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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-068685
Article Type:	Protocol
Date Submitted by the Author:	27-Sep-2022
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Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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Manuscripts

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3 1 **Effectiveness of digital adherence technologies in improving TB treatment**
4 **outcomes in four countries: a pragmatic cluster randomized trial protocol**
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55 31 Journal: **BMJ Open**
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3 34 Abstract

4
5 35 **Introduction**

6 36 Successful treatment of tuberculosis (TB) depends to a large extent on good
7 adherence to treatment regimens which in many countries relies on directly observed
8 treatment (DOT). This in turn requires frequent visits to health facilities. High costs to
9 patients, stigma, and burden to the health system challenged the DOT approach.
10 Digital adherence technologies (DATs) have emerged as possibly more feasible
11 alternatives to DOT but there is conflicting evidence on their effectiveness and
12 feasibility. Our primary objective is to evaluate whether the implementation of DATs
13 with daily monitoring and a differentiated response to patient adherence would reduce
14 poor treatment outcomes compared with the standard of care (SOC). Our secondary
15 objectives include: to evaluate the proportion of patients lost to follow-up; to compare
16 effectiveness by DAT type; to evaluate the feasibility and acceptability of DATs; to
17 describe factors affecting the longitudinal engagement of patients with the
18 intervention; and to use a simple model to estimate the epidemiological impact and
19 cost-effectiveness of the intervention from a health system perspective.
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33 51 **Methods and analysis**

34 52 This is a pragmatic multi-country two-arm cluster-randomized trial, with health
35 facilities as the unit of randomization. Facilities will first be randomized to either the
36 DAT or SOC arm, and then the DAT arm will be further randomized into medication
37 sleeve/labels or smart pill box in a 1:1:2 ratio for the smart pill box, medication
38 sleeve/label or the SOC respectively. We will use data from the digital adherence
39 platform and a separate research database of data available from routine data
40 collection. In the main analysis, we will employ an intention-to-treat approach to
41 evaluate treatment outcomes.
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50 61 **Ethics and dissemination**

51 62 The study has been approved by the WHO Ethical Review Committee (0003296), and
52 by country-specific committees. The results will be shared at national and
53 international meetings and will be published in peer-reviewed journals.
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66 Trial registration number: ISRCTN17706019

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3 68 **Strengths and limitations of this study**
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- 5 69 • This is a multi-country trial using rigorous methods to evaluate the effectiveness
6 of DAT on treatment outcomes, going beyond measuring improvements in
7 70 adherence to treatment
8 71
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10 72 • The study will provide important evidence on patient and provider acceptability
11 and feasibility necessary to provide country level guidance on decisions to adopt,
12 73 implement and scale-up DATs across varying contexts
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15 75 • Changes in the standard of care across countries due to the COVID-19 may have a
16 confounding effect as some of the changes included the use of digital technologies
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19 77

78 Introduction

79 About a quarter of the world population is infected with mycobacterium tuberculosis
80 bacilli, and about 10 million people develop active tuberculosis (TB) each year. Of
81 those with active TB, about a third are not detected by the health system.

82 Furthermore, >10% of those detected are not successfully treated. (1) As a result, the
83 global TB treatment success rate remained below the 20% reduction interim target
84 between 2015 and 2020. (2)

85
86 To improve treatment outcomes, directly observed treatment (DOT) has been the
87 standard recommendation since 1995. (3) However, DOT is no longer held as an
88 adequate patient-centered model for TB care. (4) DOT by health care workers present
89 challenges to patients owing to transportation costs, and lost income due to clinic
90 appointments which can contribute to non-adherence. The evidence that DOT
91 substantially improves treatment completion or cure relative to self-administration is
92 mixed. (5, 6)

93
94 In recent years, digital adherence technologies (DATs) such as electronic medication
95 monitors and text messaging, have emerged as alternatives to DOT. (7) Electronic
96 medication boxes are medication monitoring devices that store TB medications, give
97 audio-visual reminders to the patient, and record and transmits patients' dosing
98 history. The medication sleeve is a type of electronic medication monitor that consists
99 of medication blisters wrapped in special envelopes with printed codes. Patients use
100 these codes when making a toll-free call/text to let their health care provider know
101 when they have taken their medication. (7) In addition to reminding patients to take
102 their TB medications, DATs provide mechanisms for compiling patient dosing
103 histories that provide their health care providers with the ability to monitor adherence
104 and to provide prioritized follow-up differentiated care. While the use of DATs is
105 recommended, evidence that such technologies improve treatment outcomes is still
106 limited.

107
108 Recent randomized studies in countries in Africa and Asia documented mixed results
109 regarding effectiveness of medication monitoring to reduce poor medication
110 adherence. (8-14) For the purposes of informing policy makers with information
111 about if when and where to use DATs, inference from RCTs is difficult due to the fact

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3 112 that RCTs often do not reflect the real-life circumstances under which such tools
4 113 would be employed in programmatic settings. Furthermore, the patient and health-
5 114 care provider acceptability and uptake of these tools have been shown to be variable
6 115 in different countries and settings. (15-17). Cultural or material circumstances may
7 116 operate differently on the utility or acceptability of DATs to deliver the targeted
8 117 treatment support. Data from individual randomized trials often do not provide
9 118 country programs with the information needed to replicate their success in real-life
10 119 settings and specific contexts. A pragmatic trial design implemented under real-life
11 120 situation therefore is useful to provide the necessary evidence that can transform the
12 121 way treatment support is provided in high TB burden settings.
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22 123 The Adherence Support Coalition to End TB (ASCENT) study will evaluate
23 124 effectiveness of medication sleeves/labels and smart pill boxes linked to a web-based
24 125 adherence platform, to create a differentiated care response to patient adherence in
25 126 relation to end of treatment outcomes. A related study in Ethiopia will go further to
26 127 provide effectiveness in relation to disease free outcomes. (18). In addition to
27 128 effectiveness, ASCENT will collect data on DAT engagement and fidelity to the
28 129 adherence tools, costs, and projections of epidemiological impact and cost-
29 130 effectiveness. Taken together, the ASCENT studies will provide valuable evidence of
30 131 effectiveness as well as patient and provider acceptability and feasibility necessary to
31 132 provide country level guidance on decisions to adopt, implement and scale-up DATs
32 133 across varying contexts around the world.
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43 135 **Objectives**

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46 137 The primary objective of this study is to evaluate whether the implementation of DAT
47 138 with daily monitoring and differentiated response to patient adherence decreases the
48 139 proportion of patients with poor treatment outcome compared to the standard of care
49 140 in their respective countries. Poor treatment outcome is a composite of treatment
50 141 outcomes that include death, treatment failure, or loss to follow-up (LTFU). The
51 142 secondary objectives include evaluating individual components of the composite
52 143 outcomes i.e., the proportion of patients LTFU, and time to treatment completion.
53 144 Additionally, we will evaluate the effect of the individual DAT systems employed,
54 145 medication labels or smart pill box, in relation to the SOC. Furthermore, we will
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3 146 describe: the longitudinal engagement of patients with the DAT; the fidelity to the
4 147 intervention including device and technological failures (e.g., poor cellular service
5 148 coverage); the wider epidemiological impact of the interventions through
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7 149 mathematical models; the cost-effectiveness of the intervention from a health system
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9 150 perspective; and evaluate the feasibility and acceptability of DATs for patients as well
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11 151 as health care workers.
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15 153 **Methods/ Design**

16 154 ***Study design***

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20 156 Figure 1 shows an overview of the study design. These are pragmatic two-arm cluster-
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22 157 randomized trials, with health facilities as the unit of randomization, conducted in
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24 158 four countries. Facilities in each country were randomized (1:1) to either the
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26 159 intervention (DAT) or SOC arm. A second randomization among the intervention arm
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28 160 clusters (1:1) was conducted to determine which of two interventions to employ
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30 161 (medication sleeve/label or smart pill box). In each country facilities from multiple
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32 162 regions/districts were randomized using stratification and restriction. Since labels
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34 163 were not implemented in Ukraine, the randomization was 1:1.
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37 165 ***Study setting***

38
39 166 The study is operating in four countries that are among the top 30 high-burden TB or
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41 167 MDR-TB countries: Ukraine, Tanzania, South Africa and the Philippines. These
42
43 168 countries were selected based on epidemiological, socio- economic, geographic,
44
45 169 infrastructural and health system factors. Facilities will include a mix of both large
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47 170 and small, urban and rural facilities. Eligible facilities needed to have previously
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49 171 notified TB patients and expressed willingness and capability to participate in study
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51 172 activities.
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184 ***Study population***

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

192

193 ***Interventions***

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

203

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

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3 211 the ASCENT adherence platform to support the health facility staff to operationalize
4 212 the DAT intervention and (b) use this de-identified data as well as accessing data on
5 213 treatment outcomes to evaluate effectiveness and fidelity of the intervention.
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10 215 Figure 1- overview of the study design
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13 216 **Intervention arm 1 – smart pill box (all countries)**

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15 217 Upon providing informed consent, participants receive a smart pill box ((also known
16 218 as the Medication Event Reminder Monitor system or MERM). The TB drugs are
17 219 placed in the smart pill box that is configured to routinely signal a reminder to the
18 220 patient by either an audible signal (beep) and/or a blinking light once a day at a time
19 221 based on the patient’s preference. On a daily basis, an electronic device embedded in
20 222 the box sends a signal through a built-in mobile internet connection with all box
21 223 openings of the patient to the ASCENT digital adherence platform. If the internet
22 224 connectivity is unavailable, the opening events are stored on the device to be uploaded
23 225 upon resumption of connectivity.
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33 227 **Intervention arm 2 – medication sleeves/labels**

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35 228 Upon providing informed consent, participants with secure access to a mobile phone
36 229 employ one of two analogous methods to send notification of their dosing to the
37 230 ASCENT platform. Participants who do not have access to a mobile phone are given a
38 231 smart pill box.
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44 233 Medication sleeves- participants have their Fixed Dose Combination (FDC) blister
45 234 pack containing their medication placed in a custom card-stock medication sleeve
46 235 with a series of unpredictable hidden codes that are revealed only upon removal of the
47 236 daily pill.
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51 237
52 238 Medication labels - In countries where the FDC packaging was variable and therefore
53 239 difficult to reliably supply custom cardstock, we employed a modified system.
54 240 Participants have a label, containing a code, placed on each of their fixed-dosed
55 241 blister-packaged TB medication.
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3 243 For both methods, when their daily dose is taken, participants message the code using
4 244 a toll-free text, which automatically logs their daily dose to the ASCENT web-based
5 245 application. Box open or short message service (SMS) sent by patient is assumed to
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7 246 be dose taken.
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13 248 **The Standard of Care arm**

14 249 Patients in health facilities randomized to the control arm receive the current standard
15 250 of care according to their country guidelines. In the Philippines and Tanzania, a
16 251 treatment partner (TP) is identified by the patient and Public Health Nurse and
17 252 patients are either observed by the TP or self-administer “with trust”. In South Africa
18 253 patients employ self-administration, recording their taking medication on a TB card.
19 254 Non-adherence according to this may prompt DOT (either at home or in the clinic). In
20 255 Ukraine, outpatient adherence is monitored using either home-based or facility-based
21 256 DOT.
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31 258 **Differentiated care delivery based on adherence to treatment**

32 259 Patients utilizing the DAT at facilities randomized to the intervention arm have their
33 260 adherence data recorded on the ASCENT adherence platform. These data are
34 261 displayed in real-time in a single view via the mobile Android app to allow health
35 262 care providers to visualize the data analytics and evaluate their medication taking
36 263 behavior. Health care providers are then able to identify patients who have not taken
37 264 their medication according to the patient calendar or by viewing Task Lists that
38 265 contain patients with 1, 2 or 3 days of non-adherence. They then employ constructive
39 266 measures to encourage timely medication adherence according to the differentiated
40 267 response algorithm approved by the National TB Program (NTP). These measures
41 268 include messaging educational reinforcements, reminders, phone calls and home visits
42 269 progressively. Each country has a differentiated response algorithm that has been
43 270 arrived at in consultation with the community advisory board, civil society stake
44 271 holders, and approved by the country NTP.
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272 **Randomization**

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

280 Table 1. Stratification and restriction variables per country

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

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

284 **Trial outcomes**

285 **Primary outcome**

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

288 **Secondary outcomes**

289 **Secondary outcomes – effectiveness and feasibility**

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

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3 292 • Time to treatment completion, among DS-TB patients
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5 293 • The proportion of adult DS-TB patients with poor treatment outcomes for
6
7 294 standard of care versus (1) medication sleeves/labels and (2) smart pill box
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9 295 • Intervention arm only:
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11 296 • Patterns of longitudinal technology engagement in the intensive- and
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13 297 continuation phase
14
15 298 • The proportion of patients who had a differentiated response due to non-
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17 299 adherence, among all patients and among non-adherent patients
18
19 300 • The proportion of patients who received phone calls, home visits, and
20
21 301 motivational counselling due to non-adherence

302 **Secondary outcomes - impact modelling**

- 22
23 303 • The change in the incidence of TB arising from the impact that DATs may
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25 304 have on TB transmission compared to current standard of care if the
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27 305 intervention were to be scaled up
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29 306 • A simplified cost-effectiveness of DAT compared to standard of care relative,
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31 307 considering changes in relevant cost drivers such as number of clinic visits,
32
33 308 technology and training costs.

309 **Secondary outcomes – DR-TB patients**

- 34
35 310 • Patterns of longitudinal technology engagement in the intensive- and
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37 311 continuation phase
38
39 312 • The proportion of adult DR-TB patients with poor (interim) treatment
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41 313 outcomes
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44 315 There are several secondary outcomes which will be assessed in sub studies described
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46 316 further below.
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318 ***Sample size***

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52 319 For each country, we collected data from the TB registries in health facilities of the
53
54 320 selected regions/districts to provide an estimate of the harmonic mean of the number
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56 321 of DS-TB registrations over an 18-month period and the percentage with poor
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58 322 treatment outcome (treatment failure, and death and lost to follow-up during
59
60 323 treatment). We assumed a (conservative) coefficient of variation of poor outcome of

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

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332 Table 2. Estimated cluster size and associated assumptions per country

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

333

334 ***Study procedures***335 **Study procedures in SOC and intervention facilities**

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

340

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

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

351

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

360

361

362

363 **Table 3: Comparison of activities between intervention and standard of care**364 **facilities**

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

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60**369 Study procedures in intervention facilities only**

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

378

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

384

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

393

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

399

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

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3 403 facilities who do not consent to use the DAT take their medication according to
4 404 standard of care for the facility and under the NTP guidelines (See supplemental
5 405 information). Adherence data and treatment follow-up is also according to the country
6 406 specific NTP guidelines.
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11 12 13 408 ***Data Management***

14
15 409 Data from the DATs will be collected from the ASCENT adherence platform (patients
16 410 on the intervention only) using the Everwell Hub, a cloud-based or in-country
17 411 (Tanzania) hosted infrastructure according to country regulations. Patient data are
18 412 collected on the ASCENT adherence platform, with permission from the participant
19 413 provided in the informed consent. The ASCENT platform allows the TB health care
20 414 providers to review patient medication adherence logged from the DAT and track
21 415 SMS communications with patients. Data privacy is protected with access to the
22 416 platform being password protected with defined data access that allows health care
23 417 providers, but not researchers, to view personal identifying data.
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32 419 Treatment outcome data are from the routine reporting to the NTP and are electronic
33 420 in the Philippines and Ukraine and abstracted from paper TB registers in Tanzania
34 421 and South Africa. These data are collected for all patients (excluding those who opt-
35 422 out) and are imported/entered into the ASCENT research database hosted in-country
36 423 using REDcap, a secure web database application. (19)
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42 425 The routine data in the ASCENT research database are linked to deidentified
43 426 individual patient data from the ASCENT platform using a corresponding electronic
44 427 or paper record that has the TB registration number and ASCENT platform ID.
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49 50 429 ***Trial Governance***

51
52 430 A Technical Advisory Group (TAG) has been set up to provide oversight, monitor
53 431 and oversee progress for this four-country study and its companion study in Ethiopia.
54 432 The TAG meets every 6 months and is composed of representatives from the five
55 433 countries and chaired by a senior researcher in Uganda.
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3 435 Diverse in-country stakeholders provide input to the study through a Community
4 436 Advisory Board (CAB) and/or other Civil Society Organizations (Tanzania).
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6 437 Consultation was sought in order to involve former TB patients and their care
7
8 438 providers and various other stakeholders. The CABs were engaged beginning in the
9
10 439 preparatory phase to provide input and advice into the facility selection and
11
12 440 randomization procedures. They were further consulted after the preparatory phase in
13
14 441 order to arrive at the specific country differentiated response algorithm.
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17 18 443 ***Statistical Analysis Plan***

19
20 444 Statistical analyses will employ appropriate methods for the cluster randomized trial
21
22 445 design. We will conduct an intention-to-treat approach to evaluate treatment outcomes
23
24 446 in the DAT arm relative to the SOC. Additionally, two separate analyses will be
25
26 447 performed to evaluate the individual DAT - smart pill box or medication label/sleeve
27
28 448 – in relation to the SOC. For South Africa, Tanzania and the Philippines we will
29
30 449 employ a logistic regression model with random effects (to account for clustering at
31
32 450 the facility-level) to estimate the respective intervention effect as an odds ratio and
33
34 451 associated 95% confidence interval adjusted for variables employed in randomization
35
36 452 strata. Adjustment for other patient level covariates will be employed where
37
38 453 imbalance exists between the study arms. Sub-group analyses will be examined to
39
40 454 examine heterogeneity of effect among patient characteristics including, urban/rural,
41
42 455 gender and country specific health care delivery circumstances, and type of TB
43
44 456 (pulmonary or extra-pulmonary). (20) A detailed statistical analysis plan will be
45
46 457 finalized before the end of follow-up and data are unblinded.

47 48 458 ***Sub-studies***

49
50 459 As part of the process evaluation of DAT interventions in each of the four countries, a
51
52 460 series of sub-studies are administered by ASCENT research personnel to a sub-set of
53
54 461 patients, health care workers and key stakeholders in a selection of facilities employed
55
56 462 in the effectiveness evaluation. In sub-study 1, acceptability and feasibility data will
57
58 463 be collected from TB patients. In sub-study 2, qualitative methods will explore the TB
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60 464 patient experience using the DAT and explore differences in the experience by
465
466 gender. In sub-study 3, qualitative methods will explore the acceptability and

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3 466 feasibility of implementing DAT and differentiated response among the health care
4 467 workers providing TB care and relevant stakeholders.
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9 469 ***Economic Evaluation and Impact Modelling***

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11 470 The decision to scale-up DATs in countries will need to consider the benefit to both
12 471 the health system as well as to the individual. As TB is known to disproportionately
13 472 affect the poor, the use of DATs may decrease the economic burden placed on TB
14 473 patients and address the END TB Strategy milestone of eliminating families facing
15 474 catastrophic health costs due to TB. We will use effectiveness data as well as
16 475 estimates of costs incurred by patients (collected in sub-study 1) and the service level
17 476 costs to estimate the cost-effectiveness of utilizing DATs relative to the standard of
18 477 care.
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27 479 To the extent that DATs may impact treatment outcomes, it will be useful to
28 480 understand the result on TB epidemiology in the country. The change in the treatment
29 481 outcome from DAT relative to the SOC will inform a simple cohort model, in order to
30 482 project the epidemiological impact, in terms of cases, incidence and prevalence, of
31 483 scaling up of DAT in the respective countries.
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38 485 ***Ethical considerations and dissemination***

39
40 486 The study has been approved by the WHO Ethical Review Committee (0003296) and
41 487 London School of Hygiene & Tropical Medicine Ethics Committee, United Kingdom
42 488 (19135) following external peer review. Individual protocols have been reviewed and
43 489 approved by relevant country specific committees: Single Joint Research Ethics Board
44 490 (Philippines SJREB 2019-57); Wits Human Research Ethics Committee (South Africa
45 491 AUR2-1-268); Tanzania Medical Research Coordinating Committee (MRCC) at
46 492 National Institute for Medical Research, Dar es Salaam (Tanzania
47 493 NIMR/HQ/R.8a/Vol.IX/3431); and Ukraine Ethics Committee of Public Health
48 494 Center of the MOH of Ukraine (Ukraine IRB 2019-33).
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57 496 Written informed consents of TB patients for the main effectiveness study are
58 497 collected from TB patients by the TB care providers at the intervention facilities. In
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3 498 addition, a waiver of consent was obtained to access TB register data. Patients agree
4
5 499 to use the DAT and consent to have researchers use anonymized data collected to the
6
7 500 ASCENT Adherence platform. Informed consents for the sub-studies are collected by
8
9 501 research associates prior to the interviews. The individual-level data sets visible to
10
11 502 research staff to monitor the study and conduct analysis are de-identified. All
12
13 503 databases are maintained in password-protected systems. Where paper records exist,
14
15 504 they are stored in the participating facilities in locked cabinets with access permitted
16
17 505 to only relevant facility health care providers and research team members.

17 506
18
19 507 The research findings will be presented first to national stakeholders, and
20
21 508 disseminated to the Community Advisory Board, stakeholders and participants in
22
23 509 each country at local meetings, and presented at national and international
24
25 510 conferences. The primary results of the study will be written as country-specific
26
27 511 articles for submission to suitable scientific journals along with deidentified research
28
29 512 datasets for the sake of reproducibility. Exclusive use of the data for further
30
31 513 publications will be given to the ASCENT consortium as well as the country's local
32
33 514 research community. Major changes to the study are communicated to the CAB and
34
35 515 TAG, updated to the protocol and trial registration, and reported to the ethics
36
37 516 committee for approval.

37 517 38 518 **Funding**

39 519 The study is funded by Unitaid (Grant Agreement Number: 2019-33-ASCENT).

40 520 41 521 **Contributorship statement**

42
43 522 DJ contributed to designing the study, supervised implementation, wrote the first and
44
45 523 subsequent drafts and approved the final version. JL led the designing of the study,
46
47 524 coordinated ethical review processes, contributed to acquisition of resources, initiated
48
49 525 the write up of the first draft of the manuscript, and approved the final version. KvK
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51 526 led acquisition of resources, contributed to study design, oversaw project
52
53 527 implementation, reviewed the first and subsequent drafts, and approved the final draft.
54
55 528 JvR contributed to resource acquisition and supervision of implementation and
56
57 529 reviewed the draft manuscript. CFM and MQ designed the transmission modelling,
58
59 530 contributed to supervising implementation, reviewed the draft manuscript, and
60
531 531 approved the final version. SC and NM contributed to study design, supervised

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3 532 implementation in South Africa, and reviewed and approved the manuscript. KG, YT
4 533 and AB supervised study implementation in Ukraine, and reviewed and approved the
5 534 manuscript. AMCG and LM supervised study implementation in the Philippines and
6 535 Tanzania respectively and reviewed and approved the manuscript. KF contributed to
7 536 designing the study, developed statistical analysis plans, supervised implementation,
8 537 and reviewed and approved the manuscript. The contents of the article are the
9 538 responsibility of the authors alone and do not necessarily reflect the views of donors
10 539 or employers of the authors.

17 540 **Competing interests**

18 541 We declare we have no competing interest.

19 542

23 543 **References**

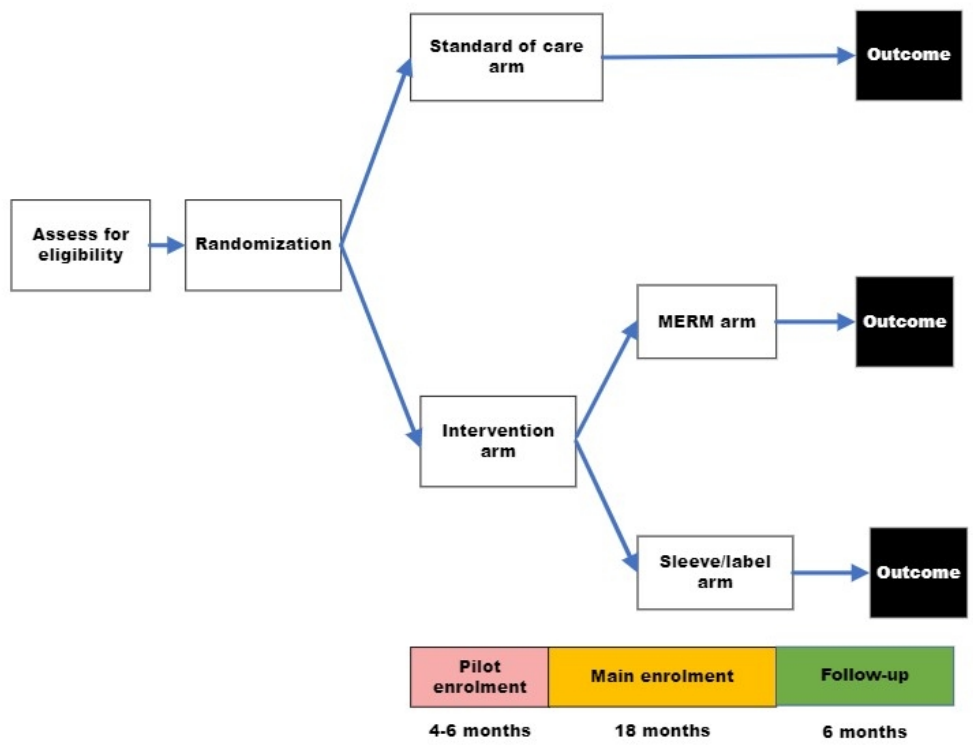
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Overview of study design

155x118mm (120 x 120 DPI)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-068685.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Jan-2023
Complete List of Authors:	<p>Jerene, Degu; KNCV Tuberculosis Foundation, Levy, Jens; KNCV Tuberculosis Foundation van Kalmthout, Kristian; KNCV Tuberculosis Foundation Rest, Job; KNCV Tuberculosis Foundation McQuaid, Christopher; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology Quaiife, Matthew; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology Charalambous, Salome; Aurum Institute, 29 Queens Road, Johannesburg, 2041, South Africa. Gamazina, Katya; PATH Garfin, AM Celina; Department of Health Mleoh , Liberate ; National Tuberculosis and Leprosy Programme, Dodoma, Tanzania, Department of Preventive Services Terleieva, Yana ; 7DepartmentDepartment of Coordination of TB Treatment Programs Bogdanov, Alexsey ; PATH Maraba, Noriah; Aurum Institute, 29 Queens Road, Johannesburg, 2041, South Africa. Fielding, Katherine; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology</p>
Primary Subject Heading:	Global health
Secondary Subject Heading:	Infectious diseases
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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

4
5
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32 Journal: **BMJ Open**

1
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3 35 Abstract

4
5 36 **Introduction**

6
7 37 Successful treatment of tuberculosis (TB) depends to a large extent on good
8
9 38 adherence to treatment regimens which relies on directly observed treatment (DOT).
10
11 39 This in turn requires frequent visits to health facilities. High costs to patients, stigma,
12
13 40 and burden to the health system challenged the DOT approach. Digital adherence
14
15 41 technologies (DATs) have emerged as possibly more feasible alternatives to DOT but
16
17 42 there is conflicting evidence on their effectiveness and feasibility. Our primary
18
19 43 objective is to evaluate whether the implementation of DATs with daily monitoring
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21 44 and a differentiated response to patient adherence would reduce poor treatment
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23 45 outcomes compared with the standard of care (SOC). Our secondary objectives
24
25 46 include: to evaluate the proportion of patients lost to follow-up; to compare
26
27 47 effectiveness by DAT type; to evaluate the feasibility and acceptability of DATs; to
28
29 48 describe factors affecting the longitudinal engagement of patients with the
30
31 49 intervention; and to use a simple model to estimate the epidemiological impact and
32
33 50 cost-effectiveness of the intervention from a health system perspective.

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33 51
34 52 **Methods and analysis**

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36 53 This is a pragmatic two-arm cluster-randomized trial in Philippines, South Africa,
37
38 54 Tanzania and Ukraine, with health facilities as the unit of randomization. Facilities
39
40 55 will first be randomized to either the DAT or SOC arm, and then the DAT arm will be
41
42 56 further randomized into medication sleeve/labels or smart pill box in a 1:1:2 ratio for
43
44 57 the smart pill box, medication sleeve/label or the SOC respectively. We will use data
45
46 58 from the digital adherence platform and routine health facility records for analysis. In
47
48 59 the main analysis, we will employ an intention-to-treat approach to evaluate treatment
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50 60 outcomes.

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51 62 **Ethics and dissemination**

52
53 63 The study has been approved by the WHO Research Ethics Review Committee
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55 64 (0003296), and by country-specific committees. The results will be shared at national
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57 65 and international meetings and will be published in peer-reviewed journals.

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59 67 Trial registration number: ISRCTN17706019
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69 **Strengths and limitations of this study**

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

79 Introduction

80 About a quarter of the world population is infected with mycobacterium tuberculosis
81 bacilli, and about 10 million people develop active tuberculosis (TB) each year. Of
82 those with active TB, about a third are not detected by the health system.

83 Furthermore, >10% of those detected are not successfully treated. (1) As a result, the
84 global TB treatment success rate remained below the 20% reduction interim target
85 between 2015 and 2020. (2)

86
87 To improve treatment outcomes, directly observed treatment (DOT) has been the
88 standard recommendation since 1995. (3) However, DOT is no longer held as an
89 adequate patient-centered model for TB care. (4) DOT by health care workers present
90 challenges to patients owing to transportation costs, and lost income due to clinic
91 appointments which can contribute to non-adherence. The evidence that DOT
92 substantially improves treatment completion or cure relative to self-administration is
93 mixed. (5, 6)

94
95 In recent years, digital adherence technologies (DATs) such as electronic medication
96 monitors and text messaging, have emerged as alternatives to DOT. (7) Electronic
97 medication boxes are medication monitoring devices that store TB medications, give
98 audio-visual reminders to the patient, and record and transmits patients' dosing
99 history. The medication sleeve is a type of electronic medication monitor that consists
100 of medication blisters wrapped in special envelopes with printed codes. Patients use
101 these codes when making a toll-free call/text to let their health care provider know
102 when they have taken their medication. (7) In addition to reminding patients to take
103 their TB medications, DATs provide mechanisms for compiling patient dosing
104 histories that provide their health care providers with the ability to monitor adherence
105 and to provide prioritized follow-up differentiated care. While the use of DATs is
106 recommended, evidence that such technologies improve treatment outcomes is still
107 limited.

108
109 Recent randomized studies in countries in Africa and Asia documented mixed results
110 regarding effectiveness of medication monitoring to reduce poor medication
111 adherence. (8-14) For the purposes of informing policy makers with information
112 about when and where to use DATs, inference from Randomized Controlled Trials

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3 113 (RCTs) is difficult because RCTs often do not reflect the real-life circumstances under
4 114 which such tools would be employed in programmatic settings. Furthermore, the
5 115 patient and health-care provider acceptability and uptake of these tools have been
6 116 shown to be variable in different countries and settings. (15-17).
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10 117
11 118 A more recent systematic review identified 16 RCTs that evaluated the effect of
12 119 various digital health technology (DHT) interventions on TB treatment adherence and
13 120 clinical outcomes. The DHT interventions evaluated included video directly observed
14 121 therapy (VDOT), video-observed therapy (VOT), medication monitor boxes, short
15 122 message text reminders, and ingestible sensors. (18). The interventions demonstrated
16 123 variable effects in terms of both direction and extent, and those with personalized
17 124 feedback component had a consistent and beneficial effect. Moreover, cultural or
18 125 material circumstances may operate differently on the utility or acceptability of DATs
19 126 to deliver the targeted treatment support. Data from individual randomized trials
20 127 often do not provide country programs with the information needed to replicate their
21 128 success in real-life settings and specific contexts. A pragmatic trial design
22 129 implemented under real-life situation therefore is useful to provide the necessary
23 130 evidence that can transform the way treatment support is provided in high TB burden
24 131 settings.
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37 133 The Adherence Support Coalition to End TB (ASCENT) study will evaluate
38 134 effectiveness of medication sleeves/labels and smart pill boxes linked to a web-based
39 135 adherence platform, to create a differentiated care response to patient adherence in
40 136 relation to end of treatment outcomes. These DATs were selected based on several
41 137 criteria including access to smartphones and broadband internet, type of ant-TB
42 138 medication regimens in use, and stakeholder feedback as recommended in the WHO
43 139 guidelines (7). Further, country-specific choice of DATs was decided based on
44 140 experiences from the run-in phase of the study as described in the Methods section. A
45 141 related study in Ethiopia will go further to provide effectiveness in relation to TB-free
46 142 status within 6 months of end of treatment among patients with bacteriologically
47 143 confirmed TB at baseline. (19). In addition to effectiveness, ASCENT will collect
48 144 data on DAT engagement and fidelity to the adherence tools, costs, and projections of
49 145 epidemiological impact and cost-effectiveness. Taken together, the ASCENT studies
50 146 will provide valuable evidence of effectiveness as well as patient and provider
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3 147 acceptability and feasibility necessary to provide country level guidance on decisions
4 148 to adopt, implement and scale-up DATs across varying contexts around the world.

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8 150 **Objectives**

9 151 Primary objective

10 152 The primary objective of this study is to evaluate whether the implementation of DAT
11 153 with daily monitoring and differentiated response to patient adherence decreases the
12 154 proportion of patients with poor treatment outcome compared to the standard of care
13 155 in their respective countries. Poor treatment outcome is a composite of treatment
14 156 outcomes that include death, treatment failure, or loss to follow-up (LTFU).

15 157 Secondary objectives

- 16 158 (i) To evaluate whether implementation of DAT with daily monitoring and a
17 159 differentiated response to patient adherence decreases the proportion of adult
18 160 drug-sensitive (DS-TB) patients lost to follow-up compared with the standard of
19 161 care.
- 20 162 (ii) To explore the specific effect of standard of care versus (1) medication
21 163 sleeve/label and (2) smart pill box with daily monitoring and a differentiated
22 164 response to patient adherence on treatment outcomes among adult DS-TB patients
- 23 165 (iii) To describe longitudinal technology engagement of DS-TB and drug resistant TB
24 166 (DR-TB) patients in the intervention arm
- 25 167 (iv) To describe the fidelity and characteristics associated with successful use of the
26 168 intervention among DS-TB patients, including web-based platform usage
27 169 statistics, technology failures or inability to engage with the DAT and mobile
28 170 phone access
- 29 171
- 30 172 (v) To describe the longitudinal technology engagement of the smart pill box and
31 173 video supported treatment and the (interim) treatment outcomes of patients
- 32 174 (vi) To project the epidemiological impact of scale-up of DAT with daily monitoring
33 175 and a differentiated response to patient adherence compared with the standard of
34 176 care as measured by the change in treatment outcome in the intervention relative
35 177 to the standard of care among adult DS-TB patients
- 36 178 (vii) To explore the institutional feasibility and acceptability of implementing a
37 179 DAT intervention and differentiated response to patient adherence in adult DS-TB
38 180 and DR-TB patients.

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182

183 **Methods/ Design**

184 ***Study design***

185

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

197

198

199 ***Study setting***

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

207

208

209 ***Study population***

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

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3 213 extended to all adult DS-TB patients in the selected intervention facilities upon
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5 214 initiation of their therapy. In Ukraine where patients start treatment as inpatients,
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7 215 participants start the intervention at discharge. Those providing consent will be
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9 216 enrolled onto the ASCENT adherence platform and provided with the DAT.
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12 13 218 *Interventions*

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15 219 In three countries (South Africa, Tanzania, and Philippines) facilities will be
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17 220 randomized to one of two technologies (smart pill box or medication sleeve/label) to
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19 221 transmit to the ASCENT web-based digital adherence platform for treatment
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21 222 adherence monitoring. This allows the TB care provider to use the ASCENT
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23 223 adherence data platform to evaluate daily dosing and offer differentiated care specific
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25 224 to the country as appropriate.
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27 225
28 226 The implementation starts with a run-in phase when in-country staff are trained, and
29
30 227 the DAT adherence platform is integrated into the patient care pathway, followed by
31
32 228 the main enrolment phase. After an introduction to the study and providing written
33
34 229 consent, all adults (locally defined) diagnosed with DS-TB are offered the DAT
35
36 230 technology and differentiated care intervention. By providing written informed
37
38 231 consent, patients agree to use the DAT assigned to the facility during their TB
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40 232 treatment, and for researchers to (a) access their de-identified dosing history data on
41
42 233 the ASCENT adherence platform to support the health facility staff to operationalize
43
44 234 the DAT intervention and (b) use this de-identified data as well as accessing data on
45
46 235 treatment outcomes to evaluate effectiveness and fidelity of the intervention.
47

48 236
49 237 Figure 1- overview of the study design

50 238 **Intervention arm 1 – smart pill box (all countries)**

51 239 Upon providing informed consent, participants receive a smart pill box ((also known
52
53 240 as the Medication Event Reminder Monitor system or MERM). **We used**
54
55 241 **evriMED1000C- (Wisepill Technologies <https://www.wisepill.com/evrimed>) in**
56
57 242 **this study.** The TB drugs are placed in the smart pill box that is configured to
58
59 243 routinely signal a reminder to the patient by either an audible signal (beep) and/or a
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244 blinking light once a day at a time based on the patient's preference. On a daily basis,

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3 245 an electronic device embedded in the box sends a signal through a built-in mobile
4 246 internet connection with all box openings of the patient to the Everwell Hub
5 247 application platform. The Everwell Hub is an integrated platform for adherence and
6 248 patient management where health care staff can log into a unified portal to register
7 249 and follow up with patients, whose adherence reports from 99DOTS or evriMED
8 250 devices. (20). If the internet connectivity is unavailable, the opening events are
9 251 stored on the device to be uploaded upon resumption of connectivity.
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18 253 **Intervention arm 2 – medication sleeves/labels**

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20 254 Upon providing informed consent, participants with secure access to a mobile phone
21 255 employ one of two analogous methods to send notification of their dosing to the
22 256 ASCENT platform. These were based on 99DOTS medication sleeves (99DOTS A
23 257 low-cost digital adherence engagement tool <https://www.everwell.org/99dots>).
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27 258 Participants who do not have access to a mobile phone are given a smart pill box.
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30 260 Participants have their Fixed Dose Combination (FDC) blister pack containing their
31 261 medication placed in a custom card-stock medication sleeve with a series of
32 262 unpredictable hidden codes that are revealed only upon removal of the daily pill. In
33 263 countries where the FDC packaging was variable and therefore difficult to reliably
34 264 supply custom cardstock, we employed a modified system called medication labels.
35 265 Participants have a label, containing a code, placed on each of their fixed-dosed
36 266 blister-packaged TB medication.
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44 268 For both methods, when their daily dose is taken, participants message the code using
45 269 a toll-free text, which automatically logs their daily dose to the Everwell Hub
46 270 application. Box opened or short message service (SMS) sent by patient is assumed to
47 271 be dose taken.
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52 53 273 **The Standard of Care arm**

54 274 Patients in health facilities randomized to the control arm receive the current standard
55 275 of care according to their country guidelines. In the Philippines and Tanzania, a
56 276 treatment partner (TP) is identified by the patient and Public Health Nurse and
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277 patients are either observed by the TP or self-administer “with trust”. In South Africa
 278 patients employ self-administration, recording their taking medication on a TB card.
 279 Non-adherence according to this may prompt DOT (either at home or in the clinic). In
 280 Ukraine, outpatient adherence is monitored using either home-based or facility-based
 281 DOT.

283 **Differentiated care delivery based on adherence to treatment**

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

297 **Randomization**

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

305 Table 1. Stratification and restriction variables per country

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

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

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

308

309 ***Trial outcomes***

310 **Primary outcome**

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

313 **Secondary outcomes**

314 **Secondary outcomes – effectiveness and feasibility**

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

327 **Secondary outcomes - impact modelling**

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3 328 • The change in the incidence of TB arising from the impact that DATs may
4 329 have on TB transmission compared to current standard of care if the
5 330 intervention were to be scaled up
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8 331 • A simplified cost-effectiveness of DAT compared to standard of care relative,
9 332 considering changes in relevant cost drivers such as number of clinic visits,
10 333 technology and training costs.

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14 334 **Secondary outcomes – DR-TB patients**

- 15 335 • Patterns of longitudinal technology engagement in the intensive- and
16 336 continuation phase
17
18 337 • The proportion of adult DR-TB patients with poor (interim) treatment
19 338 outcomes
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24 340 There are several secondary outcomes which will be assessed in sub studies described
25 341 further below.
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30 343 **Sample size**

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32 344 For each country, we collected data from the TB registries in health facilities of the
33 345 selected regions/districts to provide an estimate of the harmonic mean of the number
34 346 of DS-TB registrations over an 18-month period and the percentage with poor
35 347 treatment outcome (treatment failure, and death and lost to follow-up during
36 348 treatment). We assumed a (conservative) coefficient of variation of poor outcome of
37 349 0.35 to arrive at the number of facilities in each of arm (DAT or Control) required to
38 350 detect a reduction in the percentage with poor treatment outcome by 30% with 90%
39 351 power and a type 1 error of 5%. Notable exceptions were applied to Ukraine, where
40 352 health facilities are administered within rayons and randomization occurred at this
41 353 level instead of the health facility level in other countries (Table 2). In Ukraine, due to
42 354 the high proportion with poor outcomes, the study was powered to detect a reduction
43 355 of 50%.
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54 357 Table 2. Estimated cluster size and associated assumptions per country

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

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

358

359 ***Study procedures***360 **Study procedures in SOC and intervention facilities**

361 The four countries followed the same basic study procedures. In the SOC facilities,
362 the procedures imposed by the study are minimal in order to reflect the standard
363 practices relevant as the counterfactual experience for the intervention facilities. Table
364 3 summarizes procedures in the SOC and intervention facilities.

365

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

376

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

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3 383 *without using your name. If you would like the results of your treatment not to be used*
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5 384 *for this research, please inform the people giving you your TB care”.*
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For peer review only

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388 **Table 3: Comparison of activities between intervention and standard of care**389 **facilities**

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

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3 394 **Study procedures in intervention facilities only**

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5 395 All TB patients at the participating facilities are screened by the TB care provider (TB
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7 396 focal person) for eligibility. All adults (as defined by national law, male and female)
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9 397 with DS-TB who are initiated on TB treatment at the health facility are eligible for
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11 398 inclusion in the study. We have made the inclusion criteria as inclusive as possible in
12
13 399 order to reflect the real-world impact of the digital adherence technology. There are
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15 400 no specific exclusion criteria. Eligible patients are offered enrollment in the study
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17 401 followed by the process to obtain written informed consent. Consented participants
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19 402 are then registered onto the ASCENT adherence platform.

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

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

418

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

424

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

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3 428 facilities who do not consent to use the DAT take their medication according to
4 429 standard of care for the facility and under the NTP guidelines (See supplemental
5 430 information). Adherence data and treatment follow-up is also according to the country
6 431 specific NTP guidelines.
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11 12 13 433 ***Data Management***

14 434 Data from the DATs will be collected from the ASCENT adherence platform (patients
15 435 on the intervention only) using the Everwell Hub, a cloud-based or in-country
16 436 (Tanzania) hosted infrastructure according to country regulations. Patient data are
17 437 collected on the ASCENT adherence platform, with permission from the participant
18 438 provided in the informed consent. The ASCENT platform allows the TB health care
19 439 providers to review patient medication adherence logged from the DAT and track
20 440 SMS communications with patients. Data privacy is protected with access to the
21 441 platform being password protected with defined data access that allows health care
22 442 providers, but not researchers, to view personal identifying data.
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32 444 Treatment outcome data are from the routine reporting to the NTP and are electronic
33 445 in the Philippines and Ukraine and abstracted from paper TB registers in Tanzania
34 446 and South Africa. These data are collected for all patients (excluding those who opt-
35 447 out) and are imported/entered into the ASCENT research database hosted in-country
36 448 using REDcap, a secure web database application. (21)
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42 450 The routine data in the ASCENT research database are linked to deidentified
43 451 individual patient data from the ASCENT platform using a corresponding electronic
44 452 or paper record that has the TB registration number and ASCENT platform ID.
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50 454 ***Trial Governance***

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52 455 A Technical Advisory Group (TAG) has been set up to provide oversight, monitor
53 456 and oversee progress for this four-country study and its companion study in Ethiopia.
54 457 The TAG meets every 6 months and is composed of representatives from the five
55 458 countries and chaired by a senior researcher in Uganda.
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3 460 Diverse in-country stakeholders provide input to the study through a Community
4 Advisory Board (CAB) and/or other Civil Society Organizations (Tanzania).
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6 462 Consultation was sought in order to involve former TB patients and their care
7 providers and various other stakeholders. The CABs were engaged beginning in the
8 463 preparatory phase to provide input and advice into the facility selection and
9 464 randomization procedures. They were further consulted after the preparatory phase in
10 465 order to arrive at the specific country differentiated response algorithm.
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17 18 468 ***Statistical Analysis Plan***

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20 469 Statistical analyses will employ appropriate methods for the cluster randomized trial
21 design. We will conduct an intention-to-treat approach to evaluate treatment outcomes
22 470 in the DAT arm relative to the SOC. Additionally, two separate analyses will be
23 471 performed to evaluate the individual DAT - smart pill box or medication label/sleeve
24 472 – in relation to the SOC. For South Africa, Tanzania and the Philippines we will
25 473 employ a logistic regression model with random effects (to account for clustering at
26 474 the facility-level) to estimate the respective intervention effect as an odds ratio and
27 475 associated 95% confidence interval adjusted for variables employed in randomization
28 476 strata. Adjustment for other patient level covariates will be employed where
29 477 imbalance exists between the study arms. Sub-group analyses will be examined to
30 478 examine heterogeneity of effect among patient characteristics including, urban/rural,
31 479 gender and country specific health care delivery circumstances, and type of TB
32 480 (pulmonary or extra-pulmonary). (22) A detailed statistical analysis plan will be
33 481 finalized before the end of follow-up and data are unblinded.
34 482

35 36 483 ***Sub-studies***

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38 484 As part of the process evaluation of DAT interventions in each of the four countries, a
39 485 series of sub-studies are administered by ASCENT research personnel to a sub-set of
40 486 patients, health care workers and key stakeholders in a selection of facilities employed
41 487 in the effectiveness evaluation. In sub-study 1, acceptability and feasibility data will
42 488 be collected from TB patients. In sub-study 2, qualitative methods will explore the TB
43 489 patient experience using the DAT and explore differences in the experience by
44 490 gender. In sub-study 3, qualitative methods will explore the acceptability and
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3 491 feasibility of implementing DAT and differentiated response among the health care
4 492 workers providing TB care and relevant stakeholders.
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10 494 ***Economic Evaluation and Impact Modelling***

11 495 The decision to scale-up DATs in countries will need to consider the benefit to both
12 496 the health system as well as to the individual. As TB is known to disproportionately
13 497 affect the poor, the use of DATs may decrease the economic burden placed on TB
14 498 patients and address the END TB Strategy milestone of eliminating families facing
15 499 catastrophic health costs due to TB. We will use effectiveness data as well as
16 500 estimates of costs incurred by patients (collected in sub-study 1) and the service level
17 501 costs to estimate the cost-effectiveness of utilizing DATs relative to the standard of
18 502 care.
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27 504 To the extent that DATs may impact treatment outcomes, it will be useful to
28 505 understand the result on TB epidemiology in the country. The change in the treatment
29 506 outcome from DAT relative to the SOC will inform a simple cohort model, in order to
30 507 project the epidemiological impact, in terms of cases, incidence and prevalence, of
31 508 scaling up of DAT in the respective countries.
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38 510 ***Ethical considerations and dissemination***

39 511 The study has been approved by the WHO Ethical Review Committee (0003296) and
40 512 London School of Hygiene & Tropical Medicine Ethics Committee, United Kingdom
41 513 (19135) following external peer review. Individual protocols have been reviewed and
42 514 approved by relevant country specific committees: Single Joint Research Ethics Board
43 515 (Philippines SJREB 2019-57); Wits Human Research Ethics Committee (South Africa
44 516 AUR2-1-268); Tanzania Medical Research Coordinating Committee (MRCC) at
45 517 National Institute for Medical Research, Dar es Salaam (Tanzania
46 518 NIMR/HQ/R.8a/Vol.IX/3431); and Ukraine Ethics Committee of Public Health
47 519 Center of the MOH of Ukraine (Ukraine IRB 2019-33).
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57 521 Written informed consents of TB patients for the main effectiveness study are
58 522 collected from TB patients by the TB care providers at the intervention facilities. In
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3 523 addition, a waiver of consent was obtained to access TB register data. Patients agree
4 524 to use the DAT and consent to have researchers use anonymized data collected to the
5 525 ASCENT Adherence platform. Informed consents for the sub-studies are collected by
6 526 research associates prior to the interviews. The individual-level data sets visible to
7 527 research staff to monitor the study and conduct analysis are de-identified. All
8 528 databases are maintained in password-protected systems. Where paper records exist,
9 529 they are stored in the participating facilities in locked cabinets with access permitted
10 530 to only relevant facility health care providers and research team members.
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18 532 The research findings will be presented first to national stakeholders, and
19 533 disseminated to the Community Advisory Board, stakeholders and participants in
20 534 each country at local meetings, and presented at national and international
21 535 conferences. The primary results of the study will be written as country-specific
22 536 articles for submission to suitable scientific journals along with deidentified research
23 537 datasets for the sake of reproducibility. Exclusive use of the data for further
24 538 publications will be given to the ASCENT consortium as well as the country's local
25 539 research community. Major changes to the study are communicated to the CAB and
26 540 TAG, updated to the protocol and trial registration, and reported to the ethics
27 541 committee for approval.
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37 543 **Trial status**

38 544 This is protocol version 2.1.1 dated 31 March 2021. Enrolled for the main trial has
39 545 ended in August 2022 and follow up will continue through end of March 2023.
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46 547 **Funding**

47 548 The study is funded by Unitaid (Grant Agreement Number: 2019-33-ASCENT).
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51 550 **Patient and public involvement**

52 551 Patients and other members of the public were represented in the community advisory
53 552 boards of the study, but they were not directly involved in the design and conception
54 553 of the study. We will share key findings of the study with the study community
55 554 through local TB program coordinators.
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557 **Contributorship statement**

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

576

577 **Competing interests**

578 We declare we have no competing interest.

579

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Year	2021				2022				2023			
Quarters	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Effectiveness evaluation	Preparatory phase		Enrollment of participants for study									
			Data collection for effectiveness evaluation								Analysis	
Substudy 1			Preparations	Conduct survey			Present early findings		Dissemination			Final dissemination
Substudies 2, 3, 4						Preparations	Data collection & analysis			Dissemination		
Cost/modeling				Data collection and model calibration						Analysis		

SPRIT Figure showing study overview

130x103mm (120 x 120 DPI)

ASCENT study country TB profiles

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

ASCENT DATA USE AND SHARING

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

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

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

Period of exclusive use

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

1. Exclusive use will be for a fixed period of 2 (two) years after the data lock, during which time the primary results will be published.

2. De-identified analysis datasets for the primary publications will be released as required by the journal, for replication purposes (“minimal data set”). Analysis datasets supporting other manuscripts will be posted as required by journals at the time of publication.

3. This period of exclusive access will maximise publications from the ASCENT early career consortium researchers and will also be opened to the local research community in each participating country to exploit the data before the full dataset is released on open-access. During the period of exclusive use, the ASCENT study team and local research community with approved publication concepts are provided access to ASCENT de-identified data by submission of a signed Data Access Agreement. Researchers agree that they will only use the data for the analyses in the approved publication concept.

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

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

After the period of exclusive use

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

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



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

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

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2		6b	Explanation for choice of comparators	5
3				
4	Objectives	7	Specific objectives or hypotheses	6-7
5				
6	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
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12	Methods: Participants, interventions, and outcomes			
13				
14	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
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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)	9
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25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
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30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17-18
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35		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
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40		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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43	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-14
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52	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
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2	Sample size	14	Estimated number of participants needed to achieve	14
3			study objectives and how it was determined, including	
4			clinical and statistical assumptions supporting any	
5			sample size calculations	
6				
7	Recruitment	15	Strategies for achieving adequate participant	17-18
8			enrolment to reach target sample size	
9				

Methods: Assignment of interventions (for controlled trials)

Allocation:

14				
15	Sequence	16a	Method of generating the allocation sequence (eg,	N/A
16	generation		computer-generated random numbers), and list of any	
17			factors for stratification. To reduce predictability of a	
18			random sequence, details of any planned restriction	
19			(eg, blocking) should be provided in a separate	
20			document that is unavailable to those who enrol	
21			participants or assign interventions	
22				
23				
24	Allocation	16b	Mechanism of implementing the allocation sequence	N/A
25	concealment		(eg, central telephone; sequentially numbered,	
26	mechanism		opaque, sealed envelopes), describing any steps to	
27			conceal the sequence until interventions are assigned	
28				
29				
30	Implementation	16c	Who will generate the allocation sequence, who will	N/A
31			enrol participants, and who will assign participants to	
32			interventions	
33				
34	Blinding	17a	Who will be blinded after assignment to interventions	N/A
35	(masking)		(eg, trial participants, care providers, outcome	
36			assessors, data analysts), and how	
37				
38				
39		17b	If blinded, circumstances under which unblinding is	N/A
40			permissible, and procedure for revealing a	
41			participant's allocated intervention during the trial	
42				

Methods: Data collection, management, and analysis

43				
44				
45	Data collection	18a	Plans for assessment and collection of outcome,	18
46	methods		baseline, and other trial data, including any related	
47			processes to promote data quality (eg, duplicate	
48			measurements, training of assessors) and a	
49			description of study instruments (eg, questionnaires,	
50			laboratory tests) along with their reliability and validity,	
51			if known. Reference to where data collection forms	
52			can be found, if not in the protocol	
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56		18b	Plans to promote participant retention and complete	18
57			follow-up, including list of any outcome data to be	
58			collected for participants who discontinue or deviate	
59			from intervention protocols	
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2	Data	19	Plans for data entry, coding, security, and storage,	18
3	management		including any related processes to promote data	
4			quality (eg, double data entry; range checks for data	
5			values). Reference to where details of data	
6			management procedures can be found, if not in the	
7			protocol	
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10	Statistical	20a	Statistical methods for analysing primary and	19
11	methods		secondary outcomes. Reference to where other	
12			details of the statistical analysis plan can be found, if	
13			not in the protocol	
14				
15		20b	Methods for any additional analyses (eg, subgroup	19
16			and adjusted analyses)	
17				
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19		20c	Definition of analysis population relating to protocol	19
20			non-adherence (eg, as randomised analysis), and any	
21			statistical methods to handle missing data (eg,	
22			multiple imputation)	
23				
24				
25	Methods: Monitoring			
26	Data monitoring	21a	Composition of data monitoring committee (DMC);	18-19
27			summary of its role and reporting structure; statement	
28			of whether it is independent from the sponsor and	
29			competing interests; and reference to where further	
30			details about its charter can be found, if not in the	
31			protocol. Alternatively, an explanation of why a DMC	
32			is not needed	
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36		21b	Description of any interim analyses and stopping	18-19
37			guidelines, including who will have access to these	
38			interim results and make the final decision to	
39			terminate the trial	
40				
41	Harms	22	Plans for collecting, assessing, reporting, and	18-19
42			managing solicited and spontaneously reported	
43			adverse events and other unintended effects of trial	
44			interventions or trial conduct	
45				
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47	Auditing	23	Frequency and procedures for auditing trial conduct, if	N/A
48			any, and whether the process will be independent	
49			from investigators and the sponsor	
50				
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52	Ethics and dissemination			
53				
54	Research ethics	24	Plans for seeking research ethics	20-21
55	approval		committee/institutional review board (REC/IRB)	
56			approval	
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2	Protocol	25	Plans for communicating important protocol	20-21
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC/IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8				
9	Consent or assent	26a	Who will obtain informed consent or assent from	20-21
10			potential trial participants or authorised surrogates,	
11			and how (see Item 32)	
12				
13		26b	Additional consent provisions for collection and use of	N/A
14			participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
17	Confidentiality	27	How personal information about potential and enrolled	20-21
18			participants will be collected, shared, and maintained	
19			in order to protect confidentiality before, during, and	
20			after the trial	
21				
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23	Declaration of	28	Financial and other competing interests for principal	22
24	interests		investigators for the overall trial and each study site	
25				
26	Access to data	29	Statement of who will have access to the final trial	In the annex
27			dataset, and disclosure of contractual agreements that	
28			limit such access for investigators	
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31	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	N/A
32	post-trial care		for compensation to those who suffer harm from trial	
33			participation	
34				
35	Dissemination	31a	Plans for investigators and sponsor to communicate	21
36	policy		trial results to participants, healthcare professionals,	
37			the public, and other relevant groups (eg, via	
38			publication, reporting in results databases, or other	
39			data sharing arrangements), including any publication	
40			restrictions	
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44		31b	Authorship eligibility guidelines and any intended use	Standard guidelines apply
45			of professional writers	
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47		31c	Plans, if any, for granting public access to the full	In the annex
48			protocol, participant-level dataset, and statistical code	
49				
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51	Appendices			
52	Informed consent	32	Model consent form and other related documentation	In the annex
53	materials		given to participants and authorised surrogates	
54				
55	Biological	33	Plans for collection, laboratory evaluation, and storage	N/A
56	specimens		of biological specimens for genetic or molecular	
57			analysis in the current trial and for future use in	
58			ancillary studies, if applicable	
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1 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
2 Explanation & Elaboration for important clarification on the items. Amendments to the
3 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
4 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
5 license.
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For peer review only