Title	**Enrollment and follow-up for participants with co-morbidities, specific populations and COVID-19**
SOP Code	2R2 SOP15_27Apr2022
Effective Date	

1.0 Purpose

The objective of this standard operating procedure (SOP) is to give additional information on enrolment and follow-up of participants with co-morbidities (including COVID-19) or for specific populations. Detailed information on enrolment are found in **SOP02** (Screening and randomization) and on follow-up in **SOP05** (Follow-up during treatment).

The SOP will ensure:

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

2.0 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 Definitions and abbreviations

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the Sponsor on each trial participant in a clinical research study.
Clinical Trial Coordinator: the site clinical trial coordinator, who, with the PI, supervises all trial operations at the site.

Clinical Trial Officer: The research assistant at the site, working in collaboration with CTC.
Coordinating centre: research staff involved in running the $2R^2$ study who are based at Research Institute of McGill University Health Centre (RI-MUHC)
COVID-19: disease caused by the strain of coronavirus SARS-CoV-2.
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Study Doctor: treating physician, who is in charge of clinical care of participants in this trial.

5.0 Procedures

General Information

This SOP describes considerations to take into account both at enrolment and during follow-up, for participants with co-morbidities, including COVID-19 or exposure to SARS-CoV-2, or for lactating mothers. Please refer to SOP02 for all investigations and documentation needed at enrolment and to SOP05 for completed description of procedures to use for follow-up during treatment and for reporting needed during the trial.

In general, if participants whit co-morbidities are enrolled, possible interactions with their concomitant medications have to be checked before starting treatment with study medications. Several online resources are freely available and can be helpful for assessment of drug interaction, as the three web sites below:

Medscape (https://reference.medscape.com/drug-interactionchecker)

University of Liverpool HIV Drug Interactions (https://www.hiv-druginteractions.org/checker)

HIV/HCV Drug Therapy Guide from Toronto (https://hivclinic.ca/wp-content/plugins/php/app.php)

Monitoring the effect of concomitant medications, and, if needed, dose adjustment of concomitant treatment during rifampin therapy, needs to be done during follow-up. Maximal effect of rifampin on concomitant medication is expected by about two weeks into treatment and to last up to 4 weeks after stopping treatment. Note: if dosing of concomitant medications are needed during treatment with rifampin, remind to ensure readjustment to previous dosage after treatment with rifampin is over.

5.1. Consideration for participant with diabetes mellitus

General information: Rifampin accelerates metabolism of many other drugs including antidiabetic drugs. Although the interactions start as soon as rifampin is taken, it usually takes about two weeks to have the full effect. So we recommend monitoring after two weeks - as described below. After rifampin is stopped the drug metabolism goes back to normal in about 3 weeks. So you must adjust drug dosage again about 2-3 weeks after stopping rifampin - generally back to the dosages taken before rifampin was started.

5.1.1. At enrollment: ask if participant has any immunosuppressive condition or therapy. If participant has co-morbidity with diabetes mellitus, report it in **CRF3** "Initial evaluation" (see **SOP02** for details on how to fill CRF3). Report also in **CRF3** the concomitant medication prescribed for diabetes and specify if there are interactions with rifampin and if these interactions can or cannot be managed. Participants with diabetes can be enrolled only if interaction of rifampin with their treatment are considered manageable by the study doctor.

Rifampin can accelerate the metabolism of several oral hypoglycemic agents, lowering their blood level. Examples of hypoglycemic medications which have clinically significant interactions with rifampin are, but are not limited to: tolbutamide, chlorpropamide, glyburide, glimepiride,

repaglinide (ATS, Nahid et al. CID 2016:63) and rosiglitazone (Rifadin® Monograph). Please consult a pharmacist or study-coordinating center if information on interactions with specific anti diabetic treatment is needed, before starting the treatment with rifampin.

5.1.2. During follow-up:
At 2 weeks: If participants are taking medications for diabetes with potential interaction with rifampin, measure glycemia to ensure it is controlled during the period in which participants is on treatment. Report the glycemia under "Other investigations" in CRF5 (Follow-up during treatment). If glycemia is not controlled, study doctor needs to revise the antidiabetic treatment, to ensure optimal glycemic control during rifampin treatment.

At 4 weeks, check with participants if new medications for diabetes have been prescribed, and check again their interactions with rifampin.

If therapeutic drug monitoring of medication taken for diabetes is required during treatment with rifampin: this should be performed and reported in **CRF5**.

5.1.3. At end of treatment:
If any adjustment of anti-diabetic medication had been done during treatment, re-adjust them to regular dosage after rifampin treatment is over. Please remind patients and other providers involved in the patient's care that effects of interactions with rifampin can last up to 3-4 weeks after treatment is over, therefore we recommend checking glycemia again after 2 weeks after treatment with rifampin if over.

5.2. Consideration for participants with hypertension

General information: Rifampin accelerates metabolism of many other drugs including several anti-hypertension medications. Although the interactions start as soon as rifampin is taken, it usually takes about two weeks to have the full effect. So we recommend monitoring after two weeks - as described below. After rifampin is stopped the drug metabolism goes back to normal in about 3 weeks. So you must adjust drug dosage again about 2-3 weeks after stopping rifampin - generally back to the dosages taken before rifampin was started.

5.2.1. At enrollment: ask if participant has any medical conditions and if they take prescription medications. If participant has hypertension, report it in **CRF3** "Initial evaluation" (see **SOP02** for details on how to fill CRF3) as well as all participant's anti-hypertensive medications taken. Make sure that treating team is aware of these medications participants takes and of their interactions with rifampin, if any. Specify in **CRF3** if there are interactions with rifampin and if these interactions can or cannot be managed. Participants with hypertension can be enrolled only if interaction of rifampin with their treatment are considered manageable by the study doctor.

Rifampin can lower the level of many anti-hypertensive medications, resulting in higher blood pressure (BP) in a person whose BP was under control before starting LTBI treatment. Examples of antihypertensive medications which have clinically significant interactions with rifampin are, but are not limited to: Calcium-channel blockers (as amlodipine, verapamil, diltiazem), beta-

blockers (as metoprolol), ACE inhibitors (as enalapril) and angiotensin receptor blockers (as losartan).
Please consult a pharmacist or study-coordinating center if information on interactions with specific antihypertensive treatment is needed, before starting the treatment with rifampin.

5.2.2. During follow-up:
A close monitoring of BP is necessary, to identify early if there is the need for dose adjustment of anti-hypertensive medications.
First follow-up, for BP, should be done around **2 weeks after rifampin started**, regardless of arm participant is randomized to (i.e. for participants in standard arm, a 2 weeks visit needs to be added to check BP and adjust treatment if needed). Report the BP under "Other investigations" in CRF5 (Follow-up during treatment). If BP is not controlled, study doctor needs to revise the antihypertensive treatment dose, to ensure participant can reach optimal pression control during rifampin treatment.
If antihypertensive treatment was modified, BP needs to be checked again after 2 weeks. New adjustments and checks may be needed, until you are sure BP is under control.

At each follow-up visit:
Report the situation relative to BP in session F12-F15 of **CRF5** (Follow-up during treatment).
Check with participants if new medications been prescribed, and in case, if they interact with rifampin.

5.2.3. At end of treatment:
If any adjustment of antihypertensive medication had been done during treatment, re-adjust them to regular dosage after rifampin treatment is over. Please remind patients and other providers involved in the patient's care that effects of interactions with rifampin can last up to 3-4 weeks after treatment is over, therefore we recommend checking BP again after 2 weeks after treatment with rifampin if over.

5.3. Consideration for participants with HIV co-infection

5.3.1. At enrolment: if participants HIV status is known, report it in CRF3 (Initial evaluation form).

For participants who are known to be HIV+: report CD4 and Viral load at enrollment, or the most recent CD4 and viral load participant has done before enrollment. Note: if participant is followed in another clinic/service for HIV infection, you can use the CD4 and viral load results that participant has from their HIV clinic.

Report antiretroviral therapy (ART) that participant is taking. Rifampin interacts with metabolism of several antiretroviral drugs (see **appendix 3B in SOP09** "Adverse event management"). Check with pharmacist or with coordinating center that the interactions with the antiretroviral therapy assumed by participant is manageable. Report in **CRF3** the antiretroviral therapy taken (at page 1, question D12) and if it this antiretroviral treatment is judged manageable with rifampin (at page 3, questions M14-15). Participants with HIV on ART can be enrolled only if interaction of rifampin with their ART are considered manageable by the study doctor.

5.3.2. During follow-up ask at every visit if there have been any changes with the antiretroviral medication and in case check for the interactions with the new medications. If changes occurred report them in **CRF5**.

5.3.3. At end of therapy: ask for the results of a viral load performed close to the date of end of treatment. If viral load is not routinely done, perform one at the day of end of treatment and report it on **CRF5**. This is to make sure that interactions with ART did not cause a failure of antiretroviral treatment.

5.3.4. For participants for whom the HIV status is not known: HIV testing should be proposed to participants who are close contacts of patient with active TB who have HIV and for whom the HIV status is not known. Results of the HIV test should be reported on **CRF3** (in "Laboratory" section). When communicating the results of HIV testing: provide counseling to participants. If HIV test is positive: refer participant to the HIV service available at your site. Participant will continue to be followed at the TB clinic for LTBI treatment but needs to be also evaluated at the HIV clinic for assessment and antiretroviral treatment. Please include the information on participant taking rifampin as LTBI treatment and the planned duration of treatment, when referring them to the HIV team. If in standard arm, you can specify the actual dose taken. If in high dose arm: please specify that the dose of rifampin taken is ether 1200 or 1800mg per day.

5.4. Consideration for participants who are lactating mothers

5.4.1. If a breastfeeding mother is treated with rifampin, the amount of rifampin that is excreted in breast milk is expected to equal 0.05% of the total daily-ingested dose of rifampin. If a mother is taking 600mg of rifampin daily, this would mean only 0.3mg excreted in breast milk per day. For a mother taking 3 times the standard dose, this would translate to 0.9mg per day. This means that the dose to which the newborn is exposed to is much less than the daily dose of rifampin recommended by WHO for newborns (which is 20mg/kg per day). Hence, even for the smallest newborn (2 kg), we do not anticipate any problems caused by the rifampin ingested in breast milk.

5.4.2. If the newborn needs to be placed on anti TB therapy or on anti LTBI therapy with rifampin, the dose taken by the newborn does not have to be adjusted since the amount of rifampin received in the breast milk is estimated to be either 0.3 mg/day (if mother is in standard dose arm) or between 0.6 and 0.9 mg, if mother is in one of the two high dose arms - meaning less than 1 mg in total.

5.5. Consideration for enrollment and follow-up of participants affected by COVID-19

5.5.1 Before enrollment

5.5.1.1 If potential participants are identified to be contacts of a SARS-CoV2 positive person, or are awaiting the result of a COVID-19 test: postpone their appointment until their

investigations for COVID-19 have been completed and they are considered not infectious for SARS-CoV-2, according to the most up to date local public health guidance;

5.5.1.2. If during screening and initial evaluation potential participants are diagnosed with COVID-19, they cannot be seen for screening of 2R2 until they are considered NOT to be infectious for SARS-CoV-2 according to the most up to date local public health guidance.

5.5.2 During treatment follow-up

Study participants, who are already enrolled in the trial, may become infected with SARS-CoV2.

Management differ depending if they require hospitalization for COVID-19 or not.

Participants who require hospitalization:

If participants require hospitalization because of COVID-19: they **must stop study medication** for the time they are hospitalized. If the interruption of the study treatment lasts for more than 48h, report it as an adverse event (Grade 3, but not related to study drug). After participant recovers from COVID-19, you can reassess with participant the possibility to restart study medication. See point 5.4.2.1. to 5.4.2.4 for follow-up. Remind that participant can be seen in person by research team only when they are considered NOT to be infectious for SARS-CoV-2, according to the most up to date local public health guidance.

NOTE: The occurrence of COVID-19 in a study participant is NOT considered related to the study nor to the study medication. If a study participant incurs medical costs related to the diagnosis and/or care of COVID-19 (including hospitalization), these will not be covered by the study.

Participants who do not require hospitalization

If participants do not require hospitalization because of COVID-19: treatment with study medication can be continued. Follow-up, laboratory tests, medication supplies and management of adverse events (AE) for these patients are as follows:

5.5.2.1. **Study follow-up**

Follow-up for participants who do not require hospitalization must be done at distance (i.e. by telephone) until participants are considered not infectious for SARS-CoV-2 according to the most up to date local public health guidance. The research team cannot meet the participants, while they are infectious for SARS-CoV2, in any setting (meaning: not at the clinic, nor in home visit, nor in other health facilities).

5.5.2.2. **Laboratory tests**

If a study participant is diagnosed to have COVID-19 after all the routine lab tests for follow-up have been done (i.e. after 4 weeks of follow-up) and there was not a specific need to repeat the lab test, they can complete the study follow-up by telephone (including the pill count) at the intervals previously planned per protocol (see SOP 05 on follow-up).

If a study participant is diagnosed to have COVID-19 before completing all the protocol required laboratory tests (i.e. before week 4): follow the participants by phone every week asking about symptoms (i.e. call them once a week). If the participant is feeling well, it is NOT necessary to perform the protocol required laboratory tests, as this will constitute an increased risk of transmission of the disease. Once the participants are considered NOT infectious for SARS-CoV-2 (according to the most up to date local public health guidance), if they are still on study treatment, or less than 15 days since treatment ended, then perform the protocol-required laboratory tests of follow-up that were not previously done, and report them in CRF5.

5.5.2.3. **Study medications**

If study participant diagnosed to have COVID-19 did not received all the supply of study medications (for example, a participant, in any arm, is diagnosed before week 4; OR a participant in standard arm is diagnosed after week 4 but before week 8), organize the delivery of study medication supply so that no one comes in contact with the participant (i.e. delivery is done at home, but without entering the house, keeping at least at 2 meters of distance).

5.5.2.4. **Adverse events**

If participants with active and infectious COVID-19 are suspected to have an adverse event, and the symptoms reported are serious enough to stop the study medication, then you MUST ensure management of the adverse event is conducted as required by the study protocol (for details see SOP09 on AE reporting and management). This means that research team MUST ensure participants have access to the medical examinations and tests required (as listed in CRF9). This may mean referral of these participants to health care centers which are equipped to handle COVID-19 patients. If referred elsewhere, then be sure to collect, by phone or email, all information needed to complete the adverse event report.

5.5.3 During post-treatment treatment follow-up

If during follow-up post-treatment participants report symptoms which could be either due to COVID-19 or to active TB, before starting the investigations for active TB, direct them to have a test for SARS-CoV-2. Call them back in 2-3 days to know the result, and, if negative, proceed with investigations for TB. If they are diagnosed with COVID-19: follow them by phone, until they are not infectious anymore with SARS-CoV-2, at that point, if symptoms indicative of TB are still present, proceed with investigations for active TB.

6.0 References

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7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP15_06Jul2020	06 July 2020	NA (original version)
SOP15_15Oct2020	30 Oct 2020	Added a section (5.4) on comorbidity with COVID-19
SOP15_02Jun2021		Added section 5.2. on hypertension (page 3).
SOP15_27Apr2022		Added resources for checking interactions (page 2); reference (Canadian TB Standards 2022)- page 8.