Manual randomization

Title	**Manual randomization**
SOP Code	2R2 SOP03_17Mar2021
Effective Date	

1.0 Purpose(s)

The objective of this standard operating procedure (SOP) is to ensure appropriate randomization of study participants to one of three treatment regimens when the $2R^2$ website is momentarily not accessible for the randomization.

2.0 Scope: Persons/Areas affected

This SOP concerns the site principal 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)

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

5.0 Procedures

5.1. General information

5.1.1. All study participants must be randomized to either 4 months of 10mg/kg/day of rifampin or to 2 months of 20mg/kg/day of rifampin or to 2 months of 30mg/kg/day of rifampin.

5.1.2. If the web-based system in not accessible, study participants may be randomized manually to one of the three treatment regimens by using the randomization envelopes provided by the coordinating centre for this purpose. These envelopes contain: a) the duration of the study drug that the study participant will be randomized to and, b) in case of randomizations to 2 months high dose, the blind randomization code; in case of randomization to 4 months, the dose per day. The envelopes, provided to each site by coordinating center, have been pre-prepared and numbered, by the website programmer team, in sequential order – envelop 1, envelop 2 etc. to ensure the proper stratified block randomization process. **It is essential to maintain this sequence** when using these envelopes and store them in a safe, accessible location. **Note** that at each site the envelopes to use have different numbers (for example, in one site the envelopes can be 36, 37, 38, etc.; in another site they can be 49, 50, 51, 52, etc.). Please make sure that the coordinating centre is contacted if the randomization envelopes that have been provided run low.
Note: in Vietnam, there are 4 clinical sites where enrollment is taking place, but the randomization is done centrally for the whole Country, therefore for manual randomization there is only one center in charge of opening the envelopes in sequential order. The person (or persons) in charge of opening the envelopes, is(are) designated in the task delegation log, and has(have) to be reachable in real time by the research assistants at all Vietnam sites, who call them when a manual

randomization is needed. The person(s) in charge will open the envelop (following the numerical order of the envelops) and communicate the content to the site where enrolment is taking place. Site should receive the soonest possible a copy of the randomization page (scanned or in picture), to be printed and added to the participant file as proof of randomization.

5.2. Manual randomization procedures

5.2.1 Prior to randomizing a potential study participant, the INITIAL SCREENING FORM case report form 1 (CRF-1) must be filled out (printed on paper). Participant is judged eligible if they fulfill all inclusion criteria and none of the exclusion criteria. Please refer to **Appendix 1** for inclusion and exclusion criteria that need to be checked with CRF-1.

5.2.2 If participant is judged eligible after the CRF-1 has been completed, complete ELIGIBILITY AND CONSENT form, CRF-2, printed on paper. Please refer to **Appendix 2** for criteria to judge participant eligibility after the CRF-2 has been completed.

5.2.3 If participant is still judged to be eligible after the CRF-2 has been completed, the EVALUATION FORM (CRF-3) must be filled out (printed on paper). **Refer to Appendix 2 of SOP2 "Screening, recruitment and randomization" for essential data that needs to be collected in CRF-3.**

5.2.4 After completing all information needed in CRF-1, CRF-2 and CRF-3, if study participant is still eligible to participate, and is not a family member of an already randomized participant, open **the next available randomization envelope**. It is essential to open these envelopes in sequential order as this will maintain the stratified, block randomization. Note: once the envelop is open, it is important to staple the envelop and the paper randomization with the CRF-3 in the participant study folder.

5.2.5 The study participant will be randomized to the study duration and dose (or code) named on the paper contained with the randomization envelope. Record on the CRF-3 which study medication the participant has been randomized to and add the study participant to the Participant Enrollment Log (refer to "Screening, recruitment and randomization **SOP02**").

5.2.6 In the case where the study participant is a family member of an already randomized participant, the new participant should be allocated to the same regimen as the first member of that household (assuming that they have consented within 14 days of the randomization of the first member). In this situation, it is not necessary to use the randomization envelopes.

Note: for instructions regarding exclusion after randomization, refer to SOP2 "Screening, recruitment and randomization".

5.3. Data entry into website

5.3.1. As soon as the web-base system becomes available again, the information from the CRF-1, CRF-2 and CRF-3 must be transferred in the study website.

5.3.2. Please refer to "**SOP02**_Screening, recruitment and randomization" for instruction on how to enter the data of CRF-1, CRF-2 and CRF-3 which were already completed on paper, into the 2R2 website.

5.3.3. If at any point during the data entry into the 2R2 website a message of "non eligibility" appears, review the data entered into the website to ensure that no data entry errors

were made or that no essential information is missing. If the participant remains ineligible according to the website, contact the co-coordinating centre immediately for further instructions (the study participant may have to be withdrawn from the study). If the study participant is eligible for the study and no error message shows, submit the participant for randomization by clicking on “ready to randomize” button.

5.3.4. At this point, the randomization displayed by the website will have to be changed to correspond to the arm the participant has been already assigned to with the manual randomization. To do so: enter a note to file in the 2R2 website for this participant including the following information: the study participant’s identification number, the duration and dose (or code) of the study medication they were **manually randomized to,** the date in which randomization has been done, and the explanation that they were manually randomized and the website randomization has to be modified.

5.3.5. The co-coordinating centre will be automatically notified by the 2R2 website and the study medication assigned will be modified on the website. Once the requested “note to file” has been completed, it will show in green on the participants dashboard for (refer to “Management of study data” SOP).

Note: All completed paper CRFs must be kept in a secure cabinet.

6.0 References

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

MUHC SOP. SOP-CR-009_07 Subject Recruitment and Screening 01-Sept-2018

Appendix 1 – Inclusion and exclusion criteria that need to be checked with CRF1 during the manual randomization

Before a participant is randomized, you need to check that study participant meets **all of the inclusion** criteria and has **none of the exclusion** criteria. The first check will be done using CRF-1.

Inclusion criteria to check with CRF1 (CRF-1 initial Screening form) are:
1) Treatment of LTBI has been recommended, and the study participant has agreed to meet with the research personnel
2) The participant is over 10 years old
3) Participant has evidence of LTBI: this means that participant has to have either positive QTF or TST≥ 5mm. **Note**: date of TST ≥5 or positive QTF has to be collected in CRF1.

Exclusion criteria to check with CRF-1 (initial Screening form) are:
1) The study participant is a contact of a TB patient known to have TB resistant to RIF.
2) The study participant has a history of allergy/hypersensitivity to Rifampin, Rifabutin or Rifapentine.
3) The study participant is pregnant.
4) The study participant has Active TB.
5) The study participant is already started treatment for LTBI.
6) The study participant takes medications (including hormonal birth control medications) that the medical team judge not manageable with Rifampin and that participant does not want to change.
7) The study participant was already treated for TB disease or LTBI.
8) The study participant has AST or ALT 3 times or more the upper normal limit at baseline.

Appendix 2 – Eligibility criteria that need to be checked with CRF-2 during the manual randomization

If all checks required by CRF-1 are done and the potential participant is still deemed to be eligible, then the consent process can take place. CRF2 documents the result of the consent process.

In particular the following are checked and recorded in CRF-2:
1) Participant has to have signed consent form, if 18 years old or older. If participant is less than 18 years old: the legal guardian has to have signed consent form AND the child has to have provided signed (or verbally given) assent. **Note 1**: the age at which a minor can sign an inform consent may vary by jurisdictions, check with local REB which is the age at which consent can be signed and keep record of REB communication on this regard in the study master binder. **Note 2**: the date that the participant consented needs to be recorded in CRF-2.
2) If a participant is from the same household of other study participants, the first participant of that household cannot have been randomized more than 2 weeks prior to consent of the new participant. This is to avoid preferential enrolment in one arm, as all participants from the same households will be enrolled in the same arm.

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP03_25Nov2019	25 November 2019	NA (original version)
SOP03_17Mar2021		-added specifications for Vietnam (page 1-2)

		-added date of randomization to be reported in Note to file (page 3).