine care. Secondary aims
13
14 129 include 1) comparing short-term treatment outcomes and loss to follow-up between the
15
16 130 intervention and routine care arms; 2) assessing the reach, adoption and implementation of the
17
18 131 99DOTS-based strategy; and 3) evaluating the incremental costs and cost-effectiveness of the
19
20 132 99DOTS-based strategy as compared to routine care from the health system perspective. Our
21
22 133 primary hypothesis is that 99DOTS-based TB treatment supervision will improve TB treatment
23
24 134 outcomes. Our secondary hypotheses are that the 99DOTS-based strategy will have high uptake
25
26 135 among patients and providers, and be cost-effective.
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28 136

29 137 **Study design**

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31 138 This is a pragmatic, stepped-wedge randomized trial, with a hybrid type 2 implementation-
32
33 139 effectiveness design.(19) We included repeated cross-sectional samples of eligible individuals
34
35 140 initiating TB treatment at participating health facilities at 8 time points (months). Patient outcomes
36
37 141 were assigned to the health facility and month in which they initiated treatment. As depicted in
38
39 142 **Figure 1**, the intervention strategy was sequentially introduced at 3 sites each in Months 2-6, with
40
41 143 all sites under routine care in Month 1 and all sites using the intervention strategy in Month 8.
42
43 144 Following implementation of the intervention at each site, health facility staff were instructed to
44
45 145 offer 99DOTS to all new eligible patients initiating treatment and to continue supervising patients
46
47 146 already on treatment using routine care. The month of switch from control to intervention (buffer
48
49 147 period) will be excluded from analysis. We chose the stepped-wedge trial design to maximize
50
51 148 equity and acceptability (all sites will receive the intervention), minimize logistical constraints
52
53 149 associated with introducing the intervention simultaneously at a large number of sites, account for
54
55 150 secular outcome trends, and allow for iterative learning and changes in intervention roll-out as
56
57 151 would occur during eventual scale-up. We chose a highly pragmatic approach to trial
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3 152 implementation, as described in sections below, to understand the real-world impact of the
4
5 153 99DOTS-based intervention strategy.

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8 155 **Study Setting**

9
10 156 The trial is being conducted at 18 TB treatment units within hospitals and health centers across 15
11
12 157 districts of Uganda. The TB treatment units are affiliated with the Uganda National Tuberculosis
13
14 158 and Leprosy Program (NTLP) and provide TB treatment free of charge using a mix of facility- and
15
16 159 community-based DOTS. Uganda was chosen as the trial setting due to its high TB burden (200
17
18 160 cases/100,000 in 2018) and low treatment success rate (72% in 2017).(1) Previous studies have
19
20 161 found 69-75% of TB patients in Uganda have access to a phone.(21, 22)

21 162
22 163 Study sites were selected after reviewing 2016 TB treatment outcomes and 2017 TB case finding
23
24 164 data reported to the NTLP from all 1514 registered TB treatment units. We included treatment
25
26 165 units that 1) diagnosed >10 pulmonary TB patients/month in 2017, 2) were not located within
27
28 166 Kampala District (many active ongoing projects in this district), 3) were located within 225 km of
29
30 167 Kampala City (for feasibility), and 4) had a pulmonary TB treatment success rate in 2016 <80%
31
32 168 (to be able to show an impact).

33 169
34 170 Of the 1514 treatment units registered with the Uganda NTLP, 23 treatment units met our inclusion
35
36 171 criteria (**Figure 2**). The majority (n=1435) diagnosed fewer than 10 TB patients/month in 2017,
37
38 172 17 are located within Kampala district, 31 are not within 225 km of Kampala district, and 9 had a
39
40 173 treatment success rate >80% in 2016. Of the 23 remaining treatment units, we selected 18 located
41
42 174 in 15 districts (10 in Central, 7 in Eastern and 1 in Western Uganda) in consultation with the NTLP.
43
44 175 Project staff visited the Chief Administrative Officers, District Health Officers and Facility
45
46 176 Directors for the 18 sites to discuss the study. All signed a memorandum of agreement for their
47
48 177 site to participate in the study.

48 178

49 179 **Study participants**

50 180 All adult patients treated for drug-susceptible pulmonary TB at participating treatment units during
51
52 181 the study period will be eligible for inclusion. Children, patients treated for drug-resistant or
53
54 182 extrapulmonary TB, and patients transferred to another facility to complete treatment will be

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3 183 excluded. To be enrolled on 99DOTS, a patient must also have access to a phone. Surveys to assess
4 184 99DOTS implementation will be conducted in a random subset of eligible patients and all health
5 185 workers involved in TB treatment supervision at each treatment unit. Time-and-motion studies to
6 186 assess costs will also be conducted among health workers involved in TB treatment supervision at
7 187 each treatment unit.
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13 189 **Routine care and intervention strategies**

15 190 *Routine care.* The conventional approach to TB treatment supervision in Uganda is a mix of
16 191 community- and facility-based DOT, as per NTLP guidelines. At the time of treatment initiation,
17 192 treatment unit staff record patient demographic and clinical details in the NTLP register and are
18 193 supposed to provide TB-focused counseling. Most TB patients are treated using community-based
19 194 DOT, wherein they name a treatment supporter, a family member or non-family community
20 195 member, and are provided with a 2-week supply of medicines in the first two months (intensive
21 196 phase) and a one-month supply of medicines in the next four months (continuation phase) of TB
22 197 treatment. Patients take their medicines from home (with or without observation by a treatment
23 198 supporter) and return to the health facility for medication refills. At each refill visit, health facility
24 199 staff are supposed to assess adherence via patient self-report and provide additional counseling.
25 200 Health facility staff are also supposed to call or visit patients who do not return for refills, but
26 201 patient follow-up is limited across health facilities.
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37 203 *Intervention.* The 99DOTS-based intervention strategy is comprised of four main components that
38 204 address distinct barriers to successful TB treatment (**Table 1**):

- 41 205 1) Daily automated SMS dosing reminders
- 42 206 2) Daily dosing confirmation using toll-free phone calls
- 43 207 3) Weekly automated interactive voice response (IVR) check-in phone calls
- 44 208 4) Differential management protocol based on dosing history and response to IVR check-in

45 209
46 210 **Table 1. Components of the “DOT to DAT” trial intervention and corresponding barriers**
47 211 **addressed.**
48 212

Component	Barrier addressed
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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.

213
214 Formative research using human-centered design was used to adapt the generic 99DOTS product
215 to the local context, including changes to the envelope design and addition of a rotating series of
216 educational/motivational audio messages heard when patients call in to report dosing (details of
217 the formative research will be reported in a separate publication) (**Figure 3**).

218
219 TB treatment unit staff will be requested to offer 99DOTS-based treatment supervision to all
220 eligible patients initiating TB treatment, and to register patients who accept 99DOTS-based
221 treatment supervision on the 99DOTS platform via a mobile app. Given the pragmatic nature of
222 the trial, the decision to offer and accept 99DOTS-based treatment supervision will be made by
223 treatment unit staff and patients, respectively. Once registered, treatment unit staff will instruct
224 patients on how to use the 99DOTS pill pack and make a call to the 99DOTS system using the
225 toll-free number revealed when pills are pushed out of the medication blister pack (**Figure 3**). Staff
226 will also help patients personalize their 99DOTS pill pack by choosing a decorative cover,
227 educational or motivational sticker for the inside flap, writing in their health worker's contact
228 information, and selecting a time of day to take their medication (**Figure 3**).

229
230 When patients call to confirm dosing, they hear a recorded educational or motivational message
231 about continuing and completing TB treatment. Each dose confirmed via phone call is logged by
232 99DOTS and reflected on the 99DOTS smartphone app dashboard, viewable by treatment unit
233 staff. During routine drug refill visits (same schedule as described for routine care period), health

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

238
239 Health facilities using 99DOTS to manage TB patient treatment will be provided one smartphone
240 per facility, minimal funds to cover cell phone data, and an average of 300,000 US\$ (approximately
241 \$82 USD) per month to facilitate patient follow-up. Treatment unit staff will not be provided any
242 extra compensation to reflect future conditions under eventual scale-up.

243 244 **Implementation considerations**

245 99DOTS training will occur at each health facility during the month in which it is scheduled to
246 switch to the intervention. Project staff and the District TB Officer will conduct a 2-3 day training
247 jointly at each health facility using standardized training materials. Treatment unit staff will be
248 trained on how to register patients on the 99DOTS platform via a smartphone app, counsel patients
249 regarding use of 99DOTS, use the 99DOTS application to review dosing history, and conduct
250 differential management based on dosing history and response to weekly check-ins. Mentored
251 patient enrollment on 99DOTS will be conducted as part of the training.

252
253 During the trial, treatment unit staff will make all decisions regarding management of TB patients
254 in both the routine care and intervention periods. Research staff will not be onsite after training
255 with the exception of 2-3 day quarterly site visits to resolve data cleaning queries and implement
256 surveys and health economic sub-studies. Thus, the implementation is highly pragmatic and meant
257 to approximate how 99DOTS would be used at treatment units in the absence of a research study.

258 259 **Randomization**

260 The 18 health facilities will be randomly assigned to one of the six allocation sequences (**Figure**
261 **1**) using a simple, unrestricted two-stage process. This process will occur by simple drawing during
262 a public randomization ceremony held in Kampala, Uganda. A representative from each TB
263 treatment unit, district health officers, and Uganda NTLP staff will be invited to attend the
264 ceremony. First, health facilities (*i.e.*, clusters) will be randomly assigned into six blocks of three

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3 265 by having health facility representatives each draw 1 of 18 balls (3 each labeled A-F) from an
4
5 266 opaque bag. Blocks will then be randomly assigned to an intervention initiation time, which will
6
7 267 occur at equally spaced one-month intervals during the trial, by drawing of 6 balls labeled 1-6 from
8
9 268 an opaque bag.

10 269

11 270 **Blinding**

12 271 Blinding of the assigned intervention is not feasible given intervention implementation at the
13
14 272 health facility level. Where possible, the investigators and study staff, with the exception of the
15
16 273 statistician and data manager, will be blinded to aggregate TB outcomes by study period.

17 274

18 275 **Data collection and management**

19 276 *Patient-level data collection*

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21
22 277 Consistent with the pragmatic design, TB treatment outcomes will be assessed by extracting data
23
24 278 on all eligible patients from routine Uganda NTLP TB treatment registers used at all treatment
25
26 279 units. Project staff will train two health workers at each site (one primary, one backup) identified
27
28 280 by the health facility director to take photos of the register every 2-4 weeks for the duration of the
29
30 281 project using a camera-enabled smartphone, and to upload the photos to a central secure, password-
31
32 282 protected server, only accessible to staff. Health workers will be trained to delete photos from the
33
34 283 phone after upload confirmation. Completeness of TB treatment registers will be assessed, and at
35
36 284 quarterly site visits, study staff will provide re-training as needed and resolve data cleaning queries.
37
38 285 Study staff will extract data from photos of TB registers and enter data into a secure database use
39
40 286 Research Electronic Data Capture software (REDCap).(23) Data queries for missing or
41
42 287 nonsensical data will be reviewed with treatment unit staff at quarterly site visits.

43 288

44 289 *99DOTS process metrics data collection*

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46 290 During the intervention period at each site, process metric data to assess the implementation of
47
48 291 each component of the intervention strategy will be extracted from the 99DOTS server. The server
49
50 292 logs all calls made by patients to confirm dosing and doses entered manually by providers, all SMS
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52 293 messages sent to patients, and all IVR calls sent to patients and their responses.

53 294

54 295 *Qualitative data collection*

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3 296 Surveys will be conducted with 10 randomly selected eligible patients enrolled on 99DOTS (5
4 297 women and 5 men) and 1-2 eligible providers per site (180 total patients, 18-36 total providers)
5 298 beginning in Month 10 of the trial to assess the acceptability of the 99DOTS-based intervention
6 299 strategy. Research staff will contact selected patients by phone to review the verbal consent script,
7 300 answer questions the patient may have, and administer the survey to consenting patients. Provider
8 301 surveys and interviews will be conducted during quarterly site visits beginning in Month 13 of the
9 302 trial to assess factors influencing the adoption and implementation of 99DOTS.
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16 303
17 304 *Health system cost data collection*

18 305 Costing and cost-effectiveness analyses will focus on the health system perspective. Treatment
19 306 unit staff at each site will be interviewed to gain a more complete understanding of the activities
20 307 and staff involved in the operations of 99DOTS. Time-and-motion studies of health workers
21 308 (anticipated to be 3-6 health workers per site, depending on the number of staff involved in
22 309 delivering 99DOTS) will be carried out at six clinics, sampled to ensure good representation of
23 310 clinic volume and geography. These time-and-motion studies will be performed on a quarterly
24 311 basis in conjunction with site visits and will consist of direct observation of all activities conducted
25 312 by treatment unit staff over the corresponding 1-2 day evaluation period, for a total 6-12 days of
26 313 observation every three months over the course of the 14-month study period. During these
27 314 observation periods, the time and resources required to perform all activities related to TB
28 315 treatment (e.g., medication preparation, contacting patients, observing medication doses, etc.) will
29 316 be recorded. Additional costing data will be collected to assess the cost of implementing and
30 317 maintaining 99DOTS technical assistance (budget records from Everwell Health Solutions, the
31 318 creator of 99DOTS) and the cost at point of care (surveys of project staff to track resource use
32 319 during trainings). Overhead costs will be estimated using an ingredients approach, incorporating
33 320 the cost of supplies, building/space, vehicles, and human resources with incorporation of recurrent
34 321 costs such as security, vehicle maintenance costs, and all supplies (medical and administrative).
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50 323 **Outcomes**

51 324 Trial outcomes were selected in accordance with the RE-AIM evaluation framework (**Table 2**).
52 325 The primary effectiveness outcome is the proportion of patients who complete TB treatment,
53 326 defined as having an outcome of “cured” or “treatment completed” recorded in the unit TB
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327 treatment register. Secondary effectiveness outcomes include the proportion who persist on
 328 treatment through the intensive phase (*i.e.*, 56 days of treatment), the proportion lost to follow-up
 329 and estimated number of incremental disability-adjusted life years (DALYs) averted. Reach is
 330 defined as the proportion of eligible patients enrolled on 99DOTS. Adoption metrics include the
 331 proportion of scheduled doses confirmed by patient phone calls and the proportion of weekly IVR
 332 check-in calls to which patients send a response. Implementation outcomes include delivery of the
 333 intervention (proportions of daily SMS dosing reminders and weekly IVR check-in calls sent by
 334 the 99DOTS platform and received on patient handsets), acceptability (as assessed by patient and
 335 health worker surveys and interviews) and incremental costs of the 99DOTS-based intervention
 336 strategy.

337

338 **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

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340 *Power and sample size*

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2
3 341 The trial aims to demonstrate the superiority of the 99DOTS-based strategy. The sample size was
4
5 342 calculated for the primary effectiveness outcome, proportion of patients treated successfully, using
6
7 343 formulae appropriate for stepped-wedge trials. A type I error of 5% and power of at least 90% is
8
9 344 assumed. Based on 2017 data, the harmonic mean number of patients initiating treatment for drug-
10
11 345 susceptible pulmonary TB per month across participating treatment units was 15. Thus, we
12
13 346 anticipate that approximately 1890 patients will initiate treatment over the 8-month enrollment
14
15 347 period (945 in the pre- and 945 in the post-implementation phases across treatment units). The trial
16
17 348 will have 89% power to demonstrate that our strategy increases the proportion of patients treated
18
19 349 successfully by 10% or more (assumptions: $\alpha=0.05$; intraclass correlation coefficient, ICC =
20
21 350 0.001 calculated using 2017 NTLTP data for the 18 treatment units; pre-implementation treatment
22
23 351 success = 51% based on 2017 NTLTP data for the 18 treatment units; calculations performed using
24
25 352 steppedwedge command in Stata 14).

353

354 **Analysis**

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

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3 371 Quantitative reach, adoption and implementation outcomes will be summarized descriptively.
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5 372 Comparative analyses will identify factors independently associated with reach, adoption and
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7 373 implementation of intervention components. Health economic data will be used to calculate the
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9 374 incremental cost-effectiveness of the intervention strategy from a health system perspective,
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11 375 measured as the incremental cost per successfully completed treatment, comparing 99DOTS
12 376 relative to routine care.

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15 378 **Ethics and dissemination**

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17 379 Patients can choose to use or not use 99DOTS at any time during the intervention period. 99DOTS
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19 380 enables closer patient monitoring than routine TB treatment supervision, but loss of patient privacy
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21 381 is a potential concern. Data on this are being collected through patient surveys. Because of the
22
23 382 low-risk nature of the research, the Principal Investigators will be responsible for monitoring the
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25 383 data, assuring protocol compliance, and conducting safety reviews on a quarterly basis. External
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27 384 monitoring is provided by a Stop TB Partnership project officer and Monitoring and Evaluation
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29 385 consultant. The Principal Investigator will submit regular progress reports, including
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31 386 recommendations on whether the project should continue unchanged, require modification, or
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33 387 close to enrollment.

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36 389 Ethics approval was granted by institutional review boards at Makerere University School of
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38 390 Public Health and the University of California San Francisco. To ensure that the study captures all
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40 391 eligible adults initiating treatment at study sites, a waiver of informed consent was granted to
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42 392 access routine TB treatment data recorded in standard NTLR registers, such that research staff will
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44 393 not be required to be onsite to enroll and consent patients. The protocol was registered with the
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46 394 Pan-African Clinical Trials Registry (PACTR201808609844917) on 31 August 2018, updated 7
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48 395 November 2019 and complies with reporting guidelines outlined in the stepped-wedge trial
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50 396 extension of the Consolidated Standards of Reporting Trials.(24) Any major changes in protocol
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52 397 will be approved by the Stop TB Partnership project officer and both ethics committees and
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54 398 registered with the PACTR. The full protocol and statistical code will be made available upon
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56 399 request.

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3 401 Findings will be disseminated through peer-reviewed publications, presentations at scientific
4 402 conferences and presentations to key stakeholders. Drs. Cattamanchi, Katamba and Kiwanuka will
5 403 have access to the final dataset; the participant-level dataset will be made available to other
6 404 investigators who have IRB approval to analyze the data.
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11 406 **Patient and public involvement**

12 407 Patients and members of the public were involved throughout the research process. The NTLP was
13 408 involved in identifying health facilities to participate, selecting study design, and conducting
14 409 research through partnership with District Health Officers and participating health facilities.
15 410 Patients, health workers, and community members were involved in intervention design through a
16 411 human-centered design process, which included several rounds of focus groups and interviews
17 412 with stakeholders. Health workers at the 18 health facilities implemented 99DOTS without
18 413 research staff present and assisted in data collection by completing routine TB treatment registers
19 414 and sending photos of the register to the research team through secure means.
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30 416 **DISCUSSION**

31 417 99DOTS is a low-cost DAT that has the potential to improve TB treatment outcomes and the
32 418 patient experience of TB treatment in Uganda and other high-burden settings. Here, we describe
33 419 the first randomized trial designed to evaluate the effectiveness of a 99DOTS-based TB treatment
34 420 supervision strategy as part of routine care in a high burden setting. Other novel aspects of the trial
35 421 include our use of human-centered design to adapt 99DOTS to the local context with the goal of
36 422 increasing patient engagement with the technology, the use of theory and implementation science
37 423 frameworks to guide intervention design and evaluation, and our focus on simultaneously
38 424 assessing implementation and costs to guide scale-up decisions.
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47 426 Many aspects of this trial are intentionally pragmatic to ensure the outcomes reflect what can be
48 427 expected under non-research conditions.⁽²⁵⁾ The study population will include all patients with
49 428 drug susceptible pulmonary TB, with the exception of children. A waiver of consent was obtained
50 429 for patient-level data collection such that research staff will not be required to be onsite to enroll
51 430 and consent patients. Primary and key secondary outcomes will be assessed using routine data
52 431 available through NTLP registers and the 99DOTS platform, with focused additional data
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3 432 collection for implementation and cost outcomes. The intervention will be implemented by routine
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5 433 TB treatment unit staff, who also will make all decisions to offer 99DOTS-based treatment
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7 434 supervision to patients. At the same time, the stepped-wedge randomized trial design provides a
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9 435 rigorous assessment of intervention effect. Limitations of such a pragmatic trial design include less
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11 436 control over intervention delivery and potential limited uptake of the intervention given the wide
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13 437 inclusion criteria (all adults initiating treatment for drug-susceptible pulmonary TB). In order to
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15 438 enroll enough patients to assess the effectiveness of the 99DOTS-based intervention, we selected
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17 439 facilities that treat larger numbers of TB patients. Uptake and effectiveness of 99DOTS may be
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19 440 different at lower volume health centers.

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21 441
22 442 In summary, this pragmatic, hybrid type 2 effectiveness-implementation trial is well poised to
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24 443 assess both the effectiveness of an adapted 99DOTS-based intervention and potential barriers and
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26 444 facilitators to its scale-up if successful. The design and implementation of this trial intend to
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28 445 generate results to inform decisions on whether and how to implement 99DOTS in Uganda and
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30 446 other high burden countries.

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521

522 **Authors' contributions**

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

526

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531 study sponsor is not involved in data collection, analysis or interpretation.

532

533 **Competing Interests**

534 The authors have no conflicts of interest to report.

535

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

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

545

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

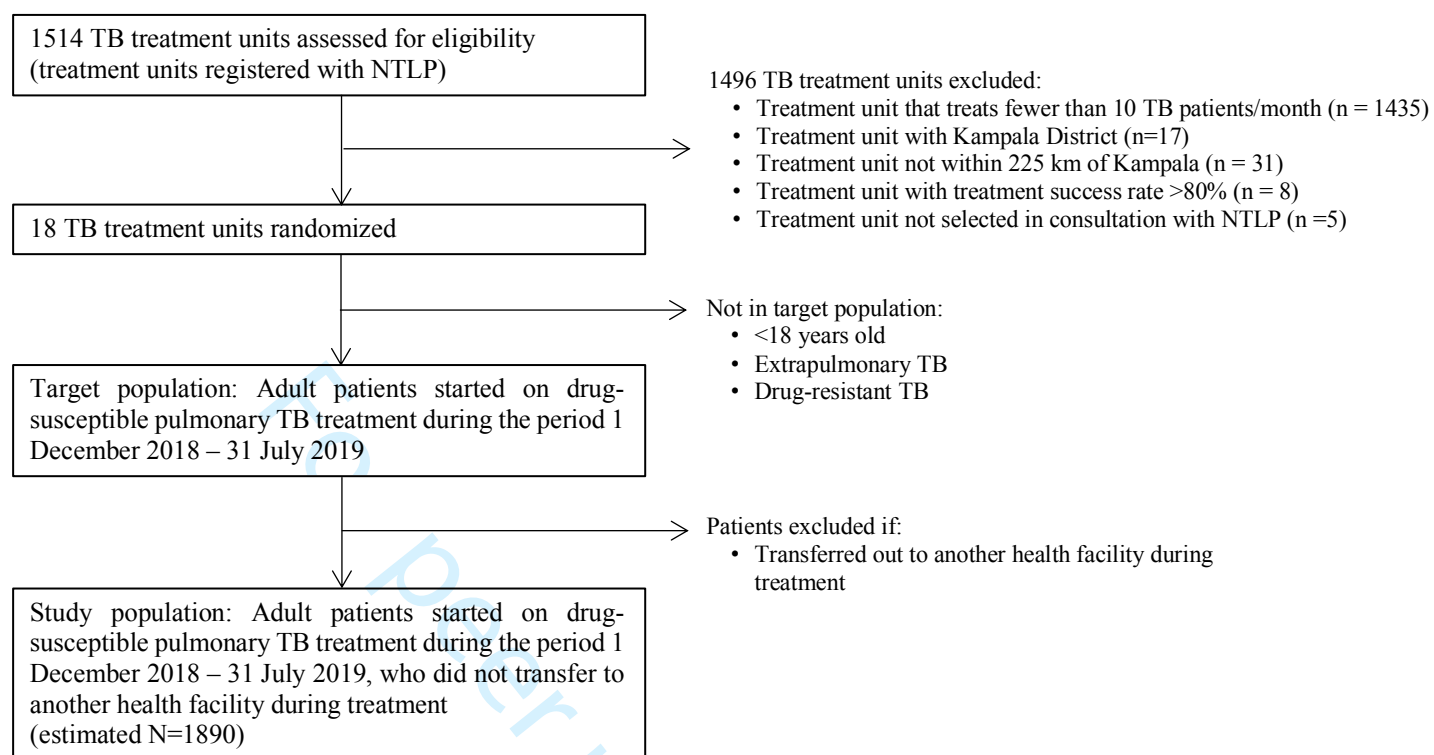
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3 552 right). In addition, the audio tone heard when patients make daily phone calls to report medication
4 553 dosing was replaced with a rotating series of educational or motivational messages recorded by
5 554 local health workers.
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For peer review only

	Month							
	1	2	3	4	5	6	7	8
Block 1								
Block 2								
Block 3								
Block 4								
Block 5								
Block 6								

	Routine care (control period)
	Switch to 99DOTS (buffer period)
	99DOTS implementation (intervention period)

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.

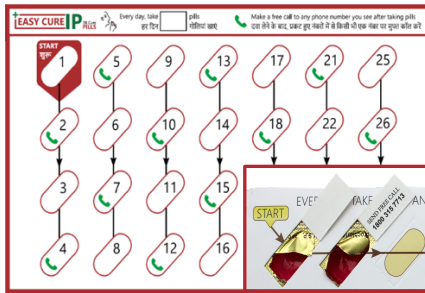


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Figure 2. Flow diagram of TB treatment units and patients included in the DOT to DAT trial. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Original 99DOTS Envelope

Front of envelope



Back of envelope

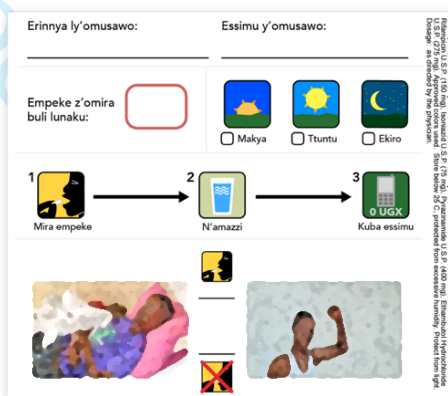


Adapted 99DOTS envelope

Front cover



Inside cover



Back of envelope

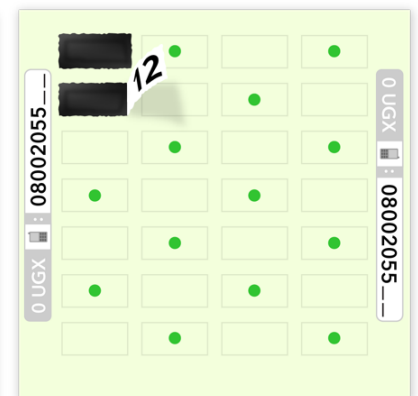


Figure 3. Original and adapted versions of the 99DOTS envelope. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space 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.	
	1b	Structured summary of trial design, methods, results, and conclusions (see separate SW-CRT checklist for abstracts).	
Introduction			
Background and objectives	2a	Scientific background. Rationale for using a cluster design and rationale for using a stepped wedge design.	
	2b	Specific objectives or hypotheses.	
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.	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.	
Participants	4a	Eligibility criteria for clusters and participants.	
	4b	Settings and locations where the data were collected.	
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.	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.	
	6b	Any changes to trial outcomes after the trial commenced, with reasons.	
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).	
	7b	When applicable, explanation of any interim analyses and stopping guidelines.	
Randomisation			
Sequence generation	8a	Method used to generate the random allocation to the sequences of treatments.	
	8b	Type of randomisation; details of any constrained randomisation or stratification, if used.	
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.	
Implementation	10a	Who generated the randomisation schedule, who enrolled clusters, and who assigned clusters to sequences.	
	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.	
	10c	Whether, from whom and when consent was sought and for what; whether this differed between treatment conditions.	
Blinding	11a	If done, who was blinded after assignment to sequences (eg, cluster level participants, individual level participants, those assessing outcomes) and how.	
	11b	If relevant, description of the similarity of treatments.	
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.	
	12b	Methods for additional analyses, such as subgroup analyses, sensitivity analyses, and adjusted analyses.	

(Continued)

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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).	
	13b	For each treatment condition or allocated sequence, losses and exclusions for both clusters and participants with reasons.	
Recruitment	14a	Dates defining the steps, initiation of intervention, and deviations from planned dates. Dates defining recruitment and follow-up for participants.	
	14b	Why the trial ended or was stopped.	
Baseline data	15	Baseline characteristics for the individual and cluster levels as applicable for each treatment condition or allocated sequence.	
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.	
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.	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended.	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.	
Harms	19	Important harms or unintended effects in each treatment condition (for specific guidance see CONSORT for harms).	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses.	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings. Generalisability to clusters or individual participants, or both (as relevant).	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.	
Other information			
Registration	23	Registration number and name of trial registry.	
Protocol	24	Where the full trial protocol can be accessed, if available.	
Funding	25	Sources of funding and other support (such as supply of drugs), and the role of funders.	
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.	

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

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





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

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2
3 **37 ABSTRACT**
4

5 **38 Introduction:** Low-cost digital adherence technologies (DAT) such as 99DOTS have emerged as
6
7 **39** an alternative to directly observed therapy, (DOT), the current standard for TB treatment
8
9 **40** supervision. However, there are limited data to support DAT scale-up. The “DOT to DAT” trial
10
11 **41** aims to evaluate the effectiveness and implementation of a 99DOTS-based TB treatment
12
13 **42** supervision strategy.

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15 **43 Methods and analysis:** This is a pragmatic, stepped-wedge cluster randomized trial, with hybrid
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17 **44** type 2 effectiveness-implementation design. The trial will include all adults (estimated N=1890)
18
19 **45** treated for drug-susceptible pulmonary TB over an 8-month period at 18 TB treatment units in
20
21 **46** Uganda. Three sites per month will switch from routine care (DOT) to the intervention (99DOTS-
22
23 **47** based treatment supervision) beginning in Month 2, with the order determined randomly. 99DOTS
24
25 **48** enables patients to be monitored while self-administering TB medicines. Patients receive daily
26
27 **49** automated SMS dosing reminders and confirm dosing by calling toll-free numbers. The primary
28
29 **50** effectiveness outcome is the proportion of patients completing TB treatment. With 18 clusters
30
31 **51** randomized into 6 steps and an average cluster size of 15 patients per month, the study will have
32
33 **52** 89% power to detect a 10% or greater increase in treatment completion between the routine care
34
35 **53** and intervention periods. Secondary outcomes include more proximal effectiveness measures as
36
37 **54** well as quantitative and qualitative assessments of the reach, adoption and implementation of the
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39 **55** intervention.

40
41 **56 Ethics and dissemination:** Ethics approval was granted by institutional review boards at
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43 **57** Makerere University School of Public Health and the University of California San Francisco.
44
45 **58** Findings will be disseminated through peer-reviewed publications, presentations at scientific
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47 **59** conferences and presentations to key stakeholders.
48

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51 **60**
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53 **61 Trial registration number:** PACTR201808609844917
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62 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

72 INTRODUCTION

73 Tuberculosis (TB) is the leading infectious cause of death worldwide despite being a preventable
74 and curable disease.(1) Poor adherence to medication continues to be a major obstacle to TB
75 elimination, resulting in prolonged infectiousness, emergence of multidrug resistance, and
76 increased risk of poor treatment outcomes. The World Health Organization (WHO)-recommended
77 strategy, directly observed therapy short-course (DOTS), has been the standard-of-care for TB
78 treatment supervision since the 1990s. As part of this strategy, a health worker is expected to
79 observe patients swallow each dose of anti-TB medication. However, directly observed therapy
80 (DOT) is time-consuming, costly and inconvenient for both patients and providers, while its
81 implementation is also difficult to monitor.(2, 3) Not surprisingly, TB treatment success rates
82 remain below the 90% target in most high-burden countries, despite reported DOT coverage over
83 90%.(1)

84
85 With the increase in mobile phone penetration among patients and healthcare workers in high TB
86 burden countries,(4) digital adherence technologies (DATs) could address some of the challenges
87 associated with implementation of the DOTS strategy in a patient-centered manner. To date, such
88 technologies have received only a conditional recommendation by the WHO due to very low
89 quality of evidence.(5) The first randomized trial of a DAT found that SMS reminders alone did
90 not improve medication adherence, but a medication event reminder monitor did.(6) However,
91 treatment outcomes did not improve and both trials and programmatic research have shown
92 variable uptake of DAT.(7-10)

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3 93
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5 94 The “DOT to DAT” trial aims to evaluate the effectiveness, implementation and cost-effectiveness
6 95 of a culturally and contextually adapted version of 99DOTS in Uganda. 99DOTS is a low-cost
7 96 DAT wherein patients self-report medication adherence by calling toll-free phone numbers hidden
8
9 97 underneath pills in blister packs.(11) We present the research methods used for the first
10
11 98 randomized trial to evaluate the effectiveness and implementation of a 99DOTS-based strategy for
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13 99 TB treatment supervision in routine care settings.
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16 100

17 101 **Conceptual basis for trial design**

18
19 102 Numerous conceptual frameworks have emerged to improve the implementation and success of
20
21 103 health interventions through theory-based design and evaluation. The PRECEDE framework(12)
22
23 104 guided the development of the 99DOTS-based intervention strategy, while the RE-AIM
24
25 105 framework guided its comprehensive evaluation. Behavior change models including the
26
27 106 Theoretical Domains Framework (TDF)(13, 14) and the Unified Theory of Acceptance and Use
28
29 107 of Technology (UTAUT)(15, 16) guided the assessment and analysis of patient- and provider-level
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31 108 barriers to adoption and implementation of 99DOTS.
32

33 109

34 110 The PRECEDE framework emphasizes the need for multi-faceted health promotion interventions
35
36 111 to address predisposing, enabling, and reinforcing factors in order to achieve behavior change.(12)
37
38 112 The 99DOTS-based intervention was designed to address key predisposing (social isolation and
39
40 113 the high direct and indirect cost of clinic visits), enabling (inability of health facility staff to focus
41
42 114 limited time and resources on non-adherent patients), and reinforcing (a lack of real-time
43
44 115 information on patient adherence to medications) factors related to TB treatment adherence
45
46 116 identified through the literature and formative human factors research that preceded the trial.(11)
47

48 117

49 118 The RE-AIM framework was designed to ensure that trials not only assess the effect of
50
51 119 interventions but also their translatability and public health impact.(17, 18) This hybrid type 2 trial
52
53 120 therefore focuses on the effectiveness of the 99DOTS-based intervention in improving TB
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55 121 treatment outcomes, but concurrently examines its reach into the target population, adoption by
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57 122 target settings and staff, and implementation fidelity and costs.(19) The goal of assessing
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3 123 translatability and public health impact is further enhanced through pragmatic design choices for
4 124 each element of the trial in order to maximize applicability in real-world settings.(20)

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7 8 126 **METHODS AND ANALYSIS**

9 10 127 **Study aims**

11 128 The primary aim of the trial is to determine whether a 99DOTS-based strategy increases the
12 129 proportion of patients who complete TB treatment in comparison to routine care. Secondary aims
13 130 include 1) comparing short-term treatment outcomes and loss to follow-up between the
14 131 intervention and routine care arms; 2) assessing the reach, adoption and implementation of the
15 132 99DOTS-based strategy; and 3) evaluating the incremental costs and cost-effectiveness of the
16 133 99DOTS-based strategy as compared to routine care from the health system perspective. Our
17 134 primary hypothesis is that 99DOTS-based TB treatment supervision will improve TB treatment
18 135 outcomes. Our secondary hypotheses are that the 99DOTS-based strategy will have high uptake
19 136 among patients and providers, and be cost-effective.

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28 29 138 **Study design**

30 139 This is a pragmatic, stepped-wedge randomized trial, with a hybrid type 2 implementation-
31 140 effectiveness design.(19) We included repeated cross-sectional samples of eligible individuals
32 141 initiating TB treatment at participating health facilities at 8 time points (months). Patient outcomes
33 142 were assigned to the health facility and month in which they initiated treatment. As depicted in
34 143 **Figure 1**, the intervention strategy was sequentially introduced at 3 sites each in Months 2-6, with
35 144 all sites under routine care in Month 1 and all sites using the intervention strategy in Month 8.
36 145 Following implementation of the intervention at each site, health facility staff were instructed to
37 146 offer 99DOTS to all new eligible patients initiating treatment and to continue supervising patients
38 147 already on treatment using routine care. The month of switch from control to intervention (buffer
39 148 period) will be excluded from analysis. We chose the stepped-wedge trial design to maximize
40 149 equity and acceptability (all sites will receive the intervention), minimize logistical constraints
41 150 associated with introducing the intervention simultaneously at a large number of sites, account for
42 151 secular outcome trends, and allow for iterative learning and changes in intervention roll-out as
43 152 would occur during eventual scale-up. We chose a highly pragmatic approach to trial

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3 153 implementation, as described in sections below, to understand the real-world impact of the
4
5 154 99DOTS-based intervention strategy.

6
7 155

8 156 **Study Setting**

9
10 157 The trial is being conducted at 18 TB treatment units within hospitals and health centers across 15
11
12 158 districts of Uganda. The TB treatment units are affiliated with the Uganda National Tuberculosis
13
14 159 and Leprosy Program (NTLP) and provide TB treatment free of charge using a mix of facility- and
15
16 160 community-based DOTS. Uganda was chosen as the trial setting due to its high TB burden (200
17
18 161 cases/100,000 in 2018) and low treatment success rate (72% in 2017).(1) Previous studies have
19
20 162 found 69-75% of TB patients in Uganda have access to a phone.(21, 22)

21
22 163

23 164 Study sites were selected after reviewing 2016 TB treatment outcomes and 2017 TB case finding
24
25 165 data reported to the NTLP from all 1514 registered TB treatment units. We included treatment
26
27 166 units that 1) diagnosed >10 pulmonary TB patients/month in 2017, 2) were not located within
28
29 167 Kampala District (many active ongoing projects in this district), 3) were located within 225 km of
30
31 168 Kampala City (for feasibility), and 4) had a pulmonary TB treatment success rate in 2016 <80%
32
33 169 (to be able to show an impact).

34
35 170

36 171 Of the 1514 treatment units registered with the Uganda NTLP, 23 treatment units met our inclusion
37
38 172 criteria (**Figure 2**). The majority (n=1435) diagnosed fewer than 10 TB patients/month in 2017,
39
40 173 17 are located within Kampala district, 31 are not within 225 km of Kampala district, and 9 had a
41
42 174 treatment success rate >80% in 2016. Of the 23 remaining treatment units, we selected 18 located
43
44 175 in 15 districts (10 in Central, 7 in Eastern and 1 in Western Uganda) in consultation with the NTLP.
45
46 176 Project staff visited the Chief Administrative Officers, District Health Officers and Facility
47
48 177 Directors for the 18 sites to discuss the study. All signed a memorandum of agreement for their
49
50 178 site to participate in the study.

51
52 179

53 180 **Study participants**

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55 181 All adult patients treated for drug-susceptible pulmonary TB at participating treatment units during
56
57 182 the study period will be eligible for inclusion. Children, patients treated for drug-resistant or
58
59 183 extrapulmonary TB, and patients transferred to another facility to complete treatment will be

184 excluded. To be enrolled on 99DOTS, a patient must also have access to a phone. Surveys to assess
 185 99DOTS implementation will be conducted in a random subset of eligible patients and all health
 186 workers involved in TB treatment supervision at each treatment unit. Time-and-motion studies to
 187 assess costs will also be conducted among health workers involved in TB treatment supervision at
 188 each treatment unit.

189

190 **Routine care and intervention strategies**

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

203

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

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

210

211 **Table 1. Components of the “DOT to DAT” trial intervention and corresponding barriers**
 212 **addressed.**

213

Component	Barrier addressed
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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.

214
215 Formative research using human-centered design was used to adapt the generic 99DOTS product
216 to the local context, including changes to the envelope design and addition of a rotating series of
217 educational/motivational audio messages heard when patients call in to report dosing (details of
218 the formative research will be reported in a separate publication) (**Figure 3**).

219
220 TB treatment unit staff will be requested to offer 99DOTS-based treatment supervision to all
221 eligible patients initiating TB treatment, and to register patients who accept 99DOTS-based
222 treatment supervision on the 99DOTS platform via a mobile app. Given the pragmatic nature of
223 the trial, the decision to offer and accept 99DOTS-based treatment supervision will be made by
224 treatment unit staff and patients, respectively. Once registered, treatment unit staff will instruct
225 patients on how to use the 99DOTS pill pack and make a call to the 99DOTS system using the
226 toll-free number revealed when pills are pushed out of the medication blister pack (**Figure 3**). Staff
227 will also help patients personalize their 99DOTS pill pack by choosing a decorative cover,
228 educational or motivational sticker for the inside flap, writing in their health worker's contact
229 information, and selecting a time of day to take their medication (**Figure 3**).

230
231 When patients call to confirm dosing, they hear a recorded educational or motivational message
232 about continuing and completing TB treatment. Each dose confirmed via phone call is logged by
233 99DOTS and reflected on the 99DOTS smartphone app dashboard, viewable by treatment unit
234 staff. During routine drug refill visits (same schedule as described for routine care period), health

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

239
240 Health facilities using 99DOTS to manage TB patient treatment will be provided one smartphone
241 per facility, minimal funds to cover cell phone data, and an average of 300,000 US\$ (approximately
242 \$82 USD) per month to facilitate patient follow-up. Treatment unit staff will not be provided any
243 extra compensation to reflect future conditions under eventual scale-up.

244 245 **Implementation considerations**

246 99DOTS training will occur at each health facility during the month in which it is scheduled to
247 switch to the intervention. Project staff and the District TB Officer will conduct a 2-3 day training
248 jointly at each health facility using standardized training materials. Treatment unit staff will be
249 trained on how to register patients on the 99DOTS platform via a smartphone app, counsel patients
250 regarding use of 99DOTS, use the 99DOTS application to review dosing history, and conduct
251 differential management based on dosing history and response to weekly check-ins. Mentored
252 patient enrollment on 99DOTS will be conducted as part of the training.

253
254 During the trial, treatment unit staff will make all decisions regarding management of TB patients
255 in both the routine care and intervention periods. Research staff will not be onsite after training
256 with the exception of 2-3 day quarterly site visits to resolve data cleaning queries and implement
257 surveys and health economic sub-studies. Thus, the implementation is highly pragmatic and meant
258 to approximate how 99DOTS would be used at treatment units in the absence of a research study.

259 260 **Randomization**

261 The 18 health facilities will be randomly assigned to one of the six allocation sequences (**Figure**
262 **1**) using a simple, unrestricted two-stage process. This process will occur by simple drawing during
263 a public randomization ceremony held in Kampala, Uganda. A representative from each TB
264 treatment unit, district health officers, and Uganda NTLP staff will be invited to attend the
265 ceremony. First, health facilities (*i.e.*, clusters) will be randomly assigned into six blocks of three

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3 266 by having health facility representatives each draw 1 of 18 balls (3 each labeled A-F) from an
4
5 267 opaque bag. Blocks will then be randomly assigned to an intervention initiation time, which will
6
7 268 occur at equally spaced one-month intervals during the trial, by drawing of 6 balls labeled 1-6 from
8
9 269 an opaque bag.

10 270

11 271 **Blinding**

12 272 Blinding of the assigned intervention is not feasible given intervention implementation at the
13
14 273 health facility level. Where possible, the investigators and study staff, with the exception of the
15
16 274 statistician and data manager, will be blinded to aggregate TB outcomes by study period.

17 275

18 276 **Data collection and management**

19 277 *Patient-level data collection*

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21
22 278 Consistent with the pragmatic design, TB treatment outcomes will be assessed by extracting data
23
24 279 on all eligible patients from routine Uganda NTLP TB treatment registers used at all treatment
25
26 280 units. Project staff will train two health workers at each site (one primary, one backup) identified
27
28 281 by the health facility director to take photos of the register every 2-4 weeks for the duration of the
29
30 282 project using a camera-enabled smartphone, and to upload the photos to a central secure, password-
31
32 283 protected server, only accessible to staff. Health workers will be trained to delete photos from the
33
34 284 phone after upload confirmation. Completeness of TB treatment registers will be assessed, and at
35
36 285 quarterly site visits, study staff will provide re-training as needed and resolve data cleaning queries.
37
38 286 Study staff will extract data from photos of TB registers and enter data into a secure database use
39
40 287 Research Electronic Data Capture software (REDCap).(23) Data queries for missing or
41
42 288 nonsensical data will be reviewed with treatment unit staff at quarterly site visits.

43 289

44 290 *99DOTS process metrics data collection*

45
46 291 During the intervention period at each site, process metric data to assess the implementation of
47
48 292 each component of the intervention strategy will be extracted from the 99DOTS server. The server
49
50 293 logs all calls made by patients to confirm dosing and doses entered manually by providers, all SMS
51
52 294 messages sent to patients, and all IVR calls sent to patients and their responses.

53 295

54 296 *Qualitative data collection*

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3 297 Surveys will be conducted with 10 randomly selected eligible patients enrolled on 99DOTS (5
4 298 women and 5 men) and 1-2 eligible providers per site (180 total patients, 18-36 total providers)
5 299 beginning in Month 10 of the trial to assess the acceptability of the 99DOTS-based intervention
6 300 strategy. Research staff will contact selected patients by phone to review the verbal consent script,
7 301 answer questions the patient may have, and administer the survey to consenting patients. Provider
8 302 surveys and interviews will be conducted during quarterly site visits beginning in Month 13 of the
9 303 trial to assess factors influencing the adoption and implementation of 99DOTS.
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17 305 *Health system cost data collection*

18 306 Costing and cost-effectiveness analyses will focus on the health system perspective. Treatment
19 307 unit staff at each site will be interviewed to gain a more complete understanding of the activities
20 308 and staff involved in the operations of 99DOTS. Time-and-motion studies of health workers
21 309 (anticipated to be 3-6 health workers per site, depending on the number of staff involved in
22 310 delivering 99DOTS) will be carried out at six clinics, sampled to ensure good representation of
23 311 clinic volume and geography. These time-and-motion studies will be performed on a quarterly
24 312 basis in conjunction with site visits and will consist of direct observation of all activities conducted
25 313 by treatment unit staff over the corresponding 1-2 day evaluation period, for a total 6-12 days of
26 314 observation every three months over the course of the 14-month study period. During these
27 315 observation periods, the time and resources required to perform all activities related to TB
28 316 treatment (e.g., medication preparation, contacting patients, observing medication doses, etc.) will
29 317 be recorded. Additional costing data will be collected to assess the cost of implementing and
30 318 maintaining 99DOTS technical assistance (budget records from Everwell Health Solutions, the
31 319 creator of 99DOTS) and the cost at point of care (surveys of project staff to track resource use
32 320 during trainings). Overhead costs will be estimated using an ingredients approach, incorporating
33 321 the cost of supplies, building/space, vehicles, and human resources with incorporation of recurrent
34 322 costs such as security, vehicle maintenance costs, and all supplies (medical and administrative).
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50 324 **Outcomes**

51 325 Trial outcomes were selected in accordance with the RE-AIM evaluation framework (**Table 2**).
52 326 The primary effectiveness outcome is the proportion of patients who complete TB treatment,
53 327 defined as having an outcome of “cured” or “treatment completed” recorded in the unit TB
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328 treatment register. Secondary effectiveness outcomes include the proportion who persist on
 329 treatment through the intensive phase (*i.e.*, 56 days of treatment), the proportion lost to follow-up
 330 and estimated number of incremental disability-adjusted life years (DALYs) averted. Reach is
 331 defined as the proportion of eligible patients enrolled on 99DOTS. Adoption metrics include the
 332 proportion of scheduled doses confirmed by patient phone calls and the proportion of weekly IVR
 333 check-in calls to which patients send a response. Implementation outcomes include delivery of the
 334 intervention (proportions of daily SMS dosing reminders and weekly IVR check-in calls sent by
 335 the 99DOTS platform and received on patient handsets), acceptability (as assessed by patient and
 336 health worker surveys and interviews) and incremental costs of the 99DOTS-based intervention
 337 strategy.

338

339 **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

340

341 *Power and sample size*

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2
3 342 The trial aims to demonstrate the superiority of the 99DOTS-based strategy. The sample size was
4
5 343 calculated for the primary effectiveness outcome, proportion of patients treated successfully, using
6
7 344 formulae appropriate for stepped-wedge trials. A type I error of 5% and power of at least 90% is
8
9 345 assumed. Based on 2017 data, the harmonic mean number of patients initiating treatment for drug-
10
11 346 susceptible pulmonary TB per month across participating treatment units was 15. Thus, we
12
13 347 anticipate that approximately 1890 patients will initiate treatment over the 8-month enrollment
14
15 348 period (945 in the pre- and 945 in the post-implementation phases across treatment units). The trial
16
17 349 will have 89% power to demonstrate that our strategy increases the proportion of patients treated
18
19 350 successfully by 10% or more (assumptions: $\alpha=0.05$; intraclass correlation coefficient, ICC =
20
21 351 0.001 calculated using 2017 NTLTP data for the 18 treatment units; pre-implementation treatment
22
23 352 success = 51% based on 2017 NTLTP data for the 18 treatment units; calculations performed using
24
25 353 steppedwedge command in Stata 14).

26 354

27 355 **Analysis**

28 356 The primary effectiveness analysis will be conducted at the health facility level using multivariable
29
30 357 mixed effect logit models with random effects for site and fixed effects for trial period, time, and
31
32 358 confounders (using Stata's `melogit` and `meqrlogit` commands). Analysis will be done for intention
33
34 359 to treat (all eligible patients) and per protocol (excluding patients who are not enrolled on 99DOTS
35
36 360 during the intervention period at each site) populations. Models will adjust for the longitudinal
37
38 361 design (indicator variable for each trial month) and clustering by site (random effect for health
39
40 362 facility). Patients initiating treatment during the month in which sites switch from routine treatment
41
42 363 supervision to the intervention strategy will be excluded (buffer period). Potential confounders,
43
44 364 selected *a priori*, including sex, HIV status, disease class (bacteriologically confirmed vs.
45
46 365 clinically diagnosed), and TB type (new vs. retreatment), will be included in the model as fixed
47
48 366 effects. Secondary effectiveness outcomes (**Table 2**) will be analyzed in the same manner.
49
50 367 Subgroup analyses will stratify by gender, HIV status, and health facility. To further assess the
51
52 368 robustness of our findings, [we will conduct sensitivity analyses that include patients who initiated
53
54 369 treatment during the buffer period, impute outcomes for patients lost to follow up and compare
55
56 370 treatment outcomes using permutation tests.](#)(24)

57 371

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3 372 Quantitative reach, adoption and implementation outcomes will be summarized descriptively.
4
5 373 Comparative analyses will identify factors independently associated with reach, adoption and
6
7 374 implementation of intervention components. Health economic data will be used to calculate the
8
9 375 incremental cost-effectiveness of the intervention strategy from a health system perspective,
10
11 376 measured as the incremental cost per successfully completed treatment, comparing 99DOTS
12 377 relative to routine care.

13
14 378

15 379 **Ethics and dissemination**

16
17 380 Patients can choose to use or not use 99DOTS at any time during the intervention period. 99DOTS
18
19 381 enables closer patient monitoring than routine TB treatment supervision, but loss of patient privacy
20
21 382 is a potential concern. Data on this are being collected through patient surveys. Because of the
22
23 383 low-risk nature of the research, the Principal Investigators will be responsible for monitoring the
24
25 384 data, assuring protocol compliance, and conducting safety reviews on a quarterly basis. External
26
27 385 monitoring is provided by a Stop TB Partnership project officer and Monitoring and Evaluation
28
29 386 consultant. The Principal Investigator will submit regular progress reports, including
30
31 387 recommendations on whether the project should continue unchanged, require modification, or
32
33 388 close to enrollment.

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35 389

36 390 Ethics approval was granted by institutional review boards at Makerere University School of
37
38 391 Public Health and the University of California San Francisco. To ensure that the study captures all
39
40 392 eligible adults initiating treatment at study sites, a waiver of informed consent was granted to
41
42 393 access routine TB treatment data recorded in standard NTLP registers, such that research staff will
43
44 394 not be required to be onsite to enroll and consent patients. The protocol was registered with the
45
46 395 Pan-African Clinical Trials Registry (PACTR201808609844917) on 31 August 2018, updated 7
47
48 396 November 2019 and complies with reporting guidelines outlined in the stepped-wedge trial
49
50 397 extension of the Consolidated Standards of Reporting Trials.(25) Any major changes in protocol
51
52 398 will be approved by the Stop TB Partnership project officer and both ethics committess and
53
54 399 registered with the PACTR. The full protocol and statistical code will be made available upon
55
56 400 request.

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3 402 Findings will be disseminated through peer-reviewed publications, presentations at scientific
4 403 conferences and presentations to key stakeholders. Drs. Cattamanchi, Katamba and Kiwanuka will
5 404 have access to the final dataset; the participant-level dataset will be made available to other
6 405 investigators who have IRB approval to analyze the data.
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10 406

11 407 **Patient and public involvement**

12 408 Patients and members of the public were involved throughout the research process. The NTLP was
13 409 involved in identifying health facilities to participate, selecting study design, and conducting
14 410 research through partnership with District Health Officers and participating health facilities.
15 411 Patients, health workers, and community members were involved in intervention design through a
16 412 human-centered design process, which included several rounds of focus groups and interviews
17 413 with stakeholders. Health workers at the 18 health facilities implemented 99DOTS without
18 414 research staff present and assisted in data collection by completing routine TB treatment registers
19 415 and sending photos of the register to the research team through secure means.
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28 416

29 417 **DISCUSSION**

30 418 99DOTS is a low-cost DAT that has the potential to improve TB treatment outcomes and the
31 419 patient experience of TB treatment in Uganda and other high-burden settings. Here, we describe
32 420 the first randomized trial designed to evaluate the effectiveness of a 99DOTS-based TB treatment
33 421 supervision strategy as part of routine care in a high burden setting. Other novel aspects of the trial
34 422 include our use of human-centered design to adapt 99DOTS to the local context with the goal of
35 423 increasing patient engagement with the technology, the use of theory and implementation science
36 424 frameworks to guide intervention design and evaluation, and our focus on simultaneously
37 425 assessing implementation and costs to guide scale-up decisions.
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45 426

46 427 Many aspects of this trial are intentionally pragmatic to ensure the outcomes reflect what can be
47 428 expected under non-research conditions.(26) The study population will include all patients with
48 429 drug susceptible pulmonary TB, with the exception of children. A waiver of consent was obtained
49 430 for patient-level data collection such that research staff will not be required to be onsite to enroll
50 431 and consent patients. Primary and key secondary outcomes will be assessed using routine data
51 432 available through NTLP registers and the 99DOTS platform, with focused additional data
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3 433 collection for implementation and cost outcomes. The intervention will be implemented by routine
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5 434 TB treatment unit staff, who also will make all decisions to offer 99DOTS-based treatment
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7 435 supervision to patients. At the same time, the stepped-wedge randomized trial design provides a
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9 436 rigorous assessment of intervention effect. Limitations of such a pragmatic trial design include less
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11 437 control over intervention delivery, potential limited uptake of the intervention given the wide
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13 438 inclusion criteria (all adults initiating treatment for drug-susceptible pulmonary TB) and inability
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15 439 to rigorously verify medication adherence during the control and intervention periods. In order to
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17 440 enroll enough patients to assess the effectiveness of the 99DOTS-based intervention, we selected
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19 441 facilities that treat larger numbers of TB patients. Uptake and effectiveness of 99DOTS may be
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21 442 different at lower volume health centers.

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24 444 In summary, this pragmatic, hybrid type 2 effectiveness-implementation trial is well poised to
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26 445 assess both the effectiveness of an adapted 99DOTS-based intervention and potential barriers and
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28 446 facilitators to its scale-up if successful. The design and implementation of this trial intend to
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30 447 generate results to inform decisions on whether and how to implement 99DOTS in Uganda and
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32 448 other high burden countries.
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525 **Authors' contributions**

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

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536 **Competing Interests**

537 The authors have no conflicts of interest to report.

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

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

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

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3 555 right). In addition, the audio tone heard when patients make daily phone calls to report medication
4 556 dosing was replaced with a rotating series of educational or motivational messages recorded by
5 557 local health workers.
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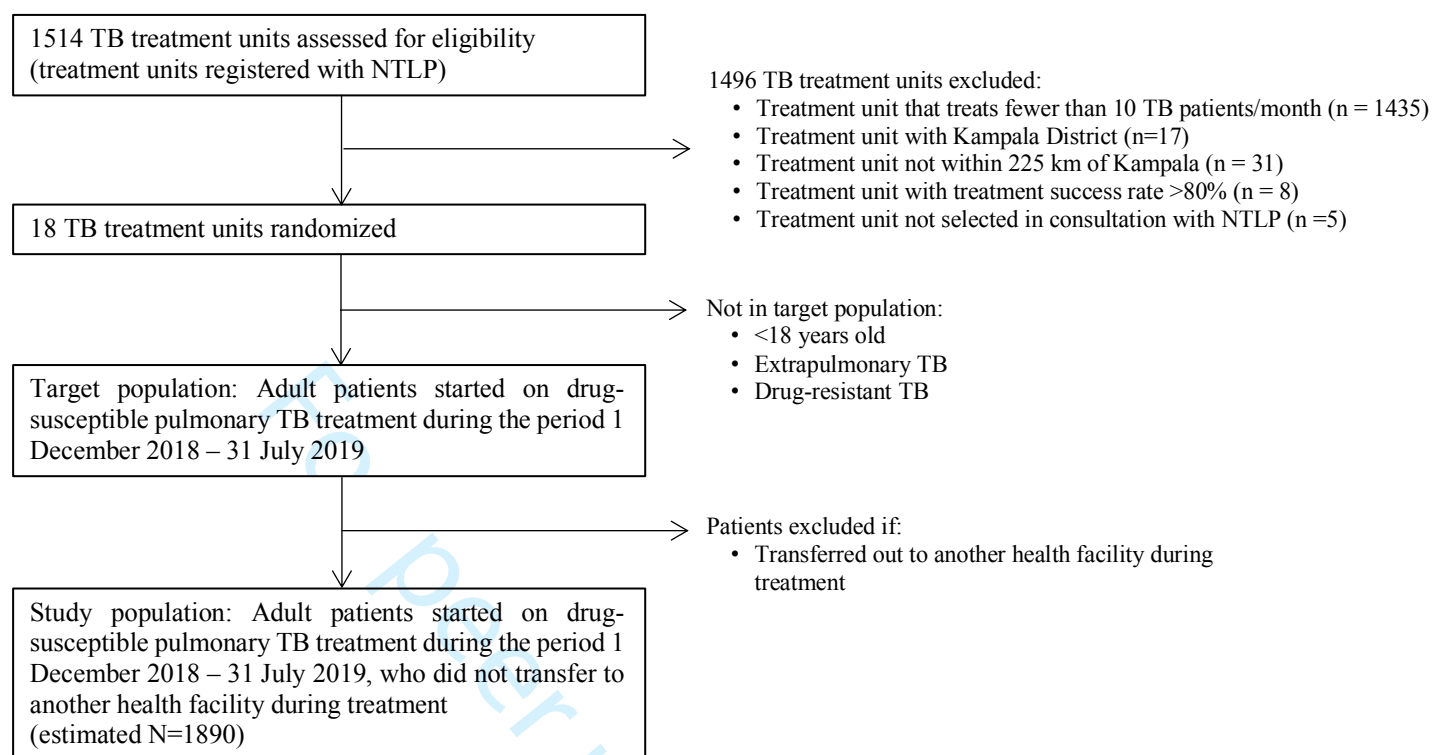
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	Month							
	1	2	3	4	5	6	7	8
Block 1								
Block 2								
Block 3								
Block 4								
Block 5								
Block 6								

	Routine care (control period)
	Switch to 99DOTS (buffer period)
	99DOTS implementation (intervention period)

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.

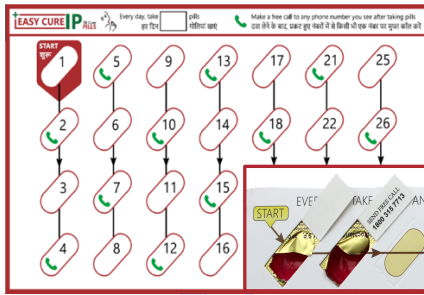


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Figure 2. Flow diagram of TB treatment units and patients included in the DOT to DAT trial. Eighteen TB treatment units were randomized, and all eligible patients initiating TB treatment at these facilities during the study period will be analyzed.

Original 99DOTS Envelope

Front of envelope



Back of envelope

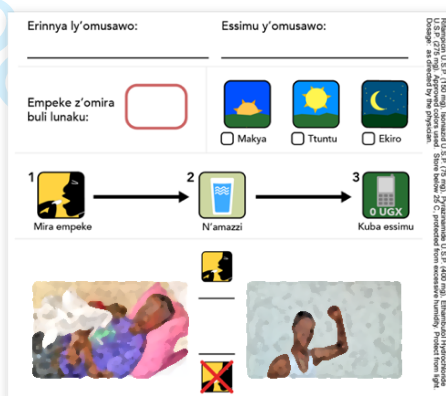


Adapted 99DOTS envelope

Front cover



Inside cover



Back of envelope

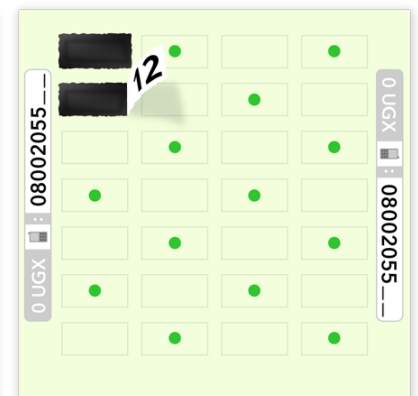


Figure 3. Original and adapted versions of the 99DOTS envelope. The original 99DOTS envelope was two-sided (top left and right). The original envelope was adapted using human-centered design to add a decorative front cover to hide pills (and thereby reduce potential stigma; bottom left); include space 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.	
	1b	Structured summary of trial design, methods, results, and conclusions (see separate SW-CRT checklist for abstracts).	
Introduction			
Background and objectives	2a	Scientific background. Rationale for using a cluster design and rationale for using a stepped wedge design.	
	2b	Specific objectives or hypotheses.	
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.	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.	
Participants	4a	Eligibility criteria for clusters and participants.	
	4b	Settings and locations where the data were collected.	
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.	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.	
	6b	Any changes to trial outcomes after the trial commenced, with reasons.	
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).	
	7b	When applicable, explanation of any interim analyses and stopping guidelines.	
Randomisation			
Sequence generation	8a	Method used to generate the random allocation to the sequences of treatments.	
	8b	Type of randomisation; details of any constrained randomisation or stratification, if used.	
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.	
Implementation	10a	Who generated the randomisation schedule, who enrolled clusters, and who assigned clusters to sequences.	
	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.	
	10c	Whether, from whom and when consent was sought and for what; whether this differed between treatment conditions.	
Blinding	11a	If done, who was blinded after assignment to sequences (eg, cluster level participants, individual level participants, those assessing outcomes) and how.	
	11b	If relevant, description of the similarity of treatments.	
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.	
	12b	Methods for additional analyses, such as subgroup analyses, sensitivity analyses, and adjusted analyses.	

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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).	
	13b	For each treatment condition or allocated sequence, losses and exclusions for both clusters and participants with reasons.	
Recruitment	14a	Dates defining the steps, initiation of intervention, and deviations from planned dates. Dates defining recruitment and follow-up for participants.	
	14b	Why the trial ended or was stopped.	
Baseline data	15	Baseline characteristics for the individual and cluster levels as applicable for each treatment condition or allocated sequence.	
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.	
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.	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended.	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.	
Harms	19	Important harms or unintended effects in each treatment condition (for specific guidance see CONSORT for harms).	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses.	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings. Generalisability to clusters or individual participants, or both (as relevant).	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.	
Other information			
Registration	23	Registration number and name of trial registry.	
Protocol	24	Where the full trial protocol can be accessed, if available.	
Funding	25	Sources of funding and other support (such as supply of drugs), and the role of funders.	
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.	

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.