Title	Screening, Recruitment and Randomization
SOP Code	2R2 SOP02_13Oct2021
Effective Date	

1.0 Purpose(s)

The objective of this standard operating procedure (SOP) is to ensure appropriate screening, recruitment and randomization of study participants.
The SOP will ensure:

- these actions are in compliance with the standards of Good Clinical Practice
- the safety and protection of study participants
- the quality of the data produced from the study

2.0 Scope: Persons affected

This SOP concerns the co-investigators and their respective research teams involved in conducting research with human participants for the study entitled $2R^2$: *Higher dose Rifampin for 2 months vs Standard dose Rifampin for Latent TB: a 3-arm randomized trial.*

3.0 Responsibilities.

The trial coordinating center is responsible for developing and maintaining this SOP and for making it available at the clinical research site. At the clinical trial site, the site principal investigator is responsible for adoption of the processes described in the SOP.

4.0 Definition(s)

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the coordinating center on each trial participant in this research study.

Coordinating centre: research staff involved in running the $2R^2$ study who are based at Research Institute of McGill University Health Centre (RI-MUHC)

ICF: Informed consent form.

ICH: International council for harmonization of technical requirements for pharmaceuticals for human use. Section E of the ICH are the reference for good clinical practice (GCP) used in the trial's SOPs.

IRB: Institutional Review Board

5.0 Procedures

5.1. Responsibilities of the site Principal Investigator

The site principal investigator is responsible for: **1)** Identifying qualified personnel to be involved in recruitment, and documenting delegation of their responsibilities and qualifications (see SOP 1 "Site Startup and Running of trial", Appendix 1, Task Delegation of Responsibilities Form); **2)** Before initiating a study, informing and having approval from the Institutional Review Board (IRB) for the recruitment methods, advertisements and participant information materials, as well as for participants' compensation if applicable (ICH, E6 4.4.1 and E6 4.8.10); and **3)** Demonstrating a potential for recruiting the required number of suitable participants within the agreed recruitment period, as outlined in the protocol (ICH, E6 4.2.1).

Recruitment methods, as approved by the IRB, should be appropriate and non-coercive. Strategies intended to motivate potential participants should not force or unduly influence a potential participant to take part in the study. They may include but are not limited to:

I. leaflets;

II. advertisement on television, radio, newspaper, etc;

III. having clinical staff ask patients if they wish to hear about the study;

During the recruitment process, the Principal Investigator and study team should be particularly vigilant concerning factors that might affect their participants' ability to participate, such as:

I. Difficulties in follow-up (e.g. participants residing far from the study site);

II. Inability of participants to follow the protocol constraints (e.g. linguistic problems);

III. Possible conflicts (e.g. attending physician, participant is already taking part in other study).

If patient's health records will be accessed as a screening method and approval to access this information is required at the site, the appropriate approval from the site's Director of Professional Services (DPS) must be obtained in order to access their health records.

5.2 Recruitment Process

General information

Normally, for a clinical study requiring regular (i.e. non-urgent) care, and for other studies, as appropriate, the following process should be followed during recruitment:

5.2.1. Regardless of how potential participants are identified, the person who first contacts them should be known to them and/or in their routine care duties. (i.e. clinical nurse, clinical secretary).

5.2.2. A person who knows the study protocol well should be available to explain it to the participant in simple terms. Generally, this person should not be the participant's treating

physician but this is dependent on the site specific IRB. If the treating physician is the person obtaining consent, they may need to explain to the IRB why it is necessary. If the IRB approves this, the physician must disclose his dual role to the participant.

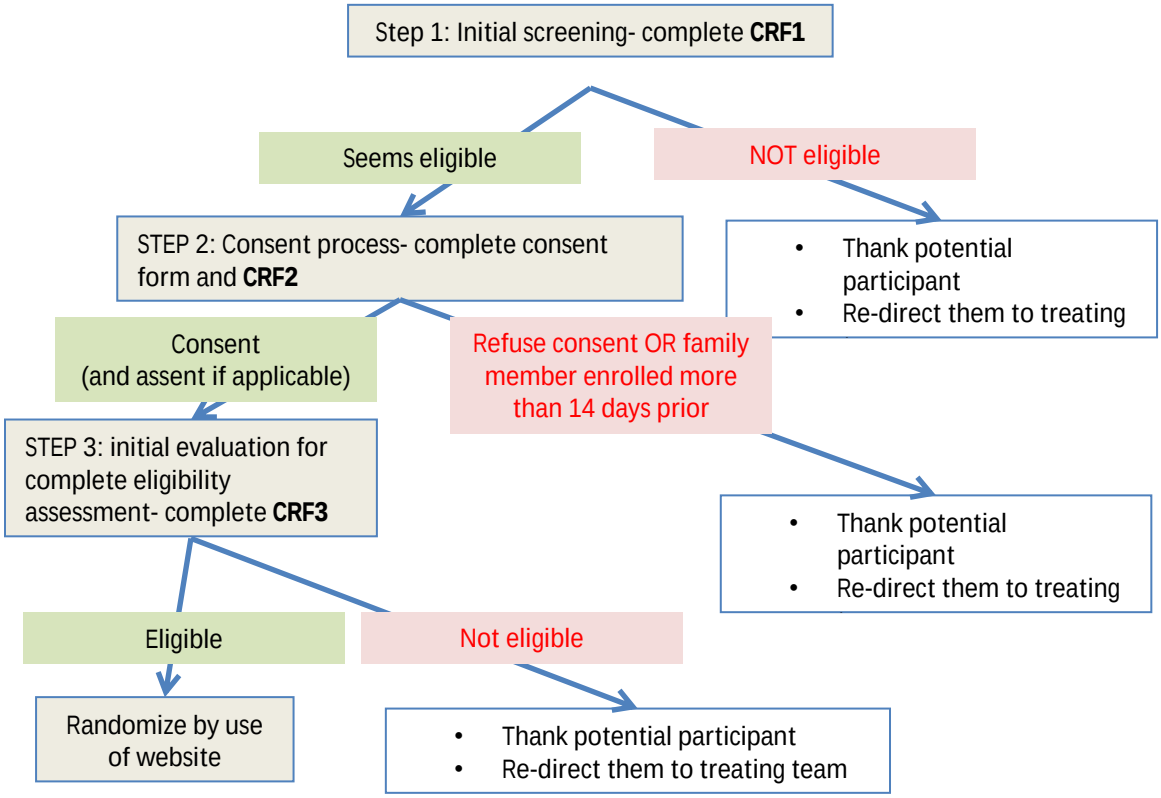
5.2.3. No research activity should be conducted before the participant has signed the informed consent form (ICF). The participant should not be asked to provide biological samples, refrain from taking usual medication, fasting, etc., for study purpose, before signing the ICF.

Overview of recruitment process for this trial

5.2.4. The recruitment process for this trial includes 3 steps (see figure 1). Information that is collected in each of these three steps is documented in the following CRFs: CRF1 for step1, CRF2 for step2 and CRF3 for step 3.

5.2.5. These three CRFs need to be completed in sequential order (CRF1 before 2, CRF2 before CRF3) in paper version. Once they have been completed in paper version they need to be entered in the 2R2 website. **Note**: you can complete and enter one CRF at the time, or complete the 3 CRFs and then enter them all at the same time, as it works better for your setting.

Figure 1. Summary of the recruitment process



5.3 Step 1: Initial screening

5.3.1. The fist step is an initial screening that is performed by completing CRF-1. This is an initial quick check for general eligibility. See detailed instructions to complete CRF1 in **Appendix 1**.

5.3.2. If after this first check potential participant seems eligible, then the consent process can take place. Otherwise, it this initial check reveals reasons for which potential participant is not eligible then the recruitment process ends here, thank the potential participant and direct them to the treating team for them to receive standard care.

5.3.3. The completed **CRF1**, for both eligible and ineligible potential participants for whom this first step was done, **constitutes the screening log of this study**.

5.4. Step 2: Informed consent process

5.4.1. Only the most recent version of the informed consent form (ICF) approved by the IRB should be used for participant consent.

5.4.2. The ICF should provide the participant with all necessary pertinent information. They should have ample time and opportunity to inquire about the details of the study and to decide whether or not to participate.

5.4.3. During the course of discussion concerning the informed consent, all elements included in the ICF as well as any other written information provided to the participant should be explained to the participant (ICH, E6 4.8.10).

5.4.4. All questions about the study should be answered to the satisfaction of the participant or the participant's legal representative (ICH, E6 4.8.7).

5.4.5. Prior to the participant's participation in the study and before any procedure referred to in the protocol, the approved version of the ICF should be read, understood, signed and dated by the participant or the participant's legal representative, and by the person who conducted the informed consent discussion (ICH, E6 4.8.8). If the participant is a minor, his/her assent, written or verbal, is also necessary and has to be documented in the consent form. The consent process should be documented in the participant's medical chart noting that a copy of the ICF was given to the study participant.

5.4.6. Neither the Principal Investigator nor the study staff should coerce or unduly influence a participant to participate or to continue to participate in a study (ICH, E6 4.8.3).

5.4.7. The requirement for free and informed consent should not disqualify participants who are not proficient in the language used by the researchers from the opportunity to participate in potential research. Such individuals may give consent providing that one or more of the following are observed to the extent deemed necessary by the IRB (note if you use a translator during the consent process you will likely require one during treatment and post-treatment follow-up):

- An intermediary not involved in the research study, who is competent in the language used by the researchers as well as that chosen by the participant, is involved in the consent process.

• The intermediary has translated the consent form or approved an existing translation of the information relevant to the participant.
• The intermediary has assisted the participant in the discussion of the study.
• The participant has acknowledged in his or her own language, that he or she understands the study, the nature and extent of his or her participation, including the risks involved, and freely gives consent.

5.4.8. Prior to participating in the study, the participant or the participant's legal representative should receive a copy of the signed and dated ICF and any other written information provided to the participant (ICH 4.8.11).

5.4.9. If new information becomes available during the research study that may be relevant to the participant's willingness to continue to participate in the study, a new ICF should be developed (ICH, E6 4.8.2). This new version, once approved by the IRB, should be read, understood, signed and dated by all participants who remain active in the study, as well as by all new participants or their legal representatives. This new version should be signed by the person who conducted the discussion with the participants.

5.4.10. During the participant's participation in the study, the participant or the participant's legal representative should receive a copy of the updated signed and dated consent form and a copy of any amendments to the written information provided to the participants (ICH, E6 4.8.11).

5.4.11. The original ICF, signed and dated by the participant and the designated signatories at randomization, should be kept with the essential study documents, as described in "Site Start-up & Running of Trial" (SOP1).

5.4.12. The Principal Investigator may give each study participant a wallet-size information card (i.e. business card), at the beginning of the study that provides the following information:

a. study title;

b. name of study drug under investigation;

c. emergency instructions and contact numbers.

5.4.12 Once consent process is completed, fill in ELIGIBILITY AND CONSENT FORM- CRF2. Consent or refusal of consent for each potential eligible participant has to be reported on CRF-2. If the participant refuses to consent, ask them for their reason and record it on the CRF-2.

5.4.13. If consent is done at-distance, to comply with COVID-19 related measures, the research team conducting the consent process via phone must ensure that the participant understand what participation to the study implies and can ask all questions needed to have clear all study parts. The agreement to participate is then written and signed by the research team in the Consent form. Information on study title; name of study drug under investigation; and emergency instructions and contact numbers have to be given by phone, making sure that

they have been correctly recorded by participants. An impartial witness must be present during the consent and sign it, if required by the local ethic committee.

5.5.Step 3: In depth assessment of eligibility

The following procedures are specific to the third step of recruitment for this trial: the collection of participant information to enable completed and appropriate assessment of eligibility. A case report form (CRF) has been created for this component of the research study – EVALUATION FORM (CRF-3). This CRF comprises of 4 sections: i) Demographics & TB history; ii) Medication, Allergies & Medical evaluation; iii) Initial investigations and iv) Randomization.

The four sections of EVALUATION FORM (CRF-3) must be filled out for each study participant (See **Appendix 2** for detailed instructions to complete CRF-3).

Once CRF-1, CRF-2 and CRF-3 are completed, the information from these three forms must be entered into the study website for randomization to take place.

5.6 Instruction for data entry:

5.6.1. To enter data from paper CRFs to the website, go on to the website (http://2r2.crc.chus.qc.ca) and select "Add/select record" (Note – after 20 minutes of inactivity users will be automatically logged off of the website). If unable to log on to the site, the participant can be randomized manually (refer to Manual Randomization SOP3). If randomization is done manually, the study coordinating center must be informed.

5.6.2. Enter first the appropriate study participant information from the completed paper version of CRF-1 (Initial Screening Form). Once entered the Initial Screening Form click first "Save/stay on page" and then, once saved, on the "Save/go to next page" button at the bottom of the screen. At this point a new participant ID has been generated. Please note that this is still a potential participant as randomization is not done yet, but the ID serves for the purpose of generating the screening logs

5.6.3. Write down the "Participant's study ID number" (provided by the website) on the paper CRF1, 2 and 3.

5.6.4. If the participant is deemed eligible by the website, continue the process by entering now CRF-2 (Eligibility and Consent).

5.6.5. Once CRF-2 is entered, If participant consented, continue with entering CRF-3 (Demographics & TB history; Medication, Allergies & Medical evaluation; Initial investigations; Randomization) into the website. At the end of each section click first "Save/stay on page" and then, once saved, on the "Save/go to next page" button at the bottom of the screen.

5.6.6. You can leave this section without randomizing the study participant by going back to other forms in the menu on the left of the page, at any point in time. It is advisable to always press the "save/stay on page" button prior to this in order to save any data that has been entered. If you do not complete the registration process the first time you enter the study participant information, you can access the study participant's record on the "Home" page by choosing their study ID number (Add/select record) and then pressing "select participant", and then pressing the form you did not complete (for example "Initial investigations" in the left menu). **Note**: Incomplete forms appear in yellow in the left menu.

5.6.7. When you are ready to randomize, click on the button "Yes, please randomize this participant" and wait for the randomization to occur and be displayed on the website. **Note**: If at any point the 2R2 website does classify the potential participant as not eligible, but you think he/she is eligible, go back and check all answers and correct errors if found. If after verification, potential participant is still considered not eligible and you think he/she should be eligible, contact the study coordinating center.

5.7 Randomization

5.7.1. Randomization for this trial occurs through a web-based computer generated random number producing algorithm, in blocks of varying length (3 – 6 participants), stratified by study centre. Randomization stratified by study centre should ensure that potential sources of bias by centre are balanced. In addition, this will ensure that balance is maintained if one or more study centres has to stop enrolling.

5.7.2. Randomization is done at the level of the individual, except if there are more than one participant from the same household enrolled in the study. If a HHC is enrolled and belongs to the same household as someone who has already been enrolled and randomized, that HHC (and all subsequent HHC from the same household) will be allocated to the same regimen as long as they are consented within 14 days of the randomization of their family members. If they are enrolled later, they will be excluded from the study.

5.7.3. When you randomize a new participant, on the Randomization page of the website, you will see all of the information that is needed to provide the participant with study medication and with instructions for their follow up. In particular you will see: total duration and daily dose if participant is randomized in control arm; or total duration, number of pills per day and a code (note: the dose will remain blind) if the participant is randomized to one of the two high dose study arms. Copy to the paper version of CRF-3 which arm the participant has been randomized to - or print a screenshot of the randomization page of the website and staple it with CRF-3.

5.7.4. Once the participant is randomized the only data that can be modified in CRF-3 are the results of the laboratory tests (i.e. liver function tests, complete blood counts, results of pregnancy test, HIV viral load -if participant is HIV+ but viral load is not known at the time

of randomization- and HIV testing -if HIV status and is not known at the time of randomization). Note that for each of these tests, the date in which the laboratory test has been ordered has to be filled in for randomization to take place. Once the participant has been randomized, any other changes to data must be done by submitting a request to the coordinating center (refer to Management of Study data SOP). Once randomization is complete, please refer to SOP4 "Blinding and Dispending study medication" for procedures of dispensing study medications.

5.7.5. Although participants are given their study medication (or a prescription for their medication) on the day of randomization, the results of laboratory test for all participants and pregnancy test (if applicable) are usually not available on the same day. Therefore participants should be advised **they must wait for a call from study staff before they actually start to take their medication**. Research staff should ensure that laboratory results are reviewed 24-48 hours after randomization, so that participants can be called and told to start their study medication as soon as possible (1-2 days maximum) after randomization (unless there are reasons for exclusion post randomization- see section 5.8.).

5.8. Exclusions post randomization allowed by the protocol

If the results of baseline tests are abnormal, the participant may meet one of the study exclusion criteria (for example elevated transaminases > 3 times upper limit of normal, or, pregnancy test positive). If the lab tests indicate that a participant should be excluded, call them immediately to tell them to **NOT START** their study medication. They are considered excluded from the study and should be referred to the treating team for re-assessment. If the treating team decides to give LTBI treatment, this will not be provided through the study; instead medications and all follow-up will be given through routine care.

Note: in settings where phenotypic DST is performed routinely for all persons with newly diagnosed active TB, the household contacts may have been enrolled and randomized before the DST results for their index patient was available. If the DST of an index TB patient reveals rifampin resistance, this participant is also excluded from the study. As soon as these results of DST are known, contact the participant and tell them to **STOP** study medication. These participants are excluded from the study and need to be referred to the treating team for re-assessment. If the treating team decides to give LTBI treatment, this will not be provided through the study; instead medications and all follow-up will be given through routine care.

If a patient is excluded post-randomization, inform the coordinating center promptly, by completing a note to file through the 2R2 website (refer to Management of Study data SOP).

5.9. Study participant identification information

The following procedures are specific to the collection of participant identification information to enable appropriate follow-up. A CRF has been created for this component of the research

study – CRF-4 IDENTIFICATION FORM. This is the only CRF that will not be entered in the website. This CRF4 will remain only on paper and kept at the study site.

5.9.1 Once the participant is enrolled into the study the participant's name, address and further contact information should be collected on the IDENTIFICATION FORM. These data will facilitate the follow-up process.

5.9.2. It is important to ensure that these data remain up to date. Inquiries can be made about planned changes to this information such as "Are you planning to move in the next 6 months? If yes do you have the new address/phone number?"

5.9.3. Try to obtain information on four individuals that could be contacted if you are unable to contact the study participant, if these additional contacts reside outside the country, collect email, WhatsApp, and mailing address information for them.

5.9.4. All contact information including names, address, telephone numbers, other contact persons, and full date of birth should be locally stored at each site, in a secure location, and safeguarded by the site Principal Investigator.

5.10. Recruitment Reports

The following information related to the recruitment of participants form part of the essential study documents (E6.8 of the ICH) (sites can use the paper versions in the appendices or create computerized files as long as the required data are captured and included in the study master binder):

I. **Participant Enrolment Log:** this document lists enrolled participants chronologically by study number (see **Appendix 3**)- a participant is added to this list when is randomized and enrolled in the study . This list is confidential and should be safeguarded appropriately.

II. **List of participant identification codes:** this document permits the identification of all participants who are enrolled in the study, in case follow-up of a participant is necessary. This log include both study ID and names of study participants, listed chronologically by study participant ID number. A participant is added to this list when is randomized and enrolled in the study. This list is confidential and should be safeguarded appropriately (see **Appendix 4**).

Note: there is not a separate Screening log for this study, as the "CRF-1 Initial screening" serves as screening log.

6.0 References

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2), Current Step 4, version dated 9 November 2016.

SOP-CR-009_07 _Subject Recruitment and Screening_01-Sept-2018 – Research Institute of the McGill University Health Centre

SOP-CR-002_07_Research Team Roles and Responsibilities_01-Sept-2018 – Research Institute of the McGill University Health Centre

SOP-CR-008_07 _Inform Consent Process _01-Sept-2018- Research Institute of the McGill University Health Centre

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP02_25Nov2019	25 November 2019	NA (original version)
SOP02_06Jul2020	06 July 2020	Update exclusion criteria and exclusion post-randomization, as per Protocol v2_15March2020 (in Appendix 1 and 2).
SOP02_21Jun2021		- Correction of exclusion criteria (Appendix 1 and 2); -Procedures when COVID-19 related measures are in place (page 5 and Appendix 2)

Appendices:
Appendix 1. Instructions for completion of CRF-1.

1. **Participant ID**: will be provided by website. Once CRF-1 is completed on paper and information are entered in the website, the ID will be provided by the website. Then you can report the ID on CRF.
2. **Dates** are all in DD/MMM/YYYY format (example: 10 SEP 2019)
3. The **Center**: is reported only in paper CRF, in website there will be user ID that will automatically link the information entered for a participant to the parson entering the data.
4. **Age** is to be reported in years
5. **Sex** is self-reported by participant
6. **TST results** are as documented by the health care worker (HCW) who assessed the results. A copy of the TST results should be made to serve as a source document. Be sure to remove any personally identifying information and record the study participant ID number on the photocopy. If no measurement is available, the following TST codes should be provided: 101 – Record indicates "Blister highly positive", 102: HCW recorded as 'positive' or as '10+ mm'; 999 – result unknown.
7. **TST converter**: A convertor usually has a negative TST result followed by a positive TST result - in the situation of a known recent TB exposure. A 2 step test - with the two tests performed 1-4 weeks apart in the absence of any known TB exposure is NOT a conversion.
8. **Time interval of conversion** is Based on what reported by participant
9. A positive **QFT** is defined as TB antigen tube - negative control tube >0.35 IU/ml. A positive QFT will be considered equivalent to a TST of 10mm.

Section on EXCLUSION CRITERIA

1. If index case's drug susceptibility test (DST) results are not yet available and treating MD is willing to put participant on treatment, then participant can be enrolled. Answer "No" to the question *"Was study participant a contact of a TB patient known to have TB resistant to RIF?"* if there is no reason to think the index patient has RIF resistant TB. If the patient has been previously treated, the risk of drug resistance is higher - so in a setting where DST are not usually performed, only for a "NEW TB case" there is no reason to think that TB is RIF resistant. As soon as DST results are available: if index case is found to be **resistant to RIF**, participant will have to be withdrawn from the study (this is a post-randomization per protocol exclusion). Contact the study coordinating center if index case is found to have RIF resistant TB after randomization.
2. **Pregnancy** is an exclusion criteria, a pregnancy test needs to be done for women of childbearing potential. If female participant is not of child bearing potential, write NA to the question "*Is study participant pregnant?*". **Note**: if result of pregnancy test is not yet known at randomization, write "no" if potential participant reports that she is not pregnant. Report the result of pregnancy test done at baseline in CRF-3 as soon as available.
3. If participant **took already at least 7 days of treatment** within the last 90 days for LTBI, they should be excluded.
4. If study participant has AST or ALT at least 3 times higher than upper limit of normal, OR has hematologic abnormalities of grade 3-4, they should be excluded. **Note**: if results of baseline laboratory test are not known yet at randomization, write "no" if there is no reason to think the potential participant has elevated AST or ALT, or abnormal hematologic results. Report the results of the baseline test in CRF-3 as soon as available.
5. Allergy or hypersensitivity to Rifampin, Rifabutin or Rifapentine is an exclusion criteria. Ask participant is ever took rifamycins before and if there is a history of allergy/hypersensitivity.

Appendix 2 – Instruction to fill CRF 3 (Initial evaluation)

General note: all information in CRF3 are obligatory (i.e. if left blank participant file will appear as incomplete on the website). There are though some information which absolutely need to be filled in before randomization can take place and others which can be filled in 24-48 hours after randomization occurred. Variables which must be completed before randomization can take place are reported in red below. Instructions appear in blue.

DEMOGRAPHIC AND HISTORY OF TB

D0. Research staff completing the form_____

D0 is reported only in paper CRF, in website is assigned by user ID

D1. Height: C . C C m **D2. Weight:** C C C . C kg

D1-D2. Height has to be reported in meters and weight in kilograms. D1 can be entered after randomization, D2 is essential for randomization to take place and ***cannot be less than 25Kg****.*

If enrolment is done at-distance, for COVID-19 related measures, find a recent weight and height in participant's medical record. If not available, ask participants to take their weight and height and report it in CRF3.

D3. In which Country were you born? _____

D4. If Country of birth is different from country of this study center, in which year did you arrive in country of this center? C C C C

If participant does not remember the exact year, ask how many years ago and write the closest approximate year you can calculate using that information (for example, if in 2019 participant says it has been about 15 years, write 2004).

D5. Immigration status: C **Visa** C **Landed immigrant/Citizen** C **Refugee** C **Unknown** C **Not applicable** (born in the same country of study center) C **Other**,
D6.Specify_____

RISK FACTORS

D7. HIV status: C **Positive** C **Negative** (go to D13) C **Unknown**(go to D13)

If HIV positive, provide: D8. **Year of diagnosis** C C C C

If participant does not remember the exact year, ask how many years ago and write the closest approximate year you can calculate using that information (for example, if in 2019 participant says it has been about 15 years, write 2004). If participants cannot remember the year (or how many years), write 9999

D9.**CD4 count** (at randomization) C C C C . C **/mm³**

D10 **Viral load** (at randomization) _____

Note: if CD4 is not know, write 9999. Note: if viral load is not know, write 9999 and **perform viral load test.**

If CD4 and viral load at this visit are not known, write 9999. Remind that viral load at baseline has to be performed if results are not already available. If viral load is undetectable, write 9. If participant is NOT HIV positive, question D10, D11 and D12 are not needed for randomization.

D11. **Antiretroviral therapy?** C **No** C **Yes**

D12. If yes, provide antiretrovirals' names here :

1)_____**2)**_____**3)**_____

_____**4)**_____

If possible, write the name of active ingredient, or the generic name, and not the commercial name of each antiretroviral. If participant is taking a combination pill, please write all the active components.

D13. Contact with a person who has active pulmonary TB (choose one)

C **No known contact with a person who has active pulmonary TB** (GO to D16)

C **Contact, on average, for one night per week OR at least one hour per day for 5 days per week, for the past 3 months with a person with untreated active pulmonary TB** (close contact)

C **Contact for 1 to 5 hours per week for at least 1 week with a person with untreated smear positive pulmonary TB** (casual contact)

If close contact or casual contact:

D14. Was a drug susceptibility test (phenotypic DST or GeneXpert) performed in the index patient with active TB?

C **No, susceptibility test was not performed, but patient with active TB is a new TB case with no prior treatment for TB** (go to D16)

Tick this answer if susceptibility test is not routinely required but there is no reason to suspect the index patient has a rifampin resistant TB.

C **Yes, susceptibility test was performed**

If performed**,** D15**. Result of susceptibility test is :**

C **NO resistance to Rifampin**

C **TB RESISTANT to Rifampin**

If susceptibility test in index patient has been requested but results are not available yet, leave D15 blank. Come back to fill D15 as soon as results become available. When the DST the results are available, if there is resistance to rifampin, call the participant to stop study medication and refer them to the treating team. Also, inform the coordinating center as this is a per-protocol exclusion post-randomization.

D16 Does the study participant have any immunosuppressive conditions or therapy?

C **No** C **Yes**

D. 17-24. **If Yes, which are the conditions or therapies causing immuno suppression in this participant** (check all that apply)**?** *Tick more than one if participant has more than one condition*

C **Diabetes** C **Renal failure (dialysis)** C **Transplant anti-rejection therapy** C **TNFα inhibitory therapy**

C **Other immunosuppressive conditions,** D22. **Specify**_____

C **Other immunosuppressive therapy** D24. **Specify**_____

D25. Smoking status (choose one)

C Never smoke C Current smoker C Ex- smoker

If current or ex-smoker D26.**Age started** C C D27. **Packs/day** C C . C

If ex-smoker D28.**Age stopped** C C

Write approximate age for starting and stopping and packs per day if participant cannot remember with precision.

D29. Alcohol: How often do you have a drink containing alcohol? (choose one)

C Never C Less than once a month C 1-3 times per month C Once a week C 2-3 times a week

C 4 or more times a week

D30. How many drinks containing alcohol do you have on a typical day when you are drinking? (choose one)

C Not applicable C 1 or 2 C 3 or 4 C 5 or 6 C 7 to 13 C 14 or more

D31. How often do you have six or more drinks on one occasion? (choose one)

C Not applicable C Never C < Monthly C Monthly C Weekly C More than once a week

D32. Do you use any recreational drug more than once a month? C **No** C **Yes**

If Yes, **choose any that apply (D33-D34):**

C **D33.Cannabis** (marijuana, hashish, etc) C **D34.Other,** D35. **If other, specify** _____

_____

HISTORY OF TB

D36. Has the participant had BCG vaccination? C **Yes** C **No** C **Unknown**

D37. Was the participant treated before for active TB? C **Yes** C **No** C **Unknown**

D38.**If yes, year of diagnosis** C C C C D39**. If yes, number of months treated** C

C

Write approximate year and duration of treatment if participant cannot remember with precision.
If participant has been treated already is NOT ELIGIBLE

D40. Was the participant treated for latent TB in the past? C **Yes** C **No** C **Unknown**

D41 **If yes, year of diagnosis** C C C C D42**. If yes, number of months treated**

C C

Write approximate year and duration of treatment if participant cannot remember with precision.
If participant has been treated already is NOT ELIGIBLE

D43. Comments _____

SECTION-2 (Medications; Allergies; Medical evaluation)

MEDICATIONS

M1. Is participant sexually active and of child bearing potential? C **Yes** C **No (go to M12)**

It is important to know if a potential participant could be pregnant or can become pregnant during the study.
If a potential participants is of childbearing potential but is not sexually active (for example a young woman who reports no sexual relations), write NO and go to question M12. If a potential participant is sexually active but not of childbearing potential (for example a woman who is in menopause) write NO and go to question M12

To all potential participants of childbearing potential who are sexually active, please ask both questions M2.1 and M2.2 below.

M2.1. If Yes to M1, is participant taking birth control pills or hormonal contraceptives?

C Yes C No

M2.2. If yes to M1, is she willing to use methods of contraception alternative to hormonal contraception? C Yes C No

If M2.2 is No (i.e. *a potential participants, who have child bearing potential and is sexually active, is not willing to use other methods of contraception than hormonal contraception) participant is NOT eligible.*

(**If NO, STOP HERE**)

M3-M10. If yes, what method does she plan to use? (choose any that applies)

C Diaphragm C Intra Uterine Device (IUD) C Condoms C Sponge/suppository C Cervical cap

C Chemical method (spermicidal foam/jelly) C Abstinence C Other, M11. Specify_____

M12. Is the study participant taking any other medications prescribed by a doctor (except antiretrovirals, which are already reported in D12)? C Yes C No

M.13 **If yes, list the names of all the medications being taken**

1)_____2)_____3)_____

Write here medications that the participant takes which are prescribed by a doctor. Some medications, such as antibiotics, may require a prescription but are often sold without a prescription in the study site. If so, please write them here. In case of doubts, write the medication down. Please write the generic name (or active ingredient) if you can, rather than the commercial name.

If the participant is taking antiretroviral treatment, these should be listed in D12 (no need to repeat them here)

M14. **Do any of the medications taken by participant (as antiretrovirals, or other medications) have potentially clinically important drug interactions with rifampin?** (see drug interaction list, contact pharmacist)

C Yes C No C N/A (participant does not take any other medication)

A list of drug interaction is provided in appendix to the protocol. As there can be other interactions, not yet included in this list, check for potential interactions with concomitant medication with a pharmacist or if you are not sure - please contact the coordinating center.

M15. **If yes, does the treating team believe interactions are manageable and therefore study participant is still eligible for the study? C Yes C No** (if NO, STOP HERE)

If the answer is NO to questions M15, participant is NOT eligible.

ALLERGIES AND COMORBIDITY

M16.Allergies to medications: C None C Any, M17, **Specify**_____

Report here allergies to any medication participant has. NOTE: A clear history of allergy/hypersensitivity to Rifampin, Rifabutin or Rifapentine is one of exclusion criteria. Questions on allergy to rifamycins should have been asked already at initial screening (see CRF1). Double check about it during Initial Evaluation (CRF3). If an allergy to rifamycins, which was not known to reseach team when completing CRF1, becomes known during Initial Evaluation (CRF3), please report it here (M16) and STOP HERE (do not enrol participant).

M18.Other medical conditions C **None** C **Any,** M19,

Specify_____

MEDICAL EVALUATION

M20. Respiratory symptoms C **None** C **Any,**

M21.**Specify**_____

M22. Other symptoms: C **None** C **Any,** M23.

Specify_____

M24. Physical exam C **Normal** C **Abnormal,**

M25.**Specify**_____

M26 . Comments (for all the above sections):

If enrolment is done at distance for COVID-19 related measures: ask participant by phone if they have respiratory symptoms or any other symptoms. Ask them if a recent medical examination has been done, if possible, retrieve the report of this evaluation from participant's medical file. If not possible, report is as ***Abnormal*** *at M24 and Specify:* ***NOT DONE because of at-distance enrolment for COVID-19 related measures*** *at M25.*

SECTION -3 Initial investigations

INVESTIGATIONS
CHEST X RAY
L1.Date of chest-x ray

D	D	M	M	M	Y	Y	Y	Y

A chest-x ray has to be done prior to randomization, and the result should be "normal" or "abnormal but not TB" in order to exclude active TB. ***The chest x ray can be used if it was done less than 6 months prior to the date of randomization.***

L2. Chest-x ray results (select one only)
☐ Normal
☐ Abnormal possible active TB. NOTE: If possible active TB complete section on microbiology :L8 to L18)
☐ Abnormal not TB. L3. Specify:

_____

If the chest-x ray report is "abnormal possible active TB", then microbiological investigations have to be done to exclude active TB, and reported in L8-L18.

L4. Other radiological tests: C **None** C **Any, L5. Specify**_____

L6. If any, Date

D	D	M	M	M	Y	Y	Y	Y

L7. **If any, Results** _____

MICROBIOLOGY

L8. Microbiology: ☐Not required ☐Done

L9. If Done, date of 1st test

D	D	M	M	M	Y	Y	Y	Y

Microbiology test is "not required" if active TB is not suspected on basis of medical history, physical exam and chest-x ray. Otherwise, if active TB is suspected on the basis of medical history, physical exam, or chest-x ray - then microbiological tests are required. If microbiological tests are done, ***date in L9 has to be less than 6 months prior to the date of randomization.*** *If answer to L8 is "Not required" then questions L9-L18 are not necessary for randomization.*

L10 **Number of spontaneous sputum samples obtained** **C**

L11**. Number of induced sputum samples obtained** **C**

L12. **Number of gastric aspirate samples obtained** **C**

L13. **AFB smear: Number done** **C** L14.**Results: C All contaminated C All Negative C At least one positive** (if at least one positive, STOP HERE)

If one (or more) AFB is positive, stop here (active TB is an exclusion criteria)

L15. **Cultures Number done** **C** L16. **Results: C All contaminated C All Negative C At least one positive** (if at least one positive, STOP HERE)

If one (or more) culture is positive, stop here (active TB is an exclusion criteria)

L17**. GeneXpert was done? C Yes C No**

L18**. Results: C Contaminated C Negative** (DNA not detected) **C Positive** (DNA detected) If Positive, STOP HERE)

If GeneXpert is positive, stop here (active TB is an exclusion criteria)

LABORATORY

L19. Date test was performed

D	D	M	M	M	Y	Y	Y	Y

The following laboratory exams need to be done before randomization can take place. If results are already available at randomization, they are considered valid if done ***less than 6 months prior to randomization****.*
NOTE: If results of the test that have been requested are not yet available, randomization can take place but ***you need to fill Lines L20-L27 in the next 24-48 hours, as soon as results are available. If results are not ready at randomization, please advise the participants that you will call them to confirm if they can start study medication once you can see the results.***

L20. Alanine transaminase (ALT) c c c c . c UL

L20.1 Upper normal limit for ALT c c c . c UL

L21. Aspartate aminotransferase (AST) c c c c . c UL

L21.1. L20.0 Upper normal limit for AST c c c . c UL

Write the upper normal limit for the AST and ALT result reported. Please note that just one of these two tests (AST or ALT) is sufficient to randomize. If you testes both, please report both AST and ALT.

If AST or ALT results, which become available after randomization, are ≥ 3 times higher than upper limit of normal, call participants immediately to tell them to NOT START their study medication This is a case of post-randomization exclusion per protocol: fill a note to file in the 2R2 database to inform coordinating center. Coordinating center will confirm with you once the exclusion is completed.

L22. Total bilirubin c c c . c umol/L

L22.1 Upper normal limit for **Total bilirubin c c c . c umol/L**

Write the upper normal limit for bilirubin only if the result is not within the normal range.

L23. Hemoglobin c c c . c g/L

L24. Hematocrit c . c c c L/L

L25. White blood cells c c c . c 10^9/L

L26. Platelets c c c . c 10^9/L

L26.1. Is there any hematological abnormality of grade 3 or 4? C Yes C No

L26.2 if Yes, please specify which is(are) the abnormal result(s) and the normal range(s):_____

If one or more of the haematological test done have a grade 3 or 4 abnormalities (refer to SOP09 Adverse Events for the grading), reply Yes to question 26.1 and specify in 26.2: the test with abnormal result, the results and the normal range for that value. For example: "low white blood cells 1.65 x10e9/L, normal range: 4.5 to 11.0 x 10e9/L" If participant has been already randomized, call participants immediately to tell them to NOT START their study medication. This is a case of post-randomization exclusion per protocol: fill a note to file in the 2R2 database to inform coordinating center. Coordinating center will confirm with you once the exclusion is completed.

NOTE: if NO hematological tests has a grade 3 or 4 abnormality, answer NO at question 26.1 and skip question 26.2.

Remind that, for patients with history of liver or hematological disease the lab test results must be available before randomization (see "Population and eligibility criteria" in protocol).

L27. If participant is HIV+, viral load : _____copies/ml

(if not already reported in D10)

L28. HIV TESTING: Has treating team offered a new HIV testing to study participant?

c Yes c No c Not required, status is known c Not appropriate according to treating team

L29. **If Yes, does study participant agree to be tested? c Yes c No**

L30**. If Yes, date test was performed**

D D M M M Y Y Y Y

L31. **HIV Test Results** c **Positive** c **Negative** c **Unknown**

If results of the HIV test that have been requested is not yet available, randomization can take place but you need to fill Line 31 as soon as the result is available after randomization. Remember that if a participant needs to start a new treatment, such as for HIV, during follow-up; this new treatment should be reported in the CRF-5- follow-up during treatment.

L32. Pregnancy test : c **Positive** c **Negative** c **N/A**
If results of pregnancy test become available after randomization, and is positive, call participants immediately to tell them to NOT START their study medication. This is a case of post-randomization exclusion per protocol: fill a note to file in the 2R2 database to inform coordinating center. Coordinating center will confirm with you once the exclusion is completed.

SECTION-4 (Randomization)

RANDOMIZATION and STUDY DRUGS

R1. Are you ready to randomize this participant? c **Yes** c **No**
If investigations prior to randomization are not completed and participant has to come back for further investigations, tick no and come back to this form once participant would be ready to be randomized and start LTBI therapy.
Once you are ready to randomize, tick Yes, the website will do the randomization.
R2. Study participant is randomized to

c **4 months of Rifampin 10mg/kg/day**

R3. **Dose should be (**auto-generated using weight)_____ mg/day

c **2 months of Rifampin high dose (either 20 or 30 mg/kg/day)**

R4. **The code given is** C C **; and (**R5) **Dose is** C **pills/day** (auto-generated using weight)
Copy these information from the website on the paper CRF (or print this page from the website and attach it to the paper CRF3)

R6. If randomized to 2 month high dose, number of pills of study medication dispensed today
C C C

For participants randomized to 2 months of rifampin, just count the pills dispensed today. For example, 90 pills (if 90 pills are given)

R7. If randomized to 4 month standard dose, number of daily doses of study medication dispensed today C C C

For participants randomized to 4 months of rifampin, count the daily doses: for example if participant has to take 2 pills of 300mg per day and has 60 pills, write 30 daily doses (60/2=30).

R8. For how many days should this supply of pills last? C C C

For all participants, write for how many days this supply should last for. Make sure that it last a few days longer than the expected date of the first visit (so that in case a participant cannot come on time to the visit, he/she does not miss any dose)

R9. Suggested date of next visit is: _____ **/** ___ ___**/**_____ **(**auto-generated to be in 2 weeks or 4 weeks)

The suggested date will be given by the 2R2 website. Please make sure that the appointment date given to participant is the closest possible to this suggested date.

List of fields that require source documents in CRF-3:
M20-M24: Physical exam result, documented in the patient file
L2: DOCUMENTED Chest-x ray result. If chest-x ray is read by treating physician, the interpretation needs to be written in the patient file for it to be considered source document.
D15: DOCUMENTED microbiology results.
L14, L16, L18: DOCUMENTED microbiology results
L20-27, L31, L32: DOCUMENTED laboratory results

APPENDIX 3– PARTICIPANT ENROLLMENT LOG

All participants enrolled in the study should be logged on the PARTICIPANT ENROLLMENT LOG. This log should list study participants chronologically by study participant ID number. The following information should be collected:

Enrollment Date (DD/MMM/YYYY)	**Study Participant's ID**	**Protocol Version/date**	**Consent Version/date**	**Study Arm**	**Start Date**	**Stop Date**	**Status in Trial**	**AEs**

Instructions:

Date – format is DD/MMM/YYYY (i.e. 16/SEP/2019)
Study Participant ID – ID number provided by the website when the study participant is enrolled
Protocol version – version number and date of protocol when participant was enrolled
Study arm – study arm participant was randomized to (4R10 if randomized in control arm; 2 digit code provided by the website if randomized in one of the two experimental arms)
Start date – date participant started study drug
Stop date – date participant stopped study drug
Status in trial – status is participant in trial: (on study drug, follow-up post study drug, completed, withdrawn)
AEs – list the dates of adverse events experienced by study participant (NA – not applicable, or enter the date of the AE)

APPENDIX 4 – LIST OF PARTICIPANT IDENTIFICATION CODES

All participants enrolled in the study should be logged on the LIST OF PARTICIPANT IDENTIFICATION. This log should list study participants chronologically by study participant ID number. This list permits the identification of all participants who have taken part in the study. This list is confidential and should be safeguarded appropriately. If this list is kept as a computerized file it must be created in a file that is password protected. The following information should be collected:

Date	Study Participant ID	Last Name	First Name	Comments

Instructions:
Date – format is DD/MMM/YYYY (i.e. 18/SEP/2019), is date of enrollment.
Study Participant ID – ID number provided by the website when the study participant is enrolled
Last Name – Study participant's last name
First Name – Study participant's first name