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An open-label, multi-centre, randomised controlled trial to evaluate the effect of short-course rifapentine-based regimens with or without enhanced behaviour-targeted treatment support on adherence and completion of treatment for latent TB infection among adults in the UK (RID-TB: Treat): a study protocol

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Secondary Subject Heading:	

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Keywords:	Tuberculosis < INFECTIOUS DISEASES, Clinical trials < THERAPEUTICS, PREVENTIVE MEDICINE

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Manuscripts

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3 **1 An open-label, multi-centre, randomised controlled trial to evaluate the effect of short-course**
4 **2 rifapentine-based regimens with or without enhanced behaviour-targeted treatment support on**
5 **3 adherence and completion of treatment for latent TB infection among adults in the UK (RID-**
6 **4 TB: Treat): a study protocol**

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31 **Keywords:** clinical trial; LTBI; medication adherence; rifapentine; tuberculosis

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34 **Abstract**

35 **Introduction**

36 The successful scale-up of a latent tuberculosis infection (LTBI) testing and treatment programme is
37 essential to achieve TB elimination. However, poor adherence compromises its therapeutic
38 effectiveness. Novel rifapentine-based regimens and treatment support based on behavioural science
39 theory may improve treatment adherence and completion.

40 **Methods and analysis**

41 A pragmatic multi-centre open-label randomised controlled trial to assess the effect of novel short-
42 course rifapentine-based regimens for TB prevention and additional theory-based treatment support on
43 treatment adherence against standard-of-care. Participants aged between 16 and 65, with a positive
44 LTBI test who are eligible to start TB preventive therapy will be recruited. A total of 920 participants
45 will be randomized to one of the six arms with an allocation ratio of 5:5:6:6:6:6: (1) daily isoniazid +
46 rifampicin for three months (3HR), routine treatment support (control arm); (2) 3HR, additional
47 treatment support; (3) weekly isoniazid + rifapentine for three months (3HP), routine treatment support;
48 (4) weekly 3HP, additional treatment support; (5) daily isoniazid + rifapentine for one month (1HP),
49 routine treatment support; (6) daily 1HP, additional treatment support. Additional treatment support
50 comprises reminders using an electronic pill box, short animation, and leaflets based on the Perceptions
51 and Practicalities Approach. The primary outcome is adequate treatment adherence, defined as taking
52 $\geq 90\%$ of allocated doses within the pre-specified treatment period, measured by electronic pill boxes.
53 Secondary outcomes include safety and TB incidence within 12 months.

54 We will also conduct process evaluation of the trial interventions and assess intervention acceptability
55 and fidelity and mechanisms for effect and estimate the cost-effectiveness of novel regimens. The
56 protocol was developed with Patient and Public Involvement, which will continue throughout the trial.

57 **Ethics and dissemination**

58 Ethics approval has been obtained from The NHS Health Research Authority (20/LO/1097). We will
59 share the results in peer-reviewed journals.

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60 **Trial registration number** EudraCT 2020-004444-29

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3 **68 Article summary**
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5 **69 Strengths and limitations of this study**
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- 7 70 • This is the first trial to assess the effect of two rifapentine-based regimens compared to the
8
9 71 standard 3-month daily rifampicin plus isoniazid, and the effect of additional treatment
10
11 72 support compared to routine support, on LTBI treatment adherence. The intervention was
12
13 73 developed through a robust iterative process including patient and public involvement,
14
15 74 semistructured interviews and questionnaires with patients and clinicians.
16
17 75 • We will perform process evaluation of the trial interventions, including assessment of
18
19 76 intervention acceptability and fidelity, and economic evaluation, which will provide
20
21 77 additional evidence to inform treatment options and treatment support.
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24 78 • The trial will involve six arms because of the potential interaction between treatment
25
26 79 regimens and treatment support. The trial is powered to evaluate novel rifapentine-based
27
28 80 regimens compared to the standard daily rifampicin plus isoniazid (3HR) and the effect of
29
30 81 additional treatment support compared to routine support; however, it does not have sufficient
31
32 82 power to evaluate all possible comparisons such as 3-month weekly rifapentine plus isoniazid
33
34 83 vs 1-month daily rifapentine plus isoniazid.
35
36 84 • The trial will be conducted in England largely in migrant populations eligible for the LTBI
37
38 85 screening programme and contacts of TB patients and thus limiting generalisability to these
39
40 86 populations and similar settings.
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43 87 • Adherence will be measured using electronic pill boxes in all arms while reminders will be
44
45 88 activated only in arms with additional treatment support; however, this may impact adherence
46
47 89 in control groups.
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49 90

91 INTRODUCTION

92 Successful implementation of screening and treatment for latent tuberculosis infection (LTBI) is
93 critical to further reduce TB incidence globally and achieve TB elimination in low TB incidence
94 countries.(1) A recent call to action issued by the World Health Organization urged for accelerating
95 the scale-up of treatment of LTBI, particularly to mitigate the negative impact from the disruption of
96 TB services caused by the pandemic of COVID-19.(2)

97 Tuberculosis (TB) in England disproportionately affects underserved communities, such as migrants
98 and homeless people, who consequently experience higher disease burden and worse clinical
99 outcomes. Consequently, in England, LTBI screening and treatment for high risk groups such as new
100 migrants from high TB incidence countries is recognized as an essential strategy to achieve TB
101 elimination.(3) Contact tracing, including testing and treatment of LTBI among contacts, is another
102 essential component of the TB strategy for England.(3)

103 Achieving optimal treatment adherence and completion is essential to ensure the efficacy of treatment
104 for LTBI and to achieve commensurate reductions in TB incidence. Standard therapeutic options in
105 the UK include 3-months of self-administered daily isoniazid/rifampicin and 6-months of daily
106 isoniazid; the former regimen is often prescribed because of the availability of fixed-dose
107 formulations and its shorter duration. Whilst these regimen are efficacious in preventing disease, their
108 effectiveness is limited by low treatment adherence and completion rates.(4, 5) According to data
109 from England in migrants whose treatment outcome is known, 75% completed LTBI treatment
110 between 2019 and 2020.(6, 7) The proportion of people who completed treatment varied by Clinical
111 Commission Group (CCG), which was less than 70% in several CCGs.(8)

112
113 People with LTBI may need additional support to adhere to effective treatments. Treatment non-
114 adherence can be intentional or unintentional, and is driven by a person's motivation and ability to
115 take medicine as prescribed, respectively.(9) Motivation is influenced by our perceptions (e.g. beliefs
116 and preferences) and ability is determined by practical factors (e.g. internal capacity and resource).(9)

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3 117 These principles are operationalised as part of the Perceptions and Practicalities approach to
4
5 118 supporting adherence (PAPA) and are applied in NICE guidelines.(10) The Necessity and Concerns
6
7 119 Framework (NCF) further explains how patients motivation to engage with treatment is based on their
8
9 120 perceived necessity for, and concerns about the treatment.(11) Necessity beliefs are influenced by
10
11 121 perceptions of the health threat (e.g LTBI) and interpretation of symptoms. The asymptomatic nature
12
13 122 of LTBI may negatively impact necessity beliefs, and heighten treatment concerns. As such,
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15 123 intervention to support treatment adherence in people with LTBI will likely be more effective if they
16
17 124 address patient beliefs and concerns around treatment, in addition to removing practical barriers.
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23 126 The need to understand perceptual and practical barriers to treatment adherence, and the potential of
24
25 127 advancing technology and drug regimens in the NHS has been highlighted. Some Mobile/digital
26
27 128 technology (mHealth) has been shown to improve adherence in TB disease studies. A recent study in
28
29 129 China found electronic reminders, using specially designed electronic medication monitors, improved
30
31 130 treatment adherence in such TB patients, but multiple two-way daily text messaging reminders,
32
33 131 didactic in nature, did not.(12) Most of the evidence available is on TB disease with little research on
34
35 132 mHealth interventions to improve LTBI treatment adherence.(13, 14) Another call to action issued by
36
37 133 the World Health Organization suggested TB preventive treatment programmes should consider
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39 134 communication technologies for medication adherence support.(15) The evidence on mHealth
40
41 135 interventions for LTBI treatment would contribute to their global scale-up.

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44 136 Another approach to promote better treatment adherence and completion is to decrease the complexity
45
46 137 of current LTBI regimens. A regimen that is given once weekly may result in better treatment
47
48 138 completion than the current daily 3-month regimen. A randomised controlled trial demonstrated that a
49
50 139 new regimen of 12 doses of weekly rifapentine and isoniazid (3HP) delivered through direct
51
52 140 observation (i.e. with patients being supervised taking each dose) is non-inferior to 9 months of daily
53
54 141 isoniazid.(16) Our network meta-analysis suggests that 3HP has similar efficacy to the UK standard-
55
56 142 of-care of a 12-week, daily isoniazid/rifampicin regimen (3HR).(17) Furthermore, a recent trial in
57
58 143 people living with HIV (23% with LTBI as demonstrated by a positive TST and/or IGRA result)

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3 144 demonstrated non-inferiority of daily one-month rifapentine plus isoniazid (1HP) compared to 9
4
5 145 months of daily isoniazid.(18) The one-month regimen resulted in better adherence and fewer serious
6
7 146 adverse events. Based on this study, and by extrapolating to HIV-negative individuals, newly
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9 147 published WHO guidelines recommend this regimen regardless of HIV status. However, there is no
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11 148 published evaluation of whether these more expensive rifapentine-based regimens lead to better
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13 149 treatment completion than the current daily administered UK standard-of-care. In particular, evidence
14
15 150 is limited on the use of 3HP with patient self-administration and no study has compared its
16
17 151 completion with 3HR.

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20 152 To develop tools to reduce TB rates, we need to evaluate advancing technology and drug regimens,
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22 153 but also understand the barriers and enablers of adherence.(3) To date, adherence interventions have
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24 154 predominantly focused on removing practical barriers to adherence (e.g reminder of shortening the
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26 155 drug regimen). However, such approaches applied in isolation ignore patient beliefs. LTBI is
27
28 156 asymptomatic which means patients might have a disconnect between medical advice and their
29
30 157 perceived need for treatment.(19) NICE guidelines recommend a Perceptions and Practicalities
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32 158 Approach (PAPA) to adherence support, whereby beliefs (necessity and concerns) are elicited and
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34 159 addressed in addition to practical barriers.(10, 11)

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38 160 We previously conducted the HALT-LTBI study, a pilot study assessing the safety and treatment
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40 161 completion of 3HP compared to standard care.(20) The HALT-LTBI demonstrated the feasibility of
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42 162 recruiting LTBI patients to such a trial; no serious adverse events defined as grade 3 or more were
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44 163 reported, supporting the safety of rifapentine and isoniazid regimens in individuals eligible for LTBI
45
46 164 treatment in the UK. 78% and 68% of participants completed treatment in the experimental and
47
48 165 standard-of-care arms, respectively, but the pilot was not powered to detect differences in treatment
49
50 166 completion. Thus, we will conduct a fully powered trial to compare treatment adherence and adverse
51
52 167 events of novel 3HP and 1HP regimens compared with 3HR and to assess the effect of additional
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54 168 treatment support in participants given each regimen.

169 **Objectives**

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3 170 The primary objective of this trial is to assess the effect of novel rifapentine-based regimens (3HP or
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5 171 1HP) compared to the standard 90-dose daily rifampicin plus isoniazid (3HR), and the effect of
6
7 172 additional treatment support compared to routine support, on LTBI treatment adherence.
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10 173 The secondary objectives are: 1) to evaluate the effect of LTBI treatment and additional treatment
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12 174 support using alternate measures of adherence outcome; and 2) to compare the frequency of adverse
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14 175 events whilst on treatment for LTBI, and development of TB within 12 months following treatment.
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16 176 Additionally, we will evaluate the process of delivering the adherence intervention and examine
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18 177 intervention fidelity and acceptability as well as the cost-effectiveness of different treatment options
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20 178 and/or additional treatment support.
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25 180 **METHOD AND ANALYSIS**

26 27 181 **Trial design**

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29 182 A multi-centre open-label randomised controlled trial with the following six parallel groups (Figure
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31 183 1):

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34 184 **ARM 1-** Daily isoniazid + rifampicin for three months (3HR), routine treatment support (SOC;
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36 185 control arm)

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39 186 **ARM 2-** Daily 3HR, additional treatment support

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41 187 **ARM 3-** Weekly isoniazid + rifapentine for three months (3HP), routine treatment support

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44 188 **ARM 4-** Weekly 3HP, additional treatment support

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47 189 **ARM 5-** Daily isoniazid + rifapentine for one month (1HP), routine treatment support

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49 190 **ARM 6-** Daily 1HP, additional treatment support

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52 191 A factorial design was not chosen for several reasons. Firstly, it is anticipated that there will be an
53
54 192 interaction between type of regimen and treatment support; additional treatment support is likely to
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56 193 confer a smaller benefit with 3HP/1HP compared to 3HR. Secondly, the power to detect the effect of
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58 194 an intervention would be reduced if the effect of the second intervention is greater than expected.
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3 195 **Study setting**
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6 196 The trial will recruit from secondary care sites that provide LTBI treatment in England, UK. RID-TB:
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8 197 Treat is part of a 5-year programme of work (RID-TB) which is funded by the National Institute for
9
10 198 Health Research (NIHR) (RP-PG-0217-20009 <https://dev.fundingawards.nihr.ac.uk/award/RP-PG->
11
12 199 0217-20009).
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17 201 **Study population**
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20 202 The trial will enrol populations who are eligible for treatment for LTBI according to the national
21
22 203 guidance. We envisage that the majority of individuals eligible for this are contacts of persons
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24 204 diagnosed with TB disease, and/or migrants eligible for the national LTBI screening programme ref.
25
26 205 The LTBI migrant screening programme includes migrants who are aged 16 to 35 years, entered the
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28 206 UK from a high incidence country ($\geq 150/100,000$) or Sub-Saharan Africa within the last five years
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30 207 and had been previously living in that high incidence country for six months or longer.(21) Inclusion
31
32 208 and exclusion criteria are shown in Box 1.

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35 209 Participants will be identified from secondary care settings in the UK where persons eligible for
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37 210 treatment for LTBI are managed. Participants will be recruited individually, but if any participants
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39 211 share a household, they will be allocated to the same arm as the first person recruited from that
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41 212 household (effectively resulting in randomisation by household).
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46 214 **Treatment**
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49 215 Participants who are randomized to arms 1 and 2 will receive the standard of care regimen: rifampicin
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51 216 plus isoniazid once daily for 90 doses (3HR).
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54 217 Participants who are randomized to arms 3 and 4 will receive rifapentine plus isoniazid once weekly
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56 218 for 12 doses (3HP) and those who are randomized to arms 5 and 6 will receive rifapentine plus
57
58 219 isoniazid once daily for 28 doses (1HP).
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3 220 In order to account for missed doses and interruption of treatment due to adverse events, participants
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5 221 given 3HR or 3HP will have 16 weeks and those given 1HP will have 6 weeks to complete treatment.
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7 222 In the study by Swindells et al, participants were given 8 weeks to complete 1HP.(18) We have
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9 223 chosen 6 weeks to make the period proportionally similar to that for 3HR and 3HP. Clinicians will
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11 224 assess the need for treatment extension based on the assessment of adherence and review of reasons
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13 225 for non-adherence but should not extend beyond recommended grace periods.
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16 226 In all arms, participants will receive vitamin B6 (pyridoxine). The dosages of study drugs are shown
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18 227 in Table 1.
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24 229 **Treatment support**

25 26 27 230 *Routine treatment support*

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30 231 Participants allocated to arms 1, 3, and 5 will receive routine treatment support. Participants will be
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32 232 given information about treatment for LTBI including expected adverse events and the importance of
33
34 233 adherence, according to local practice. Adherence will be reviewed at each follow-up visit or remote
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36 234 consultation via self-reporting and/or pill count and discussed with the participant. An electronic pill
37
38 235 monitor box, Wisepill EvriMed1000 (Wisepill, Somerset West, South Africa)(22) will collect the date
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40 236 and time of each opening to collect information on adherence. However, it will be set to silent mode
41
42 237 and not be used as an adherence reminder tool.
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45 238 *Intervention*

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48 239 Participants assigned to arms 2, 4, and 6 will receive a PAPA-based intervention designed to provide
49
50 240 additional treatment support (i.e. in addition to routine treatment support).(11) Specifically, the
51
52 241 intervention will consist of an animation which will 1) provide a rationale for treatment necessity and
53
54 242 help people understand how LTBI treatment can help them to achieve a health goal that is important
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56 243 to them, 2) address common concerns about LTBI treatment and 3) address practical barriers to
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58 244 treatment (e.g. anchoring treatment to daily activities). The animation will be supported by a leaflet
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3 245 that cover misperceptions about LTBI testing and treatment, and other frequently asked questions.
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5 246 Participants will also be asked to set reminders using an electronic pill monitor box (Wisepill
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7 247 EvriMed). The electronic pill box allows two modes of reminders: audio alarm from the box or text-
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9 248 message to participants' mobile phones.
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14 250 The reminder can be set at pre-specified times and can also be activated to send a reminder when the
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16 251 pill box is not opened. Site staff will discuss options with each participant and set reminders according
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18 252 to their preferences. Participants can opt not to receive reminders before or at the time of intended
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20 253 medication intake. However, they will still be reminded when the box is not opened within a pre-
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22 254 specified time in a day and they will receive a supportive text message automatically sent by the pill
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24 255 box. The mode of reminder can be further adjusted during the course of treatment as necessary upon
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26 256 discussion with a clinician. The pill box will electronically collect the date and time of each opening.
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31 258 **Study assessment and follow-up**

32 259 *Screening, randomisation and baseline assessment*

33 260 Randomisation and baseline assessment will occur on the same day (Week 0). In some cases, this may
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35 261 also be the same day as Screening. Following informed consent procedures, participants will be
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37 262 screened for eligibility. A TB symptom screen and urine pregnancy test will be carried out, and data on
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39 263 the participant's TB risk group category will be collected. Demographic and medical history
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41 264 information will be collected. We will check the results of clinical, laboratory, and radiological
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43 265 assessments performed under routine care before entry to the trial to confirm eligibility. A TB symptom
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45 266 screen and urine pregnancy test will be repeated at the randomization/baseline visits unless the
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47 267 screening and randomisation visits occur on the same day.
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50 268 *Assessment of Adherence*

51 269 Assessment of adherence will be primarily measured using the Wisepill, which collects the date and
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53 270 time of each opening. Adherence will also be measured through self-reporting and pill count under
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55 271 routine care either at physical clinic visits or remote consultations as per the local standard. Attending
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3 272 clinicians will count the number of remaining tablets. The difference between the number of tablets
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5 273 dispensed and the number returned will be calculated.

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7 274 *Clinical assessment during follow-up*

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9 275 As per usual practice, liver function tests (hepatic transaminases, ALT/AST, and total bilirubin) will
10
11 276 be performed at week 2 for all participants. Afterwards, liver function tests will be performed at
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13 277 weeks 4, 8, 12, and 16 while on treatment and at completion, or at other times if deemed necessary by
14
15 278 attending clinicians (e.g. abnormality in preceding tests, new onset of symptoms suggesting potential
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17 279 liver toxicity). These tests should be performed at any time during the treatment and post-treatment
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19 280 phase if the participant exhibits symptoms or signs of drug-induced liver injury (DILI).
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24 282 Symptoms and signs of adverse events expected with study drugs, including: anorexia, nausea, vomiting,
25
26 283 fatigue, weakness, jaundice, rash, peripheral neuropathy, bruising will be clinically assessed at every
27
28 284 visit. Participants who already completed treatment and have no scheduled visits will be given a phone
29
30 285 call at week 8, 12, 16 and 20 to check adverse events and TB signs and symptoms since the last dose.
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35 287 At every physical visit or remote consultation, we will review symptoms and signs of TB disease as
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37 288 well as review concomitant medications using a brief questionnaire. There will be no formal study visits
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39 289 after completion of treatment.
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44 291 **Outcomes**

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46 292 *Primary Outcome*

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48 293 The primary outcome is adequate treatment adherence, defined as taking $\geq 90\%$ of allocated doses
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50 294 within the allowable time-frame from randomisation (binary outcome). For the primary analyses,
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52 295 treatment adherence is measured using an electronic monitor box
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55 296 *Secondary Outcomes*

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58 297 The secondary outcome measures are:
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3 298 • Effectiveness: (1) Proportion of allocated doses missed over the treatment period (measured
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6 299 using monitor box); (2) Proportion of allocated pills missed over the treatment period
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8 300 (measured using pill counts); (3) Taking at least 90% of doses and pills over the treatment
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10
11 301 period (binary outcome assessed using both monitor box and pill counts); (4) Early study
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13 302 treatment discontinuation for any reason
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16 303 • Safety: (1) Permanently stop study treatment due to drug-related adverse events (i.e. adverse
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18 304 reactions) ; (2) Experience Grade ≥ 3 adverse events; (3) Develop TB disease within 12
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21 305 months.

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25 306 **Sample size**

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27 307 The six-arm design allows evaluation of:

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30 308 • the effect of the novel treatment regimens (3HP and 1HP) versus standard-of-care regimen
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32 309 (3HR), under routine treatment support
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35 310 • the effect of additional treatment support vs routine treatment support for each individual
36
37 311 regimen

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39 312 A total of 920 participants are to be recruited. This provides 80% power for each of the following
40
41 313 comparisons:

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44 314 • Arm 3 vs Arm 1- ie 3HP + routine treatment support vs 3HR + routine treatment support
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46 315 • Arm 5 vs Arm 1- ie 1HP + routine treatment support vs 3HR + routine treatment support
47
48 316 • Arm 2 vs Arm 1- ie 3HR + additional treatment support vs 3HR + routine treatment support
49
50 317 • Arm 4 vs Arm 3- ie 3HP + additional treatment support vs 3HP + routine treatment support
51
52 318 • Arm 6 vs Arm 5- ie 1HP + additional treatment support vs 1HP + routine treatment support

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54
55 319 The power calculations assume the following:

- 56
57
58 320 • 70% adherence rate in Arm 1
59
60

- 1
2
3 321 • 3HP and 1HP improve adherence rate by 15% (absolute difference) compared to 3HR,
4
5 322 respectively, with routine treatment support(18, 23, 24)
6
7 323 • Compared to routine treatment support, additional treatment support improves adherence rate
8
9 324 by 15% for 3HR, and 10% for 3HP and 1HP, respectively(12)
10
11 325 • 2-sided alpha 5% (see below for type I error considerations)
12
13
14 326 • average number of participants enrolled per household is 2, taking into account the average
15
16 327 household size in UK.(25)
17
18 328 • intra-class correlation (ICC) within a household is 0.1
19

20 329 The 70% adherence rate assumed for Arm 1 is based on the 77% LTBI treatment completion rate
21
22 330 reported from the Public Health England LTBI testing and treatment database for 2018.(26)
23
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25 331

27 332 **Randomisation and allocation**

29 333 Participants will be randomised centrally using a computerised algorithm developed and maintained
30
31 334 by the Medical Research Council Clinical Trials Unit at University College London (MRC-CTU).

33 335 To randomise a participant, the information contained on a completed Randomisation Form will be
34
35 336 entered into the secure online trial database by trial team members at the site who have been trained
36
37 337 and authorised to randomise by the MRC-CTU. The database will automatically check for eligibility.
38
39 338 Only those who meet all eligibility criteria will be able to be randomised. Randomisation will be
40
41 339 performed using minimisation with an additional random element, to be balanced with respect to
42
43 340 centre and TB exposure risk group.
44
45

47 341 **Blinding**

49 342 This is an open-label trial. Blinding of participants and care providers to the allocation group is not
50
51 343 relevant since the primary objective of this trial to examine the effect of shorter or weekly regimens
52
53 344 and additional treatment support on treatment adherence.
54
55

57 345 **Data collection methods and management**

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2
3 346 Adherence data will be collected through the Wisepill monitor box. Demographic and clinical
4
5 347 information will be collected through clinical consultation and recorded in relevant case report forms
6
7 348 (CRFs). Development of TB within 12 months after starting treatment and outcomes of pregnancy that
8
9 349 is found after enrolment will be collected using records held by NHS Digital, Public Health England,
10
11 350 and/or the National TB register.

14 351 **Statistical methods**

16
17 352 The estimands for the primary analyses are defined in Table 2. The primary analyses will compare the
18
19 353 proportion of participants with adequate adherence between arms using the following approach:

- 20
21 354 a) Arm 3 vs Arm 1- ie 3HP + routine treatment support vs 3HR + routine treatment support
22
23 355 b) Arm 5 vs Arm 1- ie 1HP + routine treatment support vs 3HR + routine treatment support
24
25 356 c) Arm 2 vs Arm 1- ie 3HR + additional treatment support vs 3HR + routine treatment support

26
27 357 If comparison (a) shows 3HP improves adherence compared to 3HR, then additional treatment
28
29 358 support will be formally tested for 3HP by comparing Arm 4 vs Arm 3 – ie 3HP + additional
30
31 359 treatment support vs 3HP + routine treatment support; otherwise, the adherence rates will be
32
33 360 compared between these arms as exploratory analyses. Additional treatment support will be similarly
34
35 361 assessed for 1HP.

36
37 362 All randomised patients will be included in the primary analyses, apart from those subsequently found
38
39 363 to have had TB disease at baseline but enrolled in error (modified intention-to-treat approach). The
40
41 364 risk ratio (with 95% confidence interval) for adequate treatment adherence comparing the relevant
42
43 365 arms will be estimated using log-binomial generalised linear mixed models (GLMMs), allowing for
44
45 366 intra-household correlation.

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47
48
49 367 Type I error adjustment for multiple comparisons is not deemed necessary since:

- 50
51 368 • The research hypotheses corresponding to comparisons (a), (b) and (c) are considered
52
53 369 sufficiently distinct.(27-29)
54
55 370 • The effect of additional treatment support versus routine support is being evaluated in non-
56
57 371 overlapping populations for 3HR, 3HP and 1HP, respectively.

- 1
2
3 372 • The closed test approach whereby the effect of additional treatment support will only be
4
5 373 formally tested for 3HP if there is evidence that 3HP improves adherence compared to 3HR
6
7 374 with routine treatment support protects the type I error. This approach will also be used for the
8
9 375 assessment of additional treatment support for 1HP.
10

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13
14 377 For participants who have collected all prescriptions but are lost to follow-up before completing
15
16 378 treatment, the adherence data until the end of allocated period can still be downloaded remotely from
17
18 379 the Wisepill monitor box to ascertain whether adequate treatment adherence is achieved; this data will
19
20 380 be included in the primary analyses. In sensitivity analyses, the primary outcome will be imputed for
21
22 381 these patients using multiple imputation by chained equations (MICE), with imputation to be
23
24 382 conducted separately by study arm. Sensitivity analyses will also be performed assuming no drug
25
26 383 intake from the last follow-up visit attended.
27

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29 384 Supplementary analyses will consider different definitions of adequate treatment by varying the
30
31 385 minimum proportion of doses required to have been taken, and different allowable time-frames for
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33 386 making up missed doses. In addition, other analysis populations will be considered, including
34
35 387 intention-to-treat and per protocol (including only participants who commenced their original
36
37 388 allocated trial intervention). Planned exploratory subgroup analyses, will examine outcomes in pre-
38
39 389 defined subgroups.
40

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43 391 **Safety reporting**

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45 392 The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of Good Clinical
46
47 393 Practice apply to this trial protocol. These definitions are given in Table 3. All Grade 3 or higher
48
49 394 adverse events, whether expected or not, will be recorded in the patient's medical notes. All adverse
50
51 395 events will be recorded up to week 20. Serious adverse events should be notified to the CTU within
52
53 396 24 hours of the investigator becoming aware of the event from the time of randomisation to the last
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55 397 assessment of adverse events, i.e. week 20. Adverse events will be graded using the DAIDS toxicity
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57 398 grading scale.(30)
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400 Monitoring and oversight

401 The trial will be monitored by the MRC-CTU. An Independent Data Monitoring Committee (IDMC)
402 will be formed. The IDMC will review study conduct and safety data regularly. The IDMC will be
403 asked to advise on whether the accumulated data from the trial, together with results from other
404 relevant trials, justify continuing recruitment of further participants. The IDMC will make
405 recommendations to the Trial Steering Committee (TSC) as to whether the trial should continue in its
406 present form.

407 Process evaluation

408 The process evaluation will follow MRC guidance using an embedded, mixed-methods evaluation
409 approach in order to assess acceptability, fidelity, and mechanisms of effects of the interventions. It will
410 be conducted by the research team, working closely with the Intervention Development Group and
411 clinicians delivering the trial.

412 Patient sample

413 Patients in the full trial sample will be administered validated questionnaires assessing the
414 psychological characteristics that we predict will mediate the effects of the interventions.
415 Questionnaire will be administered during scheduled clinic appointments at baseline (0 weeks),
416 interim (2 weeks) and treatment completion (either 4 or 12 weeks depending of regimen). Baseline
417 measure will include Beliefs about Medicines Questionnaire (BMQ-Specific/BMQ-General),
418 Perceived Sensitivity to Medicines Scale (PSM-5), Brief illness perceptions questionnaire (BIPQ),
419 The Satisfaction with Information about Medicines Scale (SIMS), Hospital Anxiety and Depression
420 Scale (HADS). At follow-up participants will complete the BIPQ and BMQ-Specific, and a measure
421 of self-reported adherence (Medication Adherence Report -5 [MARS-5]) and the Treatment
422 intrusiveness Questionnaire (TIQ). A subset of participants will also be approached for a qualitative
423 assessment of their experiences in the trial. Participants in each intervention arm will be purposively
424 sampled based on their treatment adherence (10 participants per arm: 5 high adherence, 5 low
425 adherence; total 60 interviews; adherence in line with the primary outcome). Measures will consist of
426 brief, semi-structured interviews.

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Staff sample

Healthcare professionals responsible for administering the interventions will be requested to complete a short checklist form following patient randomisation in order to assess intervention fidelity. This will confirm whether each component of the interventions was delivered per protocol. We will also purposively sample 20 service providers to take part in brief, semi-structured interviews (in person or by phone) in order to obtain feedback on the delivery of the intervention and to identify any issues that might enhance delivery in practice. In addition, we will use these interviews to investigate wider contextual issues impacting on delivery. We will also encourage implementing clinicians to report major issues that might compromise intervention delivery during the trial, rather than waiting for a formal interview on trial completion.

Health economic evaluation

This will estimate if changes to LTBI diagnosis and/or treatment are cost-effective from the perspective of the National Health Service, using a health-economic model to synthesise data obtained within the entire RID-TB programme and evidence from other sources. Participants will be asked to complete monthly EQ-5D questionnaires. We will collect information on the costs participants incur in attending appointments within this trial, to allow potential future analysis from a societal perspective.

PATIENT AND PUBLIC INVOLVEMENT (PPI)

The trial was discussed with the charity TB Alert and two community representatives drawn from a migrant charity and a patient previously treated for LTBI. A charity representative and one former patient read versions of the grant proposal and contributed suggestions on study design. At the protocol development stage, the following input was sought from TB Alert: study design, treatment support interventions, Participant Information Sheet and Consent form, patient-facing questionnaires used for behavioural studies.

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3 455 During the trial, we will engage with 1) The RID-TB PPI Advisory Group (PPAG) consisting of
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5 456 members recruited via social media accounts, TB nurses, TB patient advocates, ex-patient contacts
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7 457 and voluntary/community organisations and (2) The TB Action Group (TAG) network of people
8
9 458 personally affected by TB. We will seek input for: recruitment, patient/public engagement tools,
10
11 459 provision of translated materials on LTBI and access to recruitment sites.
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13 460

16 461 **ETHICS AND DISSEMINATION**

18 462 **Ethics approval**

21 463 Ethics approval has been obtained from the Health Research Authority (HRA) in the UK
22
23 464 (20/LO/1097). Any further substantial amendments will be submitted and approved by the main
24
25 465 Research Ethics Committee and HRA.
26

28 466 **Consent**

30 467 Participants will be screened and consented at approved trial sites that are authorised by the MRC-
31
32 468 CTU to carry out the RID-TB: Treat trial. We will provide potential participants with a copy of the
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34 469 Participant Information Sheet. We will obtain written informed consent to enter into the trial and be
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36 470 randomised after explanation of the aims, methods, benefits and potential hazards of the trial before
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38 471 any trial-specific procedures are performed.
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43 473 **Dissemination**

45 474 We will report findings of the trial through publications in national and international conferences as
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47 475 well as in peer-reviewed journals. Findings will be also disseminated via TB Aler, TB Action Group.,
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49 476 social media, and institutional websites. Trial data will be available for sharing by request after the
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51 477 primary publication upon approval by the Trial Management Group.
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54 478 **CONCLUSION**

57 479 This trial will provide evidence on the effect of novel rifapentine-based treatment regimens for LTBI
58
59 480 and enhanced treatment support on treatment adherence. Underpinned by process evaluation and
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3 481 economic evaluation, this trial will inform treatment for LTBI strategies in the UK. The results of this
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5 482 trial may also be of value in other similar settings, and possibly in low and middle-income countries.
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11 484 **Acknowledgements**

12
13 485 We thank the NIHR programme officers, UCL-NIHR Patient and Public Involvement Advisory
14
15 486 Group, MRC CTU at UCL Protocol Review Committee, and the independent Programme Steering
16
17 487 Committee for their support and inputs during the development of the protocol.
18
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20
21 488 **Authors contributions**

22
23 489 IA and MXR conceived the study. IA and MXR led the application to secure funding. IA, MXR, TD,
24
25 490 YH, HB, JC, MF, ALC, AG, VH, EOP, JS, KS, HLB, AC, CG, RH, MJ, HK, ML, MM, PJW, DZ
26
27 491 contributed to the study design. TD and AMC provided statistical oversight. MXR, TD, and YH
28
29 492 drafted and revised the manuscript. All authors contributed critical intellectual input and approved the
30
31 493 final manuscript.
32
33

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35
36
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40
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42
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46 499 **Competing interests**

47
48 500 None declared.
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52 502 **References**

53 503

54
55 504 1. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action
56
57 505 framework for low-incidence countries. *European Respiratory Journal*. 2015;45:928-52.
58
59
60

- 1
2
3 506 2. World Health Organization. Call to Action 2.0: A global drive to scale up TB.
4
5 507 8
9 509 12
13 511 3. Public Health England. Collaborative tuberculosis strategy for England: 2015 to 2020. 2015.
14
15 512 4. Hirsch-Moverman Y, Shrestha-Kuwahara R, Bethel J, et al. Latent tuberculous infection in
16
17 513 the United States and Canada: who completes treatment and why? The international journal of
18
19 514 tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and
20
21 515 Lung Disease. 2015;19:31-8.
22
23 516 5. Saunders MJ, Koh GC, Small AD, et al. Predictors of contact tracing completion and
24
25 517 outcomes in tuberculosis: a 21-year retrospective cohort study. The international journal of
26
27 518 tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and
28
29 519 Lung Disease. 2014;18:640-6.
30
31 520 6. Public Health England: LTBI testing and treatment programme for migrants: 2020 report.
32
33 521 7. Public Health England: Tuberculosis in England. 2020 report.
34
35 522 8. Public Health England: LTBI testing and treatment programme for migrants 2020: data tables.
36
37 523 9. Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers,
38
39 524 unintentional nonadherers, and intentional nonadherers: Application of the Necessity–Concerns
40
41 525 Framework. Journal of psychosomatic research. 2008;64:41-6.
42
43 526 10. NICE. Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and
44
45 527 Supporting Adherence: Full Guideline. Clinical Guideline CG76. 2009.
46
47 528 11. Horne R, Cooper V, Wileman V, et al. Supporting adherence to medicines for long-term
48
49 529 conditions: A perceptions and practicalities approach based on an extended common-sense model.
50
51 530 European Psychologist. 2019;24:82-96.
52
53 531 12. Liu X, Lewis JJ, Zhang H, et al. Effectiveness of Electronic Reminders to Improve
54
55 532 Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med.
56
57 533 2015;12:e1001876.
58
59
60

- 1
2
3 534 13. Holzschuh EL, Province S, Johnson K, et al. Use of Video Directly Observed Therapy for
4
5 535 Treatment of Latent Tuberculosis Infection - Johnson County, Kansas, 2015. MMWR Morbidity and
6
7 536 mortality weekly report. 2017;66:387-9.
- 8
9 537 14. Lam CK, McGinnis Pilote K, Haque A, et al. Using Video Technology to Increase Treatment
10
11 538 Completion for Patients With Latent Tuberculosis Infection on 3-Month Isoniazid and Rifapentine:
12
13 539 An Implementation Study. Journal of medical Internet research. 2018;20:e287.
- 14
15 540 15. World Health Organization. Overcoming key barriers to scale up tuberculosis preventive
16
17 541 treatment (TPT) A Call to Action.
18
19 542 [https://www.who.int/tb/CalltoactionTPT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6](https://www.who.int/tb/CalltoactionTPT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa)
20
21 [af&e=09bced52fa](https://www.who.int/tb/CalltoactionTPT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa) Accessed 18 May 2021.
- 22
23 543
24 544 16. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for
25
26 545 latent tuberculosis infection. The New England journal of medicine. 2011;365:2155-66.
- 27
28 546 17. Zenner D, Beer N, Harris RJ, et al. Treatment of Latent Tuberculosis Infection: An Updated
29
30 547 Network Meta-analysis. Ann Intern Med. 2017;167:248-55.
- 31
32 548 18. Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to
33
34 549 Prevent HIV-Related Tuberculosis. The New England journal of medicine. 2019;380:1001-11.
- 35
36 550 19. Horne R, Chapman SC, Parham R, et al. Understanding patients' adherence-related beliefs
37
38 551 about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-
39
40 552 Concerns Framework. PloS one. 2013;8:e80633.
- 41
42 553 20. Surey J, Stagg HR, Yates TA, et al. An open label, randomised controlled trial of rifapentine
43
44 554 versus rifampicin based short course regimens for the treatment of latent tuberculosis in England: the
45
46 555 HALT LTBI pilot study. BMC Infectious Diseases. 2021;21:90.
- 47
48 556 21. Public Health England: Latent TB Testing and Treatment for Migrants. A practical guide for
49
50 557 commissioners and practitioners. 2015.
- 51
52 558 22. evriMED1000 Dispenser <https://www.wisepill.com/wisepill-rm1000> Accessed 9 July 2021 [
53
54 559 23. Martinson NA, Barnes GL, Moulton LH, et al. New Regimens to Prevent Tuberculosis in
55
56 560 Adults with HIV Infection. New England Journal of Medicine. 2011;365:11-20.
- 57
58
59
60

- 1
2
3 561 24. Sterling TR, Villarino ME, Borisov AS, et al. Three Months of Rifapentine and Isoniazid for
4
5 562 Latent Tuberculosis Infection. *New England Journal of Medicine*. 2011;365:2155-66.
6
7 563 25. Office for National Statistics. Families and households in the UK: 2020.
8
9 564 [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/familiesandhouseholds/2020)
10
11 565 [familiesandhouseholds/2020](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/familiesandhouseholds/2020) accessed 15 Sep 2021.
12
13 566 26. Public Health England: Tuberculosis in England. 2019 report.
14
15 567 27. Howard DR, Brown JM, Todd S, et al. Recommendations on multiple testing adjustment in
16
17 568 multi-arm trials with a shared control group. *Stat Methods Med Res*. 2018;27:1513-30.
18
19 569 28. Choodari-Oskoei B, Bratton DJ, Gannon MR, et al. Adding new experimental arms to
20
21 570 randomised clinical trials: Impact on error rates. *Clin Trials*. 2020;17:273-84.
22
23 571 29. Wason JMS, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it
24
25 572 necessary and is it done? *Trials*. 2014;15:364.
26
27 573 30. U.S. Department of Health and Human Services, National Institutes of Health, National
28
29 574 Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for
30
31 575 Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017].
32
33 576 Available from: <https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf> Accessed 11
34
35 577 September 2020.
36
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580 **Box 1. Study inclusion and exclusion criteria**

Inclusion criteria
<ol style="list-style-type: none"> 1. Aged ≥ 16 years to ≤ 65 at screening 2. LTBI diagnosis defined on the basis of all of the following: <ol style="list-style-type: none"> (a) a positive result on an Interferon Gamma Release Assay (IGRA), Tuberculin Skin Test (TST) or C-Tb skin test and (b) negative TB symptoms at screening and (c) no signs of active TB on a Chest X-ray 3. Eligible for LTBI treatment at TB clinics and national LTBI screening services based on NICE guidelines, which means having one or more of the following : <ul style="list-style-type: none"> • Recent infection (contact tracing); • New entrants at risk (i.e., those that immigrated < 5 years from countries with a high incidence of TB, which is defined as ≥ 40 cases/100,000 population); or • Individuals who are assessed in the TB clinic for latent TB testing, or have been referred for treatment following testing by specialities or departments within primary or secondary care settings 4. Agree to LTBI treatment 5. Willing and able to provide written informed consent
Exclusion criteria
<ol style="list-style-type: none"> 1. Patients weighing < 30 kg. 2. Need for medications that cannot be safely taken together with study drugs (e.g. protease inhibitors in people living with HIV and people with refractory epilepsy taking phenytoin/carbamazepine) 3. Any medical condition deserving priority of treatment (such as: porphyria, malabsorption syndromes, Clostridium difficile-Associated Diarrhoea and other conditions) 4. History of sensitivity/intolerance to isoniazid or rifamycins 5. Individuals with documented liver disease, defined as: <ul style="list-style-type: none"> • LFT (ALT/AST/bilirubin) over three times upper limit of normal (ULN) at baseline. This reflects normal clinical practice. For participant safety, liver function tests are carried on a regular basis. One abnormal value prevents the patient from participating on the study. • Clinical diagnosis of cirrhosis (jaundice, hematemesis, ascites or previous episodes of liver encephalopathy), • HbsAg positive or HCV antibody positive and deemed ineligible for LTBI treatment by the clinician 6. Intending to move outside of the treatment locality within 20 weeks of starting treatment 7. Individuals who would usually be offered LTBI treatment under Directly Observed Therapy (DOT) as part of enhanced case management in complex cases such as those from under-served groups (such as people who are homeless, misuse substances, have been in prison or who are vulnerable migrants). 8. Use of another experimental investigational medicinal product that is likely to interfere with the study medication within 3 months of study enrolment. 9. Women who are breastfeeding, pregnant, or of childbearing potential who do not agree to use an effective method of contraception from the time consent is signed until 4 weeks after treatment discontinuation or completion. Males whose partners are of child-bearing potential must also agree to use an effective method of contraception. 10. Women of child bearing potential without a negative urine pregnancy test within 7 days prior to being registered for trial treatment.

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583 **Table 1. Doses of study treatment**

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	Body weight		
	< 50 KG	≥ 50 kg	
ARM 1 and 2: rifampicin plus isoniazid once daily for 90 doses (3 months)	3 x Isoniazid/Rifampicin fixed dose combination (150/100)	2 x Isoniazid/Rifampicin fixed dose combination (300/150)	
	30 to < 32 KG	32 to < 50 kg	≥ 50 kg
ARM 3 and 4: rifapentine plus isoniazid once weekly for 12 doses (3 months)	Rifapentine 600 mg + Isoniazid 15 mg/kg	Rifapentine 750 mg + Isoniazid 15 mg/kg	Rifapentine 900 mg + Isoniazid 15 mg/kg (900 mg maximum)
	30 to < 35 kg	35 to ≤ 45 kg	≥ 45kg
ARM 5 and 6: rifapentine plus isoniazid once daily for 28 doses (one month)	Rifapentine 300 mg + 300mg Isoniazid	Rifapentine 450 mg + 300 mg isoniazid	Rifapentine 600 mg + 300 mg isoniazid

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587 **Table 2.** Definition of the estimands for the primary analyses

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Attribute	Definition
Treatments	<p>The primary analyses are based on the following comparisons:</p> <p>a) Arm 3 vs Arm 1- ie <u>3HP</u> + routine treatment support vs <u>3HR</u> + routine treatment support</p> <p>b) Arm 5 vs Arm 1- ie <u>1HP</u> + routine treatment support vs <u>3HR</u> + routine treatment support</p> <p>c) Arm 2 vs Arm 1- ie <u>3HR</u> + <u>additional treatment support</u> vs <u>3HR</u> + <u>routine treatment support</u></p> <p>If comparison (a) shows 3HP improves adherence compared to 3HR, then additional treatment support will be formally tested for 3HP by comparing Arm 4 vs Arm 3 – ie <u>3HP</u> + <u>additional treatment support</u> vs <u>3HP</u> + <u>routine treatment support</u>. Additional treatment support will be similarly assessed for 1HP.</p>
Population	Adults aged 16 to 65 years diagnosed with LTBI and eligible for LTBI treatment.
Endpoint	Adequate treatment adherence, defined as taking $\geq 90\%$ of allocated doses within the allowable time-frame.
Intercurrent events	<p>The main intercurrent events and how they will be handled in the estimand are as follows:</p> <ul style="list-style-type: none"> • Failure to collect all prescriptions- composite and treatment policy strategies lead to same estimated effect. • Early treatment discontinuation for any reason including adverse event(s) and active TB: a treatment policy strategy will be used, ie the participant is considered to have stopped treatment regardless of the occurrence of the intercurrent event.
Population-level summary measure	Risk ratio for adequate treatment adherence comparing the relevant arms.

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592 **Table 3. Definitions of adverse events and reactions**

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in approved Reference Safety Information for that product in the trial.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse event, adverse reaction or unexpected adverse reaction that: <ul style="list-style-type: none"> ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

593 *The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the
594 time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example,
595 a silent myocardial infarction.

596
597 **Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a
598 precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or
599 for an elective procedure do not constitute an SAE.

600
601 *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following
602 should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in
603 death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other
604 outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring
605 intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug
606 dependency.

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608 **Figures**

609 **Figure 1. Trial schema**

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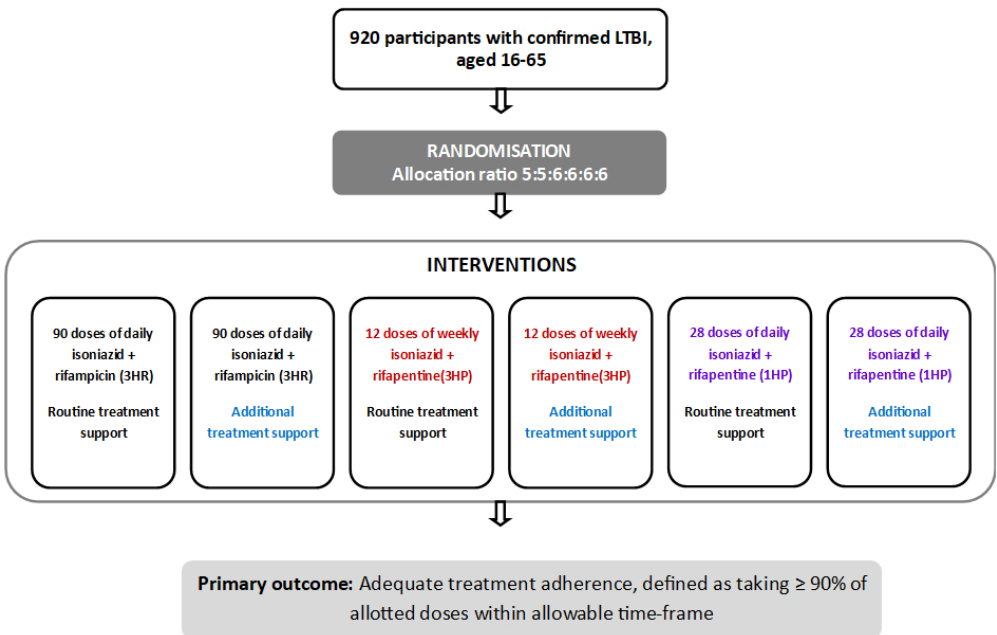


Figure 1. Trial schema

511x332mm (47 x 47 DPI)



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>3</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>In the original protocol</u>
Protocol version	3	Date and version identifier	<u>In the original protocol</u>
Funding	4	Sources and types of financial, material, and other support	<u>21</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>1, 21</u>
	5b	Name and contact information for the trial sponsor	<u>1</u>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	<u>21</u>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	<u>In the original protocol</u>

1	Introduction			
2				
3	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<u>6-8</u>
4				
5				
6		6b	Explanation for choice of comparators	<u>6-8</u>
7				
8	Objectives	7	Specific objectives or hypotheses	<u>8-9</u>
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<u>9-10</u>
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	<u>10</u>
17				
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	<u>10</u>
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>10-12</u>
23				
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	<u>In the original protocol</u>
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>11-12</u>
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>In the original protocol</u>
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	<u>13-14</u>
31				
32				
33	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<u>12-13, Figure 1</u>
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	<u>14</u>
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>10</u>
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	<u>15</u>
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	<u>15</u>
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>15</u>
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>NA</u>
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>NA</u>
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	<u>15-16</u>
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	<u>15-16</u>
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<u>15-16</u>
2				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<u>16-17</u>
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7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>16-17</u>
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<u>16-17</u>
11				
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14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	<u>18</u>
17				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	<u>18</u>
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<u>17</u>
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>18</u>
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>20</u>
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<u>20</u>
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>20</u>
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>In the original protocol</u>
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6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<u>In the original protocol</u>
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>21</u>
11				
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<u>20</u>
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<u>In the original protocol</u>
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>20</u>
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>In the original protocol</u>
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>20</u>
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Submitted to HRA and app</u>
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	<u>NA</u>
35				
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Evaluating the effect of short-course rifapentine-based regimens with or without enhanced behaviour-targeted treatment support on adherence and completion of treatment for latent tuberculosis infection among adults in the UK (RID-TB: Treat): protocol for an open-label, multicentre, randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057717.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Jan-2022
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Respiratory medicine

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Keywords:	Tuberculosis < INFECTIOUS DISEASES, Clinical trials < THERAPEUTICS, PREVENTIVE MEDICINE

SCHOLARONE™
Manuscripts

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3 **1 Evaluating the effect of short-course rifapentine-based regimens with or without enhanced**
4 **2 behaviour-targeted treatment support on adherence and completion of treatment for latent**
5 **3 tuberculosis infection among adults in the UK (RID-TB: Treat): protocol for an open-label,**
6 **4 multicentre, randomised controlled trial**
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12 Francis¹, Amy Louise Clarke⁴, Alex Ghanouni⁴, Charlotte Layton³, Vanessa Hack¹, Ellen Owen-
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32 **Keywords:** clinical trial; LTBI; medication adherence; rifapentine; tuberculosis

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1
2
3 **35 Abstract**
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6 **36 Introduction**
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9 37 The successful scale-up of a latent tuberculosis infection (LTBI) testing and treatment programme is
10
11 38 essential to achieve TB elimination. However, poor adherence compromises its therapeutic
12
13 39 effectiveness. Novel rifapentine-based regimens and treatment support based on behavioural science
14
15 40 theory may improve treatment adherence and completion.
16

17 **41 Methods and analysis**
18

19
20 42 A pragmatic multi-centre, open-label, randomised controlled trial assessing the effect of novel short-
21
22 43 course rifapentine-based regimens for TB prevention and additional theory-based treatment support on
23
24 44 treatment adherence against standard-of-care. Participants aged between 16 and 65 who are eligible to
25
26 45 start TB preventive therapy will be recruited in England. 920 participants will be randomized to one of
27
28 46 six arms with allocation ratio of 5:5:6:6:6:6: (1) daily isoniazid + rifampicin for three months (3HR),
29
30 47 routine treatment support (control); (2) 3HR, additional treatment support; (3) weekly isoniazid +
31
32 48 rifapentine for three months (3HP), routine treatment support; (4) weekly 3HP, additional treatment
33
34 49 support; (5) daily isoniazid + rifapentine for one month (1HP), routine treatment support; (6) daily 1HP,
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36 50 additional treatment support. Additional treatment support comprises reminders using an electronic
37
38 51 pillbox, a short animation, and leaflets based on the Perceptions and Practicalities Approach. The
39
40 52 primary outcome is adequate treatment adherence, defined as taking $\geq 90\%$ of allocated doses within
41
42 53 the pre-specified treatment period, measured by electronic pillboxes. Secondary outcomes include
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44 54 safety and TB incidence within 12 months. We will conduct process evaluation of the trial interventions
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46 55 and assess intervention acceptability and fidelity and mechanisms for effect and estimate the cost-
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48 56 effectiveness of novel regimens. The protocol was developed with Patient and Public Involvement,
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50 57 which will continue throughout the trial.
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53 **58 Ethics and dissemination**
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59 Ethics approval has been obtained from The NHS Health Research Authority (20/LO/1097). All
60 participants will be required to provide written informed consent. We will share the results in peer-
61 reviewed journals.

62 **Trial registration number** EudraCT 2020-004444-29

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3 70 **Article summary**
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5 71 **Strengths and limitations of this study**
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- 7 72 • The trial allows evaluation of both the effect of two rifapentine-based regimens compared to
8
9 73 the standard 3-month daily rifampicin plus isoniazid, and the effect of additional treatment
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11 74 support compared to routine support, on LTBI treatment adherence.
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- 13 75 • We will perform process evaluation of the trial interventions, including assessment of
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15 76 intervention acceptability and fidelity, and economic evaluation, which will provide
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17 77 additional evidence to inform treatment options and treatment support.
18
- 19 78 • The trial is powered to evaluate novel rifapentine-based regimens compared to the standard
20
21 79 daily rifampicin plus isoniazid (3HR) and the effect of additional treatment support compared
22
23 80 to routine support; however, it does not have sufficient power to evaluate all possible
24
25 81 comparisons such as 3-month weekly rifapentine plus isoniazid vs 1-month daily rifapentine
26
27 82 plus isoniazid.
28
- 29 83 • The trial will be conducted in England largely in migrant populations eligible for the LTBI
30
31 84 screening programme and contacts of TB patients and thus limiting generalisability to these
32
33 85 populations and similar settings.
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- 35 86 • Adherence will be measured using electronic pillboxes in all arms while reminders will be
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37 87 activated only in arms with additional treatment support; however, this may impact adherence
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39 88 in control groups.
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90 INTRODUCTION

91 Successful implementation of screening and treatment for latent tuberculosis infection (LTBI) is
92 critical to further reduce TB incidence globally and achieve TB elimination in low TB incidence
93 countries.(1) A recent call to action issued by the World Health Organization urged for accelerating
94 the scale-up of treatment of LTBI, particularly to mitigate the negative impact from the disruption of
95 TB services caused by the pandemic of COVID-19.(2)

96 Tuberculosis (TB) in England disproportionately affects underserved communities, such as migrants
97 and homeless people, who consequently experience higher disease burden and worse clinical
98 outcomes. Consequently, in England, LTBI screening and treatment for high risk groups such as new
99 migrants from high TB incidence countries is recognized as an essential strategy to achieve TB
100 elimination.(3) Contact tracing, including testing and treatment of LTBI among contacts, is another
101 essential component of the TB strategy for England.(3)

102 Achieving optimal treatment adherence and completion is essential to ensure the efficacy of treatment
103 for LTBI and to achieve commensurate reductions in TB incidence. Standard therapeutic options in
104 the UK include 3-months of self-administered daily isoniazid/rifampicin and 6-months of daily
105 isoniazid; the former regimen is often prescribed because of the availability of fixed-dose
106 formulations and its shorter duration. Whilst these regimen are efficacious in preventing disease, their
107 effectiveness is limited by low treatment adherence and completion rates.(4, 5) According to data
108 from England in migrants whose treatment outcome is known, 75% completed LTBI treatment
109 between 2019 and 2020.(6, 7) The proportion of people who completed treatment varied by Clinical
110 Commission Group (CCG), which was less than 70% in several CCGs.(8)

111
112 People with LTBI may need additional support to adhere to effective treatments. Treatment non-
113 adherence can be intentional or unintentional, and is driven by a person's motivation and ability to
114 take medicine as prescribed, respectively.(9) Motivation is influenced by our perceptions (e.g. beliefs
115 and preferences) and ability is determined by practical factors (e.g. internal capacity and resource).(9)

1
2
3 116 These principles are operationalised as part of the Perceptions and Practicalities approach to
4
5 117 supporting adherence (PAPA) and are applied in NICE guidelines.(10) The Necessity and Concerns
6
7 118 Framework (NCF) further explains how patients' motivation to engage with treatment is based on
8
9 119 their perceived necessity for, and concerns about the treatment.(11) Necessity beliefs are influenced
10
11 120 by perceptions of the health threat (e.g LTBI) and interpretation of symptoms. The asymptomatic
12
13 121 nature of LTBI may negatively impact necessity beliefs, and heighten treatment concerns. As such,
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15 122 intervention to support treatment adherence in people with LTBI will likely be more effective if they
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17 123 address patient beliefs and concerns around treatment, in addition to removing practical barriers.
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23 125 The need to understand perceptual and practical barriers to treatment adherence, and the potential of
24
25 126 advancing technology and drug regimens in the NHS has been highlighted. Some mobile/digital
26
27 127 technology (mHealth) has been shown to improve adherence in TB disease studies. A recent study in
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29 128 China found electronic reminders, using specially designed electronic medication monitors, improved
30
31 129 treatment adherence in such TB patients, but multiple two-way daily text messaging reminders,
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33 130 didactic in nature, did not.(12) Most of the evidence available is on TB disease with little research on
34
35 131 mHealth interventions to improve LTBI treatment adherence.(13, 14) Another call to action issued by
36
37 132 the World Health Organization suggested TB preventive treatment programmes should consider
38
39 133 communication technologies for medication adherence support.(15) The evidence on mHealth
40
41 134 interventions for LTBI treatment would contribute to their global scale-up.

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44 135 Another approach to promote better treatment adherence and completion is to decrease the complexity
45
46 136 of current LTBI regimens. A regimen that is given once weekly may result in better treatment
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48 137 completion than the current daily 3-month regimen. A randomised controlled trial demonstrated that a
49
50 138 new regimen of 12 doses of weekly rifapentine and isoniazid (3HP) delivered through direct
51
52 139 observation (i.e. with patients being supervised taking each dose) is non-inferior to 9 months of daily
53
54 140 isoniazid.(16) Our network meta-analysis suggests that 3HP has similar efficacy to the UK standard-
55
56 141 of-care of a 12-week, daily isoniazid/rifampicin regimen (3HR).(17) Furthermore, a recent trial in
57
58 142 people living with HIV (23% with LTBI as demonstrated by a positive TST and/or IGRA result)

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3 143 demonstrated non-inferiority of daily one-month rifapentine plus isoniazid (1HP) compared to 9
4
5 144 months of daily isoniazid.(18) The one-month regimen resulted in better adherence and fewer serious
6
7 145 adverse events. Based on this study, and by extrapolating to HIV-negative individuals, newly
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9 146 published WHO guidelines recommend this regimen regardless of HIV status. However, there is no
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11 147 published evaluation of whether these more expensive rifapentine-based regimens lead to better
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13 148 treatment completion than the current daily administered UK standard-of-care. In particular, evidence
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15 149 is limited on the use of 3HP with patient self-administration and no study has compared its
16
17 150 completion with 3HR.

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21 151 To develop tools to reduce TB rates, we need to evaluate advancing technology and drug regimens,
22
23 152 but also understand the barriers and enablers of adherence.(3) To date, adherence interventions have
24
25 153 predominantly focused on removing practical barriers to adherence (e.g reminder of shortening the
26
27 154 drug regimen). However, such approaches applied in isolation ignore patient beliefs. LTBI is
28
29 155 asymptomatic which means patients might have a disconnect between medical advice and their
30
31 156 perceived need for treatment.(19) NICE guidelines recommend a Perceptions and Practicalities
32
33 157 Approach (PAPA) to adherence support, whereby beliefs (necessity and concerns) are elicited and
34
35 158 addressed in addition to practical barriers.(10, 11)

36
37
38 159 We previously conducted the HALT-LTBI study, a pilot study assessing the safety and treatment
39
40 160 completion of 3HP compared to standard care.(20) HALT-LTBI demonstrated the feasibility of
41
42 161 recruiting LTBI patients to such a trial; no serious adverse events defined as grade 3 or more were
43
44 162 reported, supporting the safety of rifapentine and isoniazid regimens in individuals eligible for LTBI
45
46 163 treatment in the UK. 78% and 68% of participants completed treatment in the experimental and
47
48 164 standard-of-care arms, respectively, but the pilot was not powered to detect differences in treatment
49
50 165 completion. Thus, we will conduct a fully powered trial to compare treatment adherence and adverse
51
52 166 events of novel 3HP and 1HP regimens compared with 3HR and to assess the effect of additional
53
54 167 treatment support in participants given each regimen.

55 56 57 58 168 **Objectives**

1
2
3 169 The primary objective of this trial is to assess the effect of novel rifapentine-based regimens (3HP or
4
5 170 1HP) compared to the standard 90-dose daily rifampicin plus isoniazid (3HR), and the effect of
6
7 171 additional treatment support compared to routine support, on LTBI treatment adherence.
8
9

10 172 The secondary objectives are: 1) to evaluate the effect of LTBI treatment and additional treatment
11
12 173 support using alternate measures of adherence outcome; and 2) to compare the frequency of adverse
13
14 174 events whilst on treatment for LTBI, and development of TB within 12 months following treatment.
15
16 175 Additionally, we will evaluate the process of delivering the adherence intervention and examine
17
18 176 intervention fidelity and acceptability as well as the cost-effectiveness of different treatment options
19
20 177 and/or additional treatment support.
21
22

23 178

25 179 **METHOD AND ANALYSIS**

27 180 **Trial design**

28
29 181 A multi-centre open-label randomised controlled trial with the following six parallel groups (Figure
30
31 182 1):

32
33
34 183 **ARM 1-** Daily isoniazid + rifampicin for three months (3HR), routine treatment support (SOC;
35
36 184 control arm)

37
38
39 185 **ARM 2-** Daily 3HR, additional treatment support

40
41 186 **ARM 3-** Weekly isoniazid + rifapentine for three months (3HP), routine treatment support

42
43
44 187 **ARM 4-** Weekly 3HP, additional treatment support

45
46
47 188 **ARM 5-** Daily isoniazid + rifapentine for one month (1HP), routine treatment support

48
49 189 **ARM 6-** Daily 1HP, additional treatment support

50
51
52 190 A factorial design was not chosen for several reasons. Firstly, it is anticipated that there will be an
53
54 191 interaction between type of regimen and treatment support; additional treatment support is likely to
55
56 192 confer a smaller benefit with 3HP/1HP compared to 3HR. Secondly, the power to detect the effect of
57
58 193 an intervention would be reduced if the effect of the second intervention is greater than expected.
59
60

1
2
3 194 **Study setting**
4
5

6 195 The trial will recruit from secondary care sites that provide LTBI treatment in England, UK. RID-TB:
7
8 196 Treat is part of a 5-year programme of work (RID-TB) which is funded by the National Institute for
9
10 197 Health Research (NIHR) (RP-PG-0217-20009 <https://dev.fundingawards.nihr.ac.uk/award/RP-PG->
11
12 198 0217-20009). We expect to recruit participants from 15 care sites.
13

14 199
15

16
17 200 **Study population**
18
19

20 201 The trial will enrol populations who are eligible for treatment for LTBI according to the national
21
22 202 guidance. We envisage that the majority of individuals eligible for this are contacts of persons
23
24 203 diagnosed with TB disease, and/or migrants eligible for the national LTBI screening programme.(21)
25
26 204 The LTBI migrant screening programme includes migrants who are aged 16 to 35 years, entered the
27
28 205 UK from a high incidence country ($\geq 150/100,000$) or Sub-Saharan Africa within the last five years
29
30 206 and had been previously living in that high incidence country for six months or longer.(21) Inclusion
31
32 207 and exclusion criteria are shown in Box 1.

33
34
35 208 Participants will be identified from secondary care settings in the UK where persons eligible for
36
37 209 treatment for LTBI are managed. Participants will be recruited individually, but if any participants
38
39 210 share a household, they will be allocated to the same arm as the first person recruited from that
40
41 211 household (effectively resulting in randomisation by household).

42
43 212 Non-English speakers will not be excluded from the trial. We will translate patient-facing materials
44
45 213 and use interpreters to support non-English speaking participants.
46
47

48 214
49

50
51 215 **Treatment**
52

53 216 Participants who are randomized to arms 1 and 2 will receive the standard of care regimen: rifampicin
54
55 217 plus isoniazid once daily for 90 doses (3HR).
56
57
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1
2
3 218 Participants who are randomized to arms 3 and 4 will receive rifapentine plus isoniazid once weekly
4
5 219 for 12 doses (3HP) and those who are randomized to arms 5 and 6 will receive rifapentine plus
6
7 220 isoniazid once daily for 28 doses (1HP). Participants will be given a 1-month supply of the
8
9 221 medications at every visit in general but it also depends on local practice as this is a pragmatic trial.
10

11
12 222

13
14
15 223

16
17
18 224 In order to account for missed doses and interruption of treatment due to adverse events, participants
19
20 225 given 3HR or 3HP will have 16 weeks and those given 1HP will have 6 weeks to complete treatment.

21
22 226 In the study by Swindells et al, participants were given 8 weeks to complete 1HP.(18) We have
23
24 227 chosen 6 weeks to make the period proportionally similar to that for 3HR and 3HP. Clinicians will
25
26 228 assess the need for treatment extension based on the assessment of adherence and review of reasons
27
28 229 for non-adherence but should not extend beyond recommended grace periods.

29
30
31 230 In all arms, participants will receive vitamin B6 (pyridoxine). The dosages of study drugs are shown
32
33 231 in Table 1.

34
35
36 232 Rifapentine and rifampicin are known to induce the hepatic cytochrome CYP450 enzyme system.

37
38 233 Caution is recommended in using medications that are metabolized by this system. Concurrent use of
39
40 234 protease inhibitors, hepatitis-C antiviral drugs, or praziquantel is not permitted.

41 42 43 235 **Treatment support**

44 45 46 236 *Routine treatment support*

47
48 237 Participants allocated to arms 1, 3, and 5 will receive routine treatment support. Participants will be
49
50 238 given information about treatment for LTBI including expected adverse events and the importance of
51
52 239 adherence, according to local practice. Adherence will be reviewed at each follow-up visit or remote
53
54 240 consultation via self-reporting and/or pill count and discussed with the participant. An electronic pill
55
56 241 monitor box, Wisepill EvriMed1000 (Wisepill, Somerset West, South Africa)(22) will collect the date
57
58
59
60

242 and time of each opening to collect information on adherence. However, it will be set to silent mode
243 and not be used as an adherence reminder tool.

244 *Intervention*

245 Participants assigned to arms 2, 4, and 6 will receive a PAPA-based intervention designed to provide
246 additional treatment support (i.e. in addition to routine treatment support).(11) Specifically, the
247 intervention will consist of an animation which will 1) provide a rationale for treatment necessity and
248 help people understand how LTBI treatment can help them to achieve a health goal that is important
249 to them, 2) address common concerns about LTBI treatment and 3) address practical barriers to
250 treatment (e.g. anchoring treatment to daily activities). The animation will be supported by a leaflet
251 that covers misperceptions about LTBI testing and treatment, and other frequently asked questions.
252 Participants will also be asked to set reminders using an electronic pill monitor box (Wisepill
253 EvriMed). The electronic pillbox allows two modes of reminders: audio alarm from the box or text-
254 message to participants' mobile phones.

255
256 The reminder can be set at pre-specified times and can also be activated to send a reminder when the
257 pill box is not opened. Site staff will discuss options with each participant and set reminders according
258 to their preferences. Participants can opt not to receive reminders before or at the time of intended
259 medication intake. However, they will still be reminded when the box is not opened within a pre-
260 specified time in a day and they will receive a supportive text message automatically sent by the
261 pillbox. The mode of reminder can be further adjusted during the course of treatment as necessary
262 upon discussion with a clinician. The pillbox will electronically collect the date and time of each
263 opening.

264

265 **Study assessment and follow-up**

266 *Screening, randomisation and baseline assessment*

267 Randomisation and baseline assessment will occur on the same day (Week 0). In some cases, this may
268 also be the same day as Screening. Following informed consent procedures, participants will be

1
2
3 269 screened for eligibility. A TB symptom screen and urine pregnancy test will be carried out, and data on
4
5 270 the participant's TB risk group category will be collected. Demographic and medical history
6
7 271 information will be collected. We will check the results of clinical, laboratory, and radiological
8
9 272 assessments performed under routine care before entry to the trial to confirm eligibility. A TB symptom
10
11 273 screen and urine pregnancy test will be repeated at the randomization/baseline visits unless the
12
13
14 274 screening and randomisation visits occur on the same day.

15 275 *Assessment of Adherence*

16
17
18 276 Assessment of adherence will be primarily measured using the Wisepill, which collects the date and
19
20 277 time of each opening. Adherence will also be measured through self-reporting and pill count under
21
22 278 routine care either at physical clinic visits or remote consultations as per the local standard. Attending
23
24 279 clinicians will count the number of remaining tablets. The difference between the number of tablets
25
26 280 dispensed and the number returned will be calculated.

27 281 *Clinical assessment during follow-up*

28
29
30 282 As per usual practice, liver function tests (hepatic transaminases, ALT/AST, and total bilirubin) will
31
32 283 be performed at week 2 for all participants. Afterwards, liver function tests will be performed at
33
34 284 weeks 4, 8, 12, and 16 while on treatment and at completion, or at other times if deemed necessary by
35
36 285 attending clinicians (e.g. abnormality in preceding tests, new onset of symptoms suggesting potential
37
38 286 liver toxicity). These tests should be performed at any time during the treatment and post-treatment
39
40 287 phase if the participant exhibits symptoms or signs of drug-induced liver injury (DILI).

41
42
43 288

44
45 289 Adverse events expected with study drugs will be clinically assessed at every visit. These include
46
47 290 anorexia, nausea, vomiting, fatigue, weakness, jaundice, rash, peripheral neuropathy, and bruising..
48
49 291 Participants who already completed treatment and have no scheduled visits will be given a phone call
50
51 292 at week 8, 12, 16, and 20 to check adverse events and TB signs and symptoms since the last dose.

52
53
54 293

55
56 294 At every physical visit or remote consultation, symptoms and signs of TB disease will be reviewed as
57
58 295 well as concomitant medications using a brief questionnaire. There will be no formal study visits after
59
60 296 completion of treatment.

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3 297
4
56 298 **Protocol treatment discontinuation**
7

8
9 299 An individual participant may stop treatment early or trial participation be stopped early for any of the
10
11 300 following reasons: Unacceptable toxicity or adverse event including (e.g. serious adverse events
12
13 301 leading to discontinuation of treatment); intercurrent illness that prevents further treatment; active TB
14
15 302 disease; any change in the participant's condition that justifies the discontinuation of treatment in the
16
17 303 clinician's opinion; pregnancy; inadequate compliance with the protocol treatment that preclude
18
19 304 treatment within allowable time-frame in the judgement of the treating physician; and withdrawal of
20
21 305 consent for treatment by the participant.
22

23 306
2425
26 307 **Outcomes**
2728
29 308 *Primary Outcome*
30

31 309 The primary outcome is adequate treatment adherence, defined as taking $\geq 90\%$ of allocated doses
32
33 310 within the allowable time-frame from randomisation (binary outcome). For the primary analyses,
34
35 311 treatment adherence is measured using an electronic monitor box
36

37
38 312 *Secondary Outcomes*
39

40
41 313 The secondary outcome measures are:
42

- 43
44 314 • Effectiveness: (1) Proportion of allocated doses missed over the treatment period (measured
45
46 315 using monitor box); (2) Proportion of allocated pills missed over the treatment period
47
48
49 316 (measured using pill counts); (3) Taking at least 90% of doses and pills over the treatment
50
51
52 317 period (binary outcome assessed using both monitor box and pill counts); (4) Early study
53
54 318 treatment discontinuation for any reason
55
56
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- 1
2
3 319 • Safety: (1) Permanently stop study treatment due to drug-related adverse events (i.e. adverse
4
5
6 320 reactions) ; (2) Experience Grade ≥ 3 adverse events; (3) Develop TB disease within 12
7
8 321 months.

10
11
12 322 **Sample size**

13
14
15 323 The six-arm design allows evaluation of:

- 16
17 324 • the effect of the novel treatment regimens (3HP and 1HP) versus standard-of-care regimen
18
19 325 (3HR), under routine treatment support
20
21
22 326 • the effect of additional treatment support vs routine treatment support for each individual
23
24 327 regimen

25
26 328 A total of 920 participants are to be recruited. This provides 80% power for each of the following
27
28 329 comparisons:

- 29
30
31 330 • Arm 3 vs Arm 1- ie 3HP + routine treatment support vs 3HR + routine treatment support
32
33 331 • Arm 5 vs Arm 1- ie 1HP + routine treatment support vs 3HR + routine treatment support
34
35 332 • Arm 2 vs Arm 1- ie 3HR + additional treatment support vs 3HR + routine treatment support
36
37 333 • Arm 4 vs Arm 3- ie 3HP + additional treatment support vs 3HP + routine treatment support
38
39 334 • Arm 6 vs Arm 5- ie 1HP + additional treatment support vs 1HP + routine treatment support

40
41
42 335 The power calculations assume the following:

- 43
44 336 • 70% adherence rate in Arm 1
45
46 337 • 3HP and 1HP improve adherence rate by 15% (absolute difference) compared to 3HR,
47
48 338 respectively, with routine treatment support(18, 23, 24)
49
50 339 • Compared to routine treatment support, additional treatment support improves adherence rate
51
52 340 by 15% for 3HR, and 10% for 3HP and 1HP, respectively(12)
53
54 341 • 2-sided alpha 5% (see below for type I error considerations)
55
56 342 • average number of participants enrolled per household is 2, taking into account the average
57
58 343 household size in UK.(25)
59
60

- 1
2
3 344 • intra-class correlation (ICC) within a household is 0.1
4

5 345 The 70% adherence rate assumed for Arm 1 is based on the 77% LTBI treatment completion rate
6
7 346 reported from the Public Health England LTBI testing and treatment database for 2018.(26)
8
9

10 347

11
12 348 **Randomisation and allocation**
13

14 349 Participants will be randomised centrally using a computerised algorithm developed and maintained
15
16 350 by the Medical Research Council Clinical Trials Unit at University College London (MRC-CTU).
17

18 351 To randomise a participant, the information contained on a completed Randomisation Form will be
19
20 352 entered into the secure online trial database by trial team members at the site who have been trained
21
22 353 and authorised to randomise by the MRC-CTU. The database will automatically check for eligibility.
23
24 354 Only those who meet all eligibility criteria will be able to be randomised. Randomisation will be
25
26 355 performed using minimisation with an additional random element, to be balanced with respect to
27
28 356 centre and TB exposure risk group.
29
30

31
32 357 **Blinding**
33

34 358 This is an open-label trial. Blinding of participants and care providers to the allocation group is not
35
36 359 relevant since the primary objective of this trial is to examine the effect of shorter or weekly regimens
37
38 360 and additional treatment support on treatment adherence.
39
40

41
42 361 **Data collection methods and management**
43

44 362 Adherence data will be collected through the Wisepill monitor box. Demographic and clinical
45
46 363 information will be collected through clinical consultation and recorded on relevant worksheets.
47
48 364 Development of TB within 12 months after starting treatment and outcomes of pregnancy that are found
49
50 365 after enrolment will be collected using records held by NHS Digital, Public Health England, and/or the
51
52 366 National TB register.
53

54
55 367 The trial will be conducted in compliance with the UK Data Protection Act 2018 (DPA number:
56
57 368 Z6364106) and the EU Regulation General Data Protection Regulations 2016/679/ EC (GDPR) for
58
59 369 protection of personal data.
60

1
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3 370 **Statistical methods**
4
5

6 371 The estimands for the primary analyses are defined in Table 2. The primary analyses will compare the
7
8 372 proportion of participants with adequate adherence between arms using the following approach:
9

10 373 a) Arm 3 vs Arm 1- ie 3HP + routine treatment support vs 3HR + routine treatment support
11

12 374 b) Arm 5 vs Arm 1- ie 1HP + routine treatment support vs 3HR + routine treatment support
13

14 375 c) Arm 2 vs Arm 1- ie 3HR + additional treatment support vs 3HR + routine treatment support
15

16 376 If comparison (a) shows 3HP improves adherence compared to 3HR, then additional treatment
17

18 377 support will be formally tested for 3HP by comparing Arm 4 vs Arm 3 – ie 3HP + additional
19

20 378 treatment support vs 3HP + routine treatment support; otherwise, the adherence rates will be
21

22 379 compared between these arms as exploratory analyses. Additional treatment support will be similarly
23

24 380 assessed for 1HP.
25

26 381 All randomised patients will be included in the primary analyses, apart from those subsequently found
27

28 382 to have had TB disease at baseline but enrolled in error (modified intention-to-treat approach). The
29

30 383 risk ratio (with 95% confidence interval) for adequate treatment adherence comparing the relevant
31

32 384 arms will be estimated using log-binomial generalised linear mixed models (GLMMs), allowing for
33

34 385 intra-household correlation.
35
36
37

38 386 Type I error adjustment for multiple comparisons is not deemed necessary since:
39

40 387 • The research hypotheses corresponding to comparisons (a), (b) and (c) are considered
41
42 388 sufficiently distinct.(27-29)
43

44 389 • The effect of additional treatment support versus routine support is being evaluated in non-
45
46 390 overlapping populations for 3HR, 3HP and 1HP, respectively.
47

48 391 • The closed test approach whereby the effect of additional treatment support will only be
49
50 392 formally tested for 3HP if there is evidence that 3HP improves adherence compared to 3HR
51
52 393 with routine treatment support protects the type I error. This approach will also be used for the
53
54 394 assessment of additional treatment support for 1HP.
55
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3 396 For participants who have collected all prescriptions but are lost to follow-up before completing
4
5 397 treatment, the adherence data until the end of allocated period can still be downloaded remotely from
6
7 398 the Wisepill monitor box to ascertain whether adequate treatment adherence is achieved; this data will
8
9 399 be included in the primary analyses. In sensitivity analyses, the primary outcome will be imputed for
10
11 400 these patients using multiple imputation by chained equations (MICE), with imputation to be
12
13 401 conducted separately by study arm. Sensitivity analyses will also be performed assuming no drug
14
15 402 intake from the last follow-up visit attended.

16
17
18 403 Supplementary analyses will consider different definitions of adequate treatment by varying the
19
20 404 minimum proportion of doses required to have been taken, and different allowable time-frames for
21
22 405 making up missed doses. In addition, other analysis populations will be considered, including
23
24 406 intention-to-treat and per protocol (including only participants who commenced their original
25
26 407 allocated trial intervention). Planned exploratory subgroup analyses, will examine outcomes in pre-
27
28 408 defined subgroups.

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31 409
32 410 **Safety reporting**

33
34
35 411 The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of Good Clinical
36
37 412 Practice apply to this trial protocol. These definitions are given in Table 3. All Grade 3 or higher
38
39 413 adverse events, whether expected or not, will be recorded in the patient's medical notes. All adverse
40
41 414 events will be recorded up to week 20. Serious adverse events should be notified to the CTU within
42
43 415 24 hours of the investigator becoming aware of the event from the time of randomisation to the last
44
45 416 assessment of adverse events, i.e. week 20. Adverse events will be graded using the DAIDS toxicity
46
47 417 grading scale.(30)

48
49 418 Participants may be able to claim compensation for injury caused by their participation in the clinical
50
51 419 trial in accordance with the insurance policy held at UCL.

52
53 420

54
55 421 **Monitoring and oversight**

1
2
3 422 The trial will be monitored by the MRC-CTU. An Independent Data Monitoring Committee (IDMC)
4
5 423 will be formed. The IDMC will review study conduct and safety data regularly. The IDMC will be
6
7 424 asked to advise on whether the accumulated data from the trial, together with results from other
8
9 425 relevant trials, justify continuing recruitment of further participants. The IDMC will make
10
11 426 recommendations to the Programme Steering Committee (PSC) as to whether the trial should continue
12
13 427 in its present form.

14
15
16 428 The PSC has membership from the Trial Management Group (TMG) plus independent members
17
18 429 (approved by NIHR), including the Chair and Patient and Public Involvement (PPI) contributors. The
19
20 430 role of the PSC is to provide overall supervision for the trial and provide advice through its
21
22 431 independent Chair. The ultimate decision for the continuation of the trial lies with the PSC.

23 432 **Process evaluation**

24
25
26 433 The process evaluation will follow MRC guidance using an embedded, mixed-methods evaluation
27
28 434 approach in order to assess acceptability, fidelity, and mechanisms of effects of the interventions. It will
29
30 435 be conducted by the research team, working closely with the Intervention Development Group and
31
32 436 clinicians delivering the trial.

33 437 *Patient sample*

34
35
36 438 Patients in the full trial sample will be administered validated questionnaires assessing the
37
38 439 psychological characteristics that we predict will mediate the effects of the interventions.
39
40 440 Questionnaires will be administered during scheduled clinic appointments at baseline (0 weeks),
41
42 441 interim (2 weeks) and treatment completion (either 4 or 12 weeks depending of regimen). Baseline
43
44 442 measure will include Beliefs about Medicines Questionnaire (BMQ-Specific/BMQ-General),
45
46 443 Perceived Sensitivity to Medicines Scale (PSM-5), Brief illness perceptions questionnaire (BIPQ),
47
48 444 The Satisfaction with Information about Medicines Scale (SIMS), Hospital Anxiety and Depression
49
50 445 Scale (HADS). At follow-up, participants will complete the BIPQ and BMQ-Specific, and a measure
51
52 446 of self-reported adherence (Medication Adherence Report -5 [MARS-5]) and the Treatment
53
54 447 intrusiveness Questionnaire (TIQ). A subset of participants will also be approached for a qualitative
55
56 448 assessment of their experiences in the trial. Participants in each intervention arm will be purposively
57
58
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1
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3 449 sampled based on their treatment adherence (10 participants per arm: 5 high adherence, 5 low
4
5 450 adherence; total 60 interviews; adherence in line with the primary outcome). Measures will consist of
6
7 451 brief, semi-structured interviews.
8
9

10 452

11 453 *Staff sample*

12
13
14 454 Healthcare professionals responsible for administering the interventions will be requested to complete
15
16 455 a short checklist form following patient randomisation in order to assess intervention fidelity. This will
17
18 456 confirm whether each component of the interventions was delivered per protocol. We will also
19
20 457 purposively sample 20 service providers to take part in brief, semi-structured interviews (in person or
21
22 458 by phone) in order to obtain feedback on the delivery of the intervention and to identify any issues that
23
24 459 might enhance delivery in practice. In addition, we will use these interviews to investigate wider
25
26 460 contextual issues impacting on delivery. We will also encourage implementing clinicians to report
27
28 461 major issues that might compromise intervention delivery during the trial, rather than waiting for a
29
30 462 formal interview on trial completion.
31
32

33 463

34 464 **Health economic evaluation**

35
36
37 465 This will estimate if changes to LTBI diagnosis and/or treatment are cost-effective from the
38
39 466 perspective of the National Health Service, using a health-economic model to synthesise data obtained
40
41 467 within the entire RID-TB programme and evidence from other sources. Participants will be asked to
42
43 468 complete monthly EQ-5D questionnaires. We will collect information on the costs participants incur
44
45 469 in attending appointments within this trial, to allow potential future analysis from a societal
46
47 470 perspective.
48
49

50 471

51 472 **PATIENT AND PUBLIC INVOLVEMENT (PPI)**

52
53
54 473 The trial was discussed with the charity TB Alert and two community representatives drawn from a
55
56 474 migrant charity and a patient previously treated for LTBI. A charity representative and one former
57
58 475 patient read versions of the grant proposal and contributed suggestions on study design. At the
59
60

1
2
3 476 protocol development stage, the following input was sought from TB Alert: study design, treatment
4
5 477 support interventions, Participant Information Sheet and Consent form, patient-facing questionnaires
6
7 478 used for behavioural studies.
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9 479

10
11 480 During the trial, we will engage with 1) The RID-TB PPI Advisory Group (PPAG) consisting of
12
13 481 members recruited via social media accounts, TB nurses, TB patient advocates, ex-patient contacts
14
15 482 and voluntary/community organisations and (2) The TB Action Group (TAG) network of people
16
17 483 personally affected by TB. We will seek input for: recruitment, patient/public engagement tools,
18
19 484 provision of translated materials on LTBI and access to recruitment sites.
20
21

22 485

23 24 486 **ETHICS AND DISSEMINATION**

25 26 27 487 **Ethics approval**

28
29
30 488 Ethics approval has been obtained from the Health Research Authority (HRA) in the UK
31
32 489 (20/LO/1097). Any further substantial amendments will be submitted and approved by the main
33
34 490 Research Ethics Committee and HRA.

35 36 491 **Consent**

37
38
39 492 Participants will be screened and consented at approved trial sites that are authorised by the MRC-
40
41 493 CTU to carry out the RID-TB: Treat trial. We will provide potential participants with a copy of the
42
43 494 Participant Information Sheet (supplementary materials 1 and 2). We will obtain written informed
44
45 495 consent to enter into the trial and be randomised after explanation of the aims, methods, benefits and
46
47 496 potential hazards of the trial before any trial-specific procedures are performed. Additional consent to
48
49 497 participate in ancillary studies will be sought.
50

51 498

52 53 499 **Dissemination**

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55
56 500 We will report findings of the trial through publications in national and international conferences as
57
58 501 well as in peer-reviewed journals. We will follow publication policies used for clinical trials
59
60 502 coordinated by the MRC CTU. All headline authors in any publication arising from the main study or

1
2
3 503 substudies must have made a substantive academic or project management contribution to the work
4
5 504 that is being presented. Findings will be also disseminated via TB Alert, Treatment Action Group,
6
7 505 social media, and institutional websites.
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9

10 506 **Data availability statement**

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12
13 507 Trial data will be available for sharing by request after the primary publication upon approval by the
14
15 508 Trial Management Group.
16

17
18 509

19 20 510 **Trial status**

21
22
23 511 The trial has not yet started recruitment. We expect to start recruitment on 1 September 2022 and the
24
25 512 trial will close when all participants have completed follow-up (i.e. 12 months after initiation of
26
27 513 treatment), record linkage to ascertain TB has been finished, and after the trial database is locked,
28
29 514 which is anticipated to be within 3 months after information on primary and secondary outcomes have
30
31 515 been collected.
32
33

34 516 **Protocol version and date**

35
36 517 This protocol is an abbreviated version of the protocol version 3.0, October 2020.
37
38

39 518

40 41 42 519 **Acknowledgements**

43
44
45 520 We thank the NIHR programme officers, UCL-NIHR Patient and Public Involvement Advisory
46
47 521 Group, MRC CTU at UCL Protocol Review Committee, and the independent Programme Steering
48
49 522 Committee for their support and inputs during the development of the protocol.
50

51 523 **Authors contributions**

52
53
54 524 IA and MXR conceived the study. IA and MXR led the application to secure funding. IA, MXR, TD,
55
56 525 YH, HB, JC, MF, ALC, AG, VH, EOP, JS, KS, HLB, AC, CG, RH, MJ, HK, ML, MM, PJW, DZ
57
58 526 contributed to developing the study design. CL, TD and AMC provided statistical oversight. MXR,
59
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- 25 538
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28
29 539 1. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action
30
31 540 framework for low-incidence countries. *European Respiratory Journal*. 2015;45:928-52.
32
33 541 2. World Health Organization. Call to Action 2.0: A global drive to scale up TB.
34
35 542 [https://cdn.who.int/media/docs/default-source/hq-tuberculosis/call-to-action-2.0-a-global-drive-to-](https://cdn.who.int/media/docs/default-source/hq-tuberculosis/call-to-action-2.0-a-global-drive-to-scale-up-tb-prevention.pdf?sfvrsn=6f938b38_7&download=trueT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa)
36
37 543 [scale-up-tb-](https://cdn.who.int/media/docs/default-source/hq-tuberculosis/call-to-action-2.0-a-global-drive-to-scale-up-tb-prevention.pdf?sfvrsn=6f938b38_7&download=trueT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa)
38
39 544 [prevention.pdf?sfvrsn=6f938b38_7&download=trueT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&](https://cdn.who.int/media/docs/default-source/hq-tuberculosis/call-to-action-2.0-a-global-drive-to-scale-up-tb-prevention.pdf?sfvrsn=6f938b38_7&download=trueT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa)
40
41 545 [id=135bdee6af&e=09bced52fa](https://cdn.who.int/media/docs/default-source/hq-tuberculosis/call-to-action-2.0-a-global-drive-to-scale-up-tb-prevention.pdf?sfvrsn=6f938b38_7&download=trueT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa) Accessed 8 July 2021.
42
43 546 3. Public Health England. Collaborative tuberculosis strategy for England: 2015 to 2020. 2015.
44
45 547 4. Hirsch-Moverman Y, Shrestha-Kuwahara R, Bethel J, et al. Latent tuberculous infection in
46
47 548 the United States and Canada: who completes treatment and why? *The international journal of*
48
49 549 *tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and*
50
51 550 *Lung Disease*. 2015;19:31-8.
52
53 551 5. Saunders MJ, Koh GC, Small AD, et al. Predictors of contact tracing completion and
54
55 552 outcomes in tuberculosis: a 21-year retrospective cohort study. *The international journal of*
56
57
58
59
60

- 1
2
3 553 tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and
4
5 554 Lung Disease. 2014;18:640-6.
6
7 555 6. Public Health England: LTBI testing and treatment programme for migrants: 2020 report.
8
9 556 7. Public Health England: Tuberculosis in England. 2020 report.
10
11 557 8. Public Health England: LTBI testing and treatment programme for migrants 2020: data tables.
12
13 558 9. Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers,
14
15 559 unintentional nonadherers, and intentional nonadherers: Application of the Necessity–Concerns
16
17 560 Framework. Journal of psychosomatic research. 2008;64:41-6.
18
19 561 10. NICE. Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and
20
21 562 Supporting Adherence: Full Guideline. Clinical Guideline CG76. 2009.
22
23 563 11. Horne R, Cooper V, Wileman V, et al. Supporting adherence to medicines for long-term
24
25 564 conditions: A perceptions and practicalities approach based on an extended common-sense model.
26
27 565 European Psychologist. 2019;24:82-96.
28
29 566 12. Liu X, Lewis JJ, Zhang H, et al. Effectiveness of Electronic Reminders to Improve
30
31 567 Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med.
32
33 568 2015;12:e1001876.
34
35 569 13. Holzschuh EL, Province S, Johnson K, et al. Use of Video Directly Observed Therapy for
36
37 570 Treatment of Latent Tuberculosis Infection - Johnson County, Kansas, 2015. MMWR Morbidity and
38
39 571 mortality weekly report. 2017;66:387-9.
40
41 572 14. Lam CK, McGinnis Pilote K, Haque A, et al. Using Video Technology to Increase Treatment
42
43 573 Completion for Patients With Latent Tuberculosis Infection on 3-Month Isoniazid and Rifapentine:
44
45 574 An Implementation Study. Journal of medical Internet research. 2018;20:e287.
46
47 575 15. World Health Organization. Overcoming key barriers to scale up tuberculosis preventive
48
49 576 treatment (TPT) A Call to Action.
50
51 577 [https://www.who.int/tb/CalltoactionTPT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6](https://www.who.int/tb/CalltoactionTPT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa)
52
53 578 [af&e=09bced52fa](https://www.who.int/tb/CalltoactionTPT_scaleup.pdf?u=f093a7c38a3780cd9504f8d9d&id=135bdee6af&e=09bced52fa) Accessed 18 May 2021.
54
55 579 16. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for
56
57 580 latent tuberculosis infection. The New England journal of medicine. 2011;365:2155-66.

- 1
2
3 581 17. Zenner D, Beer N, Harris RJ, et al. Treatment of Latent Tuberculosis Infection: An Updated
4
5 582 Network Meta-analysis. *Ann Intern Med.* 2017;167:248-55.
6
7 583 18. Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to
8
9 584 Prevent HIV-Related Tuberculosis. *The New England journal of medicine.* 2019;380:1001-11.
10
11 585 19. Horne R, Chapman SC, Parham R, et al. Understanding patients' adherence-related beliefs
12
13 586 about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-
14
15 587 Concerns Framework. *PloS one.* 2013;8:e80633.
16
17 588 20. Surey J, Stagg HR, Yates TA, et al. An open label, randomised controlled trial of rifapentine
18
19 589 versus rifampicin based short course regimens for the treatment of latent tuberculosis in England: the
20
21 590 HALT LTBI pilot study. *BMC Infectious Diseases.* 2021;21:90.
22
23 591 21. Public Health England: Latent TB Testing and Treatment for Migrants. A practical guide for
24
25 592 commissioners and practitioners. 2015.
26
27 593 22. evriMED1000 Dispenser <https://www.wisepill.com/wisepill-rm1000> Accessed 9 July 2021 [
28
29 594 23. Martinson NA, Barnes GL, Moulton LH, et al. New Regimens to Prevent Tuberculosis in
30
31 595 Adults with HIV Infection. *New England Journal of Medicine.* 2011;365:11-20.
32
33 596 24. Sterling TR, Villarino ME, Borisov AS, et al. Three Months of Rifapentine and Isoniazid for
34
35 597 Latent Tuberculosis Infection. *New England Journal of Medicine.* 2011;365:2155-66.
36
37 598 25. Office for National Statistics. Families and households in the UK: 2020.
38
39 599 [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/
40
41 600 \[familiesandhouseholds/2020\]\(https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/familiesandhouseholds/2020\) accessed 15 Sep 2021.
42
43 601 26. Public Health England: Tuberculosis in England. 2019 report.
44
45 602 27. Howard DR, Brown JM, Todd S, et al. Recommendations on multiple testing adjustment in
46
47 603 multi-arm trials with a shared control group. *Stat Methods Med Res.* 2018;27:1513-30.
48
49 604 28. Choodari-Oskooei B, Bratton DJ, Gannon MR, et al. Adding new experimental arms to
50
51 605 randomised clinical trials: Impact on error rates. *Clin Trials.* 2020;17:273-84.
52
53 606 29. Wason JMS, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it
54
55 607 necessary and is it done? *Trials.* 2014;15:364.
56
57
58
59
60](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/familiesandhouseholds/2020)

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2
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41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

608 30. U.S. Department of Health and Human Services, National Institutes of Health, National
609 Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for
610 Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017].
611 Available from: <https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf> Accessed 11
612 September 2020.

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For peer review only

615 **Box 1. Study inclusion and exclusion criteria**

Inclusion criteria
<ol style="list-style-type: none"> 1. Aged ≥ 16 years to ≤ 65 at screening 2. LTBI diagnosis defined on the basis of all of the following: <ol style="list-style-type: none"> (a) a positive result on an Interferon Gamma Release Assay (IGRA), Tuberculin Skin Test (TST) or C-Tb skin test and (b) negative TB symptoms at screening and (c) no signs of active TB on a Chest X-ray 3. Eligible for LTBI treatment at TB clinics and national LTBI screening services based on NICE guidelines, which means having one or more of the following : <ul style="list-style-type: none"> • Recent infection (contact tracing); • New entrants at risk (i.e., those that immigrated < 5 years from countries with a high incidence of TB, which is defined as ≥ 40 cases/100,000 population); or • Individuals who are assessed in the TB clinic for latent TB testing, or have been referred for treatment following testing by specialities or departments within primary or secondary care settings 4. Agree to LTBI treatment 5. Willing and able to provide written informed consent
Exclusion criteria
<ol style="list-style-type: none"> 1. Patients weighing < 30 kg. 2. Need for medications that cannot be safely taken together with study drugs (e.g. protease inhibitors in people living with HIV and people with refractory epilepsy taking phenytoin/carbamazepine) 3. Any medical condition deserving priority of treatment (such as: porphyria, malabsorption syndromes, Clostridium difficile-Associated Diarrhoea and other conditions) 4. History of sensitivity/intolerance to isoniazid or rifamycins 5. Individuals with documented liver disease, defined as: <ul style="list-style-type: none"> • LFT (ALT/AST/bilirubin) over three times upper limit of normal (ULN) at baseline. This reflects normal clinical practice. For participant safety, liver function tests are carried on a regular basis. One abnormal value prevents the patient from participating on the study. • Clinical diagnosis of cirrhosis (jaundice, hematemesis, ascites or previous episodes of liver encephalopathy), • HbsAg positive or HCV antibody positive and deemed ineligible for LTBI treatment by the clinician 6. Intending to move outside of the treatment locality within 20 weeks of starting treatment 7. Individuals who would usually be offered LTBI treatment under Directly Observed Therapy (DOT) as part of enhanced case management in complex cases such as those from under-served groups (such as people who are homeless, misuse substances, have been in prison or who are vulnerable migrants). 8. Use of another experimental investigational medicinal product that is likely to interfere with the study medication within 3 months of study enrolment. 9. Women who are breastfeeding, pregnant, or of childbearing potential who do not agree to use an effective method of contraception from the time consent is signed until 4 weeks after treatment discontinuation or completion. Males whose partners are of childbearing potential must also agree to use an effective method of contraception. 10. Women of childbearing potential without a negative urine pregnancy test within 7 days prior to being registered for trial treatment.

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618 **Table 1. Doses of study treatment**

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	Body weight		
	< 50 KG	≥ 50 kg	
ARM 1 and 2: rifampicin plus isoniazid once daily for 90 doses (3 months)	3 x Isoniazid/Rifampicin fixed dose combination (150/100)	2 x Isoniazid/Rifampicin fixed dose combination (300/150)	
	30 to < 32 KG	32 to < 50 kg	≥ 50 kg
ARM 3 and 4: rifapentine plus isoniazid once weekly for 12 doses (3 months)	Rifapentine 600 mg + Isoniazid 15 mg/kg	Rifapentine 750 mg + Isoniazid 15 mg/kg	Rifapentine 900 mg + Isoniazid 15 mg/kg (900 mg maximum)
	30 to < 35 kg	35 to ≤ 45 kg	≥ 45kg
ARM 5 and 6: rifapentine plus isoniazid once daily for 28 doses (one month)	Rifapentine 300 mg + 300mg Isoniazid	Rifapentine 450 mg + 300 mg isoniazid	Rifapentine 600 mg + 300 mg isoniazid

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622 **Table 2.** Definition of the estimands for the primary analyses

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Attribute	Definition
Treatments	<p>The primary analyses are based on the following comparisons:</p> <p>a) Arm 3 vs Arm 1- ie <u>3HP</u> + routine treatment support vs <u>3HR</u> + routine treatment support</p> <p>b) Arm 5 vs Arm 1- ie <u>1HP</u> + routine treatment support vs <u>3HR</u> + routine treatment support</p> <p>c) Arm 2 vs Arm 1- ie <u>3HR</u> + <u>additional treatment support</u> vs <u>3HR</u> + <u>routine treatment support</u></p> <p>If comparison (a) shows 3HP improves adherence compared to 3HR, then additional treatment support will be formally tested for 3HP by comparing Arm 4 vs Arm 3 – ie <u>3HP</u> + <u>additional treatment support</u> vs <u>3HP</u> + <u>routine treatment support</u>. Additional treatment support will be similarly assessed for 1HP.</p>
Population	Adults aged 16 to 65 years diagnosed with LTBI and eligible for LTBI treatment.
Endpoint	Adequate treatment adherence, defined as taking $\geq 90\%$ of allocated doses within the allowable time-frame.
Intercurrent events	<p>The main intercurrent events and how they will be handled in the estimand are as follows:</p> <ul style="list-style-type: none"> • Failure to collect all prescriptions- composite and treatment policy strategies lead to same estimated effect. • Early treatment discontinuation for any reason including adverse event(s) and active TB: a treatment policy strategy will be used, ie the participant is considered to have stopped treatment regardless of the occurrence of the intercurrent event.
Population-level summary measure	Risk ratio for adequate treatment adherence comparing the relevant arms.

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627 **Table 3. Definitions of adverse events and reactions**

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in approved Reference Safety Information for that product in the trial.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse event, adverse reaction or unexpected adverse reaction that: <ul style="list-style-type: none"> ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

628 *The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the
629 time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example,
630 a silent myocardial infarction.

631 **Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a
632 precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or
633 for an elective procedure do not constitute an SAE.

634 *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following
635 should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in
636 death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other
637 outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring
638 intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug
639 dependency.

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3 643 **Figures**

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5 644 **Figure 1. Trial schema**

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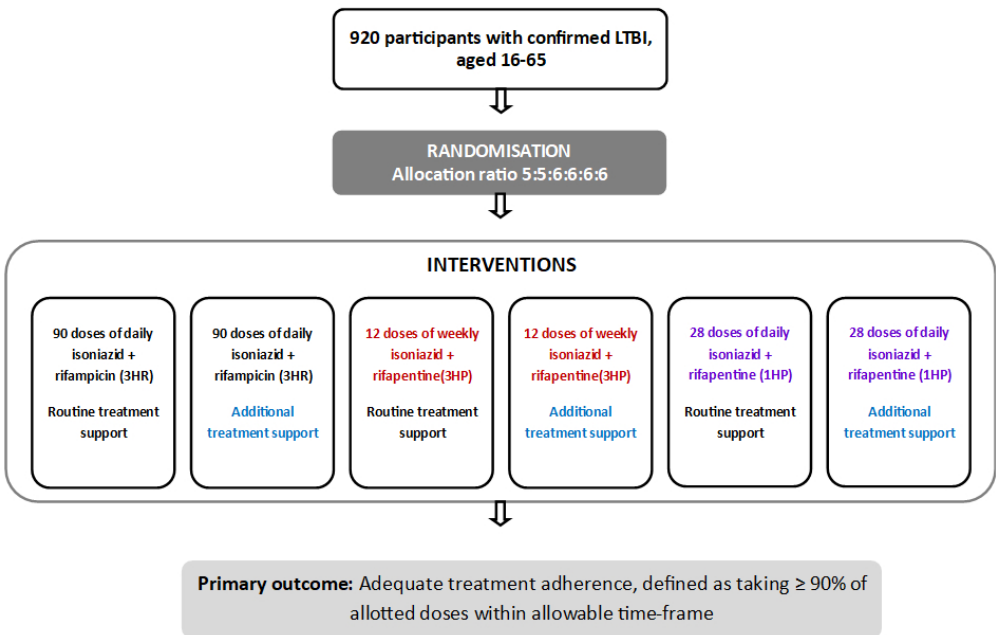


Figure 1.Trial schema

511x332mm (47 x 47 DPI)

Summary Participant Information Sheet for the RID-TB:Treat Clinical Trial

We are inviting you to take part in a research study called RID-TB:Treat.

This study aims to help people complete a course of medicines for treatment of latent tuberculosis infection or LTBI. If you have LTBI, it means you have been infected with the bacteria that cause tuberculosis (TB), but you are not ill and you do not have any symptoms. Treatment for LTBI can prevent TB.

This study is part of RID-TB, a 5-year work programme that includes several linked studies on LTBI. At this stage you are only being asked to take part in RID-TB:Treat.

This page gives you an overview of the study. Please take time to read the whole leaflet carefully so you can decide if you would like to take part. You can share this information sheet and discuss the research study with friends and relatives if you wish.

The study in brief:

This study aims to find out:

- Whether taking different LTBI medicines for a shorter amount of time (one month) than normal (three months), or once a week rather than once a day, makes it easier for people to take all of their medication.
- Whether using a pill box and reminders to take medicines as well as support materials helps people to remember to take their medicine and not miss any doses (we call this adherence support).

In addition, we would also like to find out through the following optional substudies:

- Behavioural substudy: Your thoughts, feelings, and experiences around treatment of LTBI and adherence support
- Health economics substudy: How much treatment of LTBI costs and how the treatment affects your life. This will allow us to see if new LTBI treatment and/or additional adherence support offers value for money for the NHS.

The behavioural and economics substudies are optional, include only people who agree, and will involve completing simple tick-box questions and interviews for selected individuals.

Key points you need to know:

This study investigates the use of three medicines used in two different combinations. Each combination is given with or without 'adherence support', which includes educational messages and reminders to take medicines.

There are six different groups within the study. You could be allocated to any of these groups:

GROUP 1 - Daily isoniazid + rifampicin for three months (3HR), routine adherence support (standard-of-care)

GROUP 2 - Daily isoniazid + rifampicin for three months (3HR), additional adherence support

GROUP 3 - Weekly isoniazid + rifapentine for three months (3HP), routine adherence support

GROUP 4 - Weekly isoniazid + rifapentine for three months (3HP), additional adherence support

GROUP 5 - Daily isoniazid + rifapentine for one month (1HP), routine adherence support

GROUP 6 - Daily isoniazid + rifapentine for one month (1HP), additional adherence support.

We are studying two new types of LTBI treatment: one month of daily medicines (1HP)

and three months of medicines which need to be taken once a week (3HP) . These two new types of LTBI treatment will be compared to three months of daily treatment (3HR) usually used in the UK (standard-of-care). We think the medicines should be equally effective and safe. We want to find out whether either of these ways of taking the medicines help you complete a course without missing any doses.

All LTBI medicines, including those used in this trial, can have unwanted side effects. They are usually minor and reversible, if they occur at all. The most common are allergic reactions, flu-like symptoms, headache, skin reactions, diarrhoea, liver problems, nausea, vomiting and a decrease in white blood cell and red blood cell count.

We are also testing whether reminders to take pills and adherence support materials will help you to follow your treatment schedule. You will get a special pill box which will record each time it is opened.

This study will *not* require you to visit the hospital more times than if you were being treated in the usual way for latent TB.

What happens if I am interested in taking part?

If you agree to take part in the study after reading all the information, we will check your medical records. This is to see whether you meet the study entry criteria and check it is safe for you to do take part. We will ask you to sign a consent form and will give you copies of both this information sheet and the consent form. We will also write to your GP to let them know that you have agreed to take part in this research, this is optional and you can opt for your GP not to be informed.

If you do not wish to take part in the study, or if you do not meet the study entry criteria, you are likely to receive the standard-of-care treatment, which is daily antibiotics for three months and usual support to help you remember to take your medicines.

You are free to decide whether to take part in this research study or not. If you choose not to take part, this will not affect the care you receive.

If you do agree, you can stop taking part in the study at any time, without giving a reason. Please ask your doctor or nurse if there is anything that unclear or if you would like more information.

If you have any questions about this study, please talk to your doctor or nurse:

Name of doctor or nurse:

Hospital Department:

Hospital:

Address:

Tel: 01234 XXX XXX

Email: (if applicable)

1. Why are we doing this study?

This study aims to help people complete prescribed medicines for treatment of latent TB infection (LTBI) and ensure its treatment for LTBI for latent TB works best when taken as prescribed. This study aims to find the best way to support people to take LTBI treatment

What are we trying to find out?

This study aims to find out whether taking different LTBI medicines for a shorter amount of time than normal, or once a week rather than daily, makes it easier for people to take all of their medication and not miss any doses.

We also want to know whether a support package that we have developed which includes a video animation, a pill box and text

message reminders can help people to take their medicines.

2. What is latent TB?

If you have latent TB infection (LTBI) it means you have been infected with the bacteria that causes tuberculosis (TB), but you are not ill and you do not have any symptoms. If you then become ill with “active” TB disease you could pass TB on to other people. TB bacteria are spread through the air, mainly by coughing. If you want to know more about latent TB talk to the doctor or nurse who is treating you.

How is latent TB usually treated?

Active TB can be cured with a combination of different antibiotics, which need to be taken for many months (at least 6 months). LTBI can be diagnosed and treated to help prevent TB disease from developing. The treatment for latent TB in England is usually 3 months long and fewer drugs are given compared with active disease.

3. Why am I being asked to take part?

You are being asked to take part in the RID-TB:Treat study because you have latent TB and treatment is recommended

Your doctor will perform an assessment and tests that are routinely required before treatment of LTBI for your safety. We will check if you can take part in the study using these results.

To take part in RID-TB:Treat :

- You will be diagnosed with LTBI
- You will be between 16 and 65 years of age
- You will not have signs of active TB (this includes
- You will not have a known allergy to the medicines in the study
- You will not have any liver problems that might mean you can't take the medicines safely (a blood test will be done to check this)
- You will not be pregnant or breastfeeding, or plan on becoming pregnant during the study
- Females who are able to become pregnant (of child-bearing potential) will agree to using contraception whilst on the medications (specifically, an implant or male partners using condoms. Oral contraceptives may be less effective whilst on treatment)

- Male whose female partners are able to become pregnant will agree to using contraception whilst on the medications.

4. What do I need to know about the medicines in this study?

The new LTBI medicine we want to find out more about in this study is called rifapentine, which is given in combination with another medicine called isoniazid. You will only receive rifapentine if you are in Group 3, 4, 5 or 6. There are different ways of taking this tablet: once a day for a month (1HP), or once a week for three months (3HP). It is the same dose each intake. You swallow these tablets within one hour after eating food.

An often-used treatment for LTBI is a medicine combining both rifampicin and isoniazid in a single tablet. You will receive this medicine if you are in Group 1 or 2. This medication is taken once a day, for three months (3HR). You swallow this tablet on an empty stomach (at least 30 minutes before food or 2 hours after food.)

We will also investigate whether additional adherence support helps people to take their medicine. This includes a reminder via SMS message or sound alarm using the pill box and adherence support materials such as video

animation. This support will be given in addition to usual support by clinicians.

What are the possible side-effects?

All medicines can have unwanted side-effects, including those normally used for LTBI treatment outside of this study. The most common side-effects of rifapentine, rifampicin and isoniazid are: allergic reactions and flu-like symptoms, headache, skin reactions, diarrhoea, liver problems, nausea, vomiting, and decrease in white blood cell and red blood cell count.

A common side effect rifapentine and rifampicin may cause a temporary red-orange staining of body tissues or fluids. This would include skin, teeth, tongue, urine, faeces, saliva, sputum, tears, sweat, and breast milk. Contact lenses or dentures may become permanently stained.

If you become concerned about any side-effects, please tell your doctor or nurse as soon as possible.

5. What are the possible benefits of taking part in this study?

We hope that you will directly benefit from the medicines used in this study and from the tools used to help you with treatment adherence,

but we cannot guarantee this. However, the information we will collect from this study will help us to improve future treatments for people like you diagnosed with LTBI in the future.

6. What will I need to do if I take part? Can I definitely take part?

Not everyone may be able to take part in this study. We will first check whether you are suitable for the trial by taking a medical history, checking your symptoms and assessing your physical health. We will also check results of tests which are routinely performed before treatment of latent TB.

If you agree to be part of the trial, you will also be agreeing to:

- Having some tests to check you can take part in the trial. These include, a blood test and a pregnancy test, if you are a woman who is able to become pregnant.
- Receiving any of the six groups of LTBI treatments. To make this a fair test, you cannot choose and must be happy to accept any of the groups of treatment.
- For us to collect your information whilst you are on the study

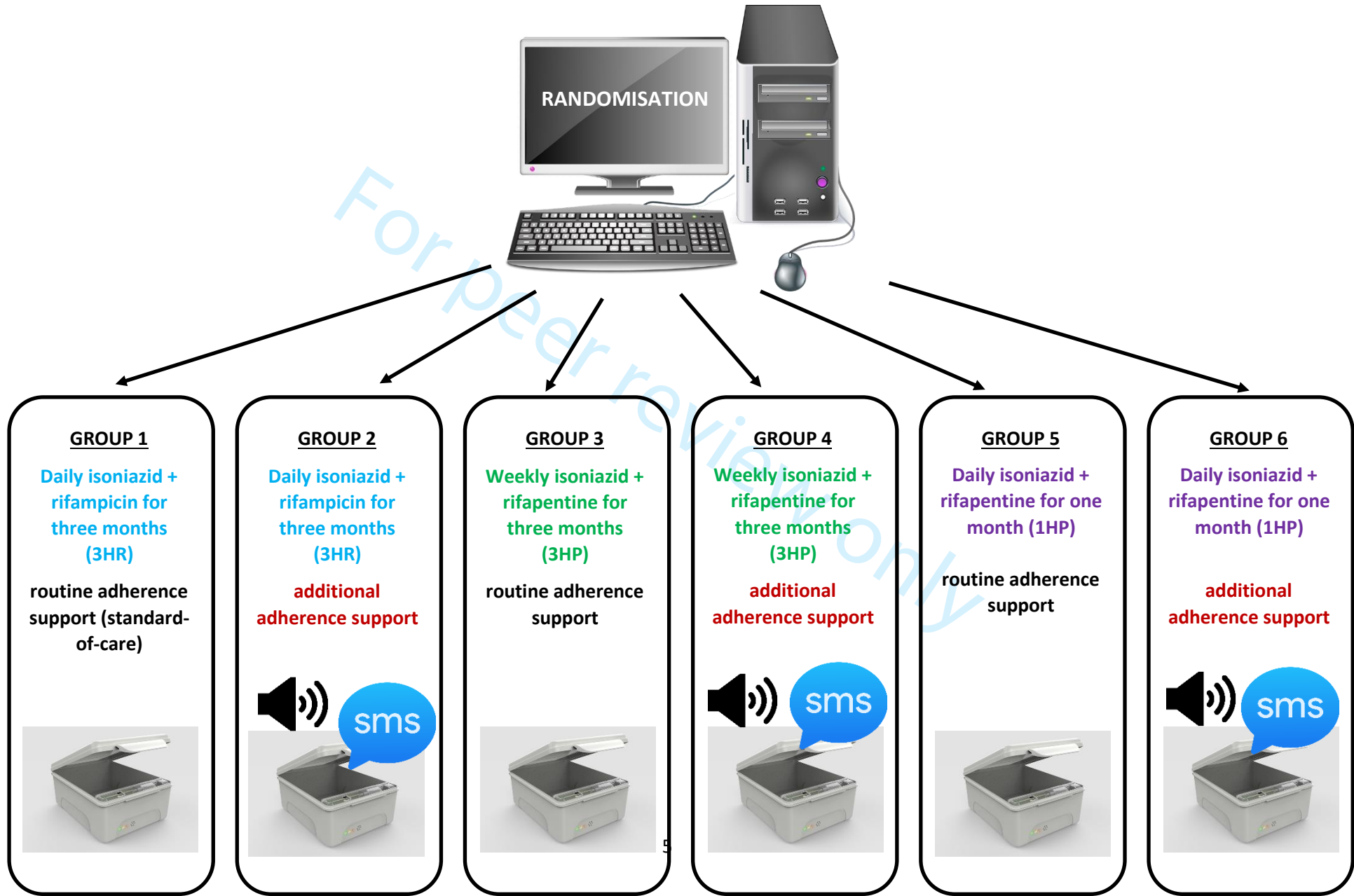
What if the tests show I can take part?

If these tests show you can take part and you agree to join the RID-TB-Treat study, we will ask you to sign a consent form. There will be six different groups in this study.

Which group will I be in?

It is important that the groups receiving each treatment are as similar as possible at the start of the study. To ensure that this happens, a process called randomisation is used to allocate people to each group. This means, a computer will randomly select which group you are in, like “the toss of a coin”. Your doctor will offer you the treatment and adherence support according to your allocated group. Neither you nor your doctor can decide which group you join. You must be willing to accept whichever treatment group you are allocated to.

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What will happen to me during the study?

Before randomisation, your doctor will again check for signs of active TB and perform a urine pregnancy test. As usual practice, your doctor will provide you with information about latent TB and why it is necessary to take pills as prescribed. As part of the study, you will be given an electronic pill box that automatically records each opening of the box and sends data to the research team via the internet.

If you are allocated to a group with additional adherence support (Groups 2, 4 and 6) you will be asked to set a reminder using the pill box. This can send an SMS message to your phone or sound an alarm at scheduled times or when the box was not opened in a day. You will also be given adherence support materials such as a video animation to watch. Your study team will collect your phone number and will share with selected members of the UCL study team in order to send an SMS message. The study team at UCL will organise the reminders to be sent.

The electronic pill box will collect data on when you open the box and this will be accessed by the team at UCL.

Once you start treatment, you will be required to visit the clinic at week 2 for blood tests to check side effects in accordance with usual care. Additionally, you will have a consultation

every month until completion of treatment to assess your health, including checks for signs of active TB and side effects. You will be requested to bring the pill box to check remaining tablets. Blood tests may be performed if your doctor finds it necessary to check liver problems or other side effects. Pregnancy tests will be done at every visit for women of who are able to become pregnant. After completion of treatment, you will receive a phone call every 4 weeks until 20 weeks after start of treatment to check for signs of active TB and side effects.

If you agree to take part in the optional /or substudies you will be required to complete additional questionnaires at every visit.

8. What are the possible disadvantages and risks of taking part?

As with the standard treatment for LTBI, there is a risk of side effects such as liver problems, allergic reactions and flu-like symptoms. The drugs in this study should not be used during pregnancy, therefore women and their partners must use contraception. For women who are able to become pregnant, pregnancy tests will be repeated throughout the study

and treatment will be stopped immediately if a participant becomes pregnant.

9. More information about taking part

Do I have to take part in the RID-TB-Treat study?

No, it is up to you to decide whether to take part or not. ,

If you decide not to take part in this study you are likely to receive the standard treatment for LTBI which is antibiotics for three months (daily) and usual care to check and support your adherence. A decision not to take part at any time will not affect the standard of care you receive.

Will I get back any travel costs?

There will not be any reimbursement for travel costs because this study will not require you to visit the hospital more times than if you were being treated in the usual way for latent TB.

Can I stop taking part after I've joined the study?

You can stop taking part in all of this study, or any part of it, at any time and without giving a reason. However, you must talk to your study doctor or nurse first. They can advise you about any concerns you may have.

If you decide to stop taking your study treatment, we will need to continue collecting information about you. This is important because it helps us to ensure that the results of the study are reliable.

If you stop taking part in this study you are likely to receive the standard treatment. A decision to stop taking part at any time will not affect the standard of care you receive.

How will my personal information be used?

University College London (UCL) is the sponsor for this study, based in the United Kingdom. University College London (UCL) will be using information from you and your medical records in order to undertake this study and will act as data controller for this study. University College London (UCL) will be responsible for looking after your information and using it properly, and will keep identifiable information

about you for 25 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at www.ctu.mrc.ac.uk/general/privacy-policy

How will my data be stored and collected?

Your hospital will collect information from you and your medical records for this research study in accordance with our instructions. Your hospital will use your name, NHS number and contact details to: contact you about the research study, make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

UCL will collect information about you for this research study from your hospital, NHS Digital and Public Health England (PHE). This information will include your name, postcode

and NHS number and health information. Health information is regarded as a special category of information as defined by the General Data Protection Regulation (GDPR). We will use this information to check whether you develop active TB or become pregnant up until one year after study treatment (<https://digital.nhs.uk/>).

Where information could identify you, the information will be held securely with strict arrangements about who can access the information.

Future research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this and other organisations. They may be universities, NHS institutions or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with relevant legislation, ethics and NHS research policy requirements.

We won't share information that can identify you with others. The information will only be used for the purpose of health and care research, and cannot be used to contact you or

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4 to affect your care. It will not be used to make
5 decisions about future services available to
6 you, such as insurance. If there is a risk that
7 you can be identified, your data will only be
8 used in research that has been independently
9 reviewed by an ethics committee.

11 **What will happen to the results of the RID- 12 TB:Treat study?**

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15 When the study is completed, we will publish a
16 summary of the results on the website of the
17 MRC CTU at UCL: <http://www.ctu.mrc.ac.uk/>

18
19 We will also publish the results in a medical
20 journal, so that other doctors can see them.
21 You can ask your doctor for a copy of any
22 publication. Your identity and any personal
23 details will be kept confidential. No named
24 information about you will be published in any
25 report of this study.

27 **Who is organising and funding the study?**

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30 This study is organised by the MRC CTU at UCL
31 on behalf of The Whittington NHS Trust. The
32 MRC CTU at UCL has run trials for many years.
33 The study coordination, data collection and
34 analysis and administration will be provided by
35 the MRC CTU at UCL. You can find out more
36 about us at www.ctu.mrc.ac.uk

Your doctor is not receiving any money or
other payment for asking you to be part of the
study. UCL has overall responsibility for the
conduct of the study. We are responsible for
ensuring the study is carried out ethically and
in the best interests of the study participants.
A patient representative has been involved in
the design of this study and in writing of this
information.

37 **Who has reviewed the RID-TB-Treat study?**

The study has been reviewed by scientists. It
has been approved by the Research Ethics
Committee of London Riverside and the
National Institute of Health Research (NIHR)
who are the funders of the study. It has been
authorised by the Medicines and Healthcare
products Regulatory Agency (MHRA), as well as
by the NHS Health Research Authority (HRA)
and the hospital's Research and Development
Office.

40 **What if new information becomes available during the course of the study?**

Sometimes during a study, new information
becomes available about the medicines and
procedures that are being studied. If this

happens your doctor will tell you about it and
discuss with you whether you want to continue
the study. If you decide to stop taking part,
your doctor will arrange for your care to
continue outside of the study.

Your doctor might also suggest that it is in your
best interest to stop taking part in the study.
They will explain the reasons and arrange for
your care to continue outside the study.

43 **What happens if the RID-TB-Treat study stops early?**

Very occasionally a study is stopped early. If it
happens, the reasons will be explained to you
and your doctor will arrange for your care to
continue outside of the study.

45 **What if something goes wrong for me?**

If you have any concerns about the way you
have been approached or treated during the
study, please talk to your study doctor or
nurse. If you are still unhappy, or if you wish to
complain, please use the normal NHS
complaints process.

If you are harmed by taking part in the study,
or if you are harmed because of someone's
negligence, then you may be able to take legal
action. The study is covered by the sponsor's

1
2
3 insurance. Further information can be obtained
4 from the study team on request.
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7 8 **10. Contacts for further information**

9 If you want further information about the
10 RIDTB-Treat study, contact your study doctor
11 or nurse (see below).
12

13 [Insert address and telephone number of study
14 doctor and/or nurse]

15 Thank you for taking the time to consider
16 taking part in this study.
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20 **RID-TB:Treat protocol version 3.0, 23-Oct-**
21 **2020**
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(To be presented on local headed paper)

RID-TB:Treat Informed Consent Form
Version 1.0, 26-Aug-2020
IRAS ID: 282304

Centre Name & Number	
Patient ID Number	
Name of Researcher	

#		Initial to Agree	
1	I have read and understood the information sheet for the RID-TB:Treat research study [Version 1.0, 26-Aug-2020] and have been given a copy to keep. I have had the chance to ask questions about the project and discuss it with the study staff. I have received answers to all of my questions.		
2	I understand that my medical notes may be looked at by individuals from the Medical Research Council (MRC) Clinical Trials Unit (CTU), or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to access my records. I understand that my confidentiality will be maintained.		
3	I understand that participation in this trial is voluntary and that I am free to withdraw from the trial at any time, without giving any reason and without my medical care or legal rights being affected.		
4	I understand that I may not benefit directly by participating in this study but that the research may help people with this condition in the future.		
5	In order to follow-up on my health status after my participation in the trial, I give permission for my personal details (such as NHS number, name and date of birth) to be used to obtain information about my health status from records held by NHS Digital, Public Health England, the National TB register, or any applicable national or NHS information system. I understand that this information may be obtained about me during the study and after (up to 25 years).		
6	I agree to take part in the RID-TB:Treat study.		
Optional Items:		Yes	No
<i>If you wish to give permission, put your initials in the 'Yes' box. If you do <u>not</u> wish to give permission, put your initials in the 'No' box. If you do not agree to any of the following items, you can still take part in the main study.</i>			
7	I agree for my GP to be informed of my participation in the research study.		
8	I agree to participate in the Behavioural Sub-study and to complete the questionnaires.		
9	I agree to participate in the Health Economics Sub-study and to complete the questionnaires.		

Signatures

Name of Participant (BLOCK CAPITALS)	Date (Day/month/year)	Signature (or thumbprint)
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Name of Witness (BLOCK CAPITALS)	Date (Day/month/year)	Signature (if thumbprint used above)
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Name of person taking consent (BLOCK CAPITALS)	Date (Day/month/year)	Signature
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IMPORTANT: Signed original to be kept in the Investigator Site File
 One copy to be given to the participant
 One copy to be kept with the participant's medical notes



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1-20
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	1
	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	21
	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

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 6-8
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention
 5

6 6b Explanation for choice of comparators 6-8
 7

8 Objectives 7 Specific objectives or hypotheses 8-9
 9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
 11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 9-10
 12
 13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 10
 17 be collected. Reference to where list of study sites can be obtained
 18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 10
 20 individuals who will perform the interventions (eg, surgeons, psychotherapists)
 21

22

23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 10-12
 24 administered
 25

26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 13-14
 27 change in response to harms, participant request, or improving/worsening disease)
 28

29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 11-12
 30 (eg, drug tablet return, laboratory tests)
 31

32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 11
 33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 13-14
 35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
 36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
 37 efficacy and harm outcomes is strongly recommended
 38

39

40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 12-13, Figure 1
 41 participants. A schematic diagram is highly recommended (see Figure)
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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 14
 2 clinical and statistical assumptions supporting any sample size calculations
 3

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 10
 5
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7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

9
 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 15
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions
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16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, 15
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism
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21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 15
 22 interventions
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 15
 25 assessors, data analysts), and how
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's 15
 28 allocated intervention during the trial
 29
 30

31 **Methods: Data collection, management, and analysis**

32
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 15-16
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol
 37
 38

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 15-16
 40 collected for participants who discontinue or deviate from intervention protocols
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<u>15-16</u>
2				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<u>16-17</u>
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>16-17</u>
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<u>16-17</u>
11				
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14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	<u>18</u>
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	<u>18</u>
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<u>17</u>
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>18</u>
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>20</u>
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36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<u>20</u>
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>20</u>
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>20</u>
5				
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<u>16</u>
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>21</u>
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<u>20</u>
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<u>18</u>
18				
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>20</u>
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>21</u>
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>20</u>
27				
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Supplementary</u>
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	<u>NA</u>
35				
36				

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