Title	**Study participant follow-up during treatment**
SOP Code	2R2 SOP05_13Oct2021
Effective Date	

1.0 Purpose

The objective of this standard operating procedure (SOP) is to ensure appropriate follow-up of study participants while on treatment.
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 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

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

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.

COVID-19: Coronavirus Disease caused by SARS-cov-2 virus.

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

PK: Pharmacokinetic study, which will be conducted in 2R2

5.0 Procedures

5.1. Follow-up of study participant during treatment

General Information

The study will ascertain treatment safety by measuring treatment completion and adverse events possibly or probably associated with the study drug. Follow-up will be essential to collect both these primary outcomes and to ensure participants' safety and it will be guided by these three principles**:**

1. Action done in follow up by research teams should **minimize** influence on treatment completion (which is one primary outcome of the study).
2. Research teams **MUST not** generate a bias by influencing outcome in different ways for high dose and standard dose arms.
3. Safety of participants is a priority; and it is the other primary outcome of the study.

Follow-up will be for the most possible in line with standard practice, and conducted by the primary treating physicians, nurses and other TB clinic staff. Scheduling of follow-up visits will be different for the high dose and standard dose arms, but the total number is the same. Follow-up during treatment will be mainly handled by the medical team. If an adverse event or active TB are suspected, then the research staff become **very closely involved** - to ensure that proper investigation and management are conducted and to conduct the reporting in a timely fashion. In study sites where participants are not generally treated for latent tuberculosis, the research team will have a more active role in the follow-up during treatment.

Note: follow-up visits are in-person visits at the clinic. Exceptionally, during COVID-19 related measures, follow-up visits can be done by phone. During these virtual visits all data should be collected as planned. Dosage count will be asked to participant (see part C at 5.1.1. below). **Blood draws and drugs dispensing need to be maintained during COVID-19 related measures, even when visits are done virtually.**

Data collected during follow-up are reported on CRF5. Please refer to Appendix 1, for detailed information on how to fill CRF5.

5.1.1. At each visit:

A) The study participant should be met and asked how they are doing. It is important to check if there are symptoms of active TB as well as inquiring about any symptoms that could be related to adverse reactions to study medications. It is important to ask if any new symptoms have appeared as well as for intercurrent problems. If there are any new symptoms suggestive of medication side effects or of active TB, the treating team should perform a physical exam, as appropriate. If the symptoms have resolved (not present on day of visit) it is a matter of judgement whether to record this. If the symptoms were disruptive to the patient, they may be recorded. If further investigations are ordered, these should be recorded. Results from inquiry

about symptoms, physical exam and any lab testing, should be reported in the CRF-5 follow-up during treatment (in the "CURRENT SYMPTOMS" section). **If an adverse event is suspected, the participant should be followed until resolution of the event.** If the study drug is stopped permanently, or suspended for 48 hours or more, an initial adverse event report needs to be completed. Please refer to **SOP09** "AE reporting and management" for instruction on AE reporting.

B) Participant's **address and contact information** should be verified and reported in CRF-4 if changed since previous visit.

C) **Dosage count** of remaining pills needs to be done, using the bottle of medication brought back by participants. It is important to remind participant to bring back their bottles at each visit, especially the last visit at the end of treatment. If participants forget to bring the bottle, ask them to estimate how many pills they think are remaining in the bottle. They should then be strongly encouraged to bring the bottle to the next visit.
Before doing the pill count, verify that the bottle belongs to the correct participant, by verifying the name of the participant in the bottle label.
After the pill count, give back the bottle with the remaining pills to participant.
Note: for all participants who are randomized in the $4R_{10}$ arm, count the number of "daily doses", for participants who are randomized to $2R_{20}$ or $2R_{30}$ count the number of pills.

Ask the participant to bring back the bottles, even if empty. They should also be reminded to bring back bottles they forgot to bring on previous visits. All bottles used to dispense study medications must be returned after use to the site pharmacy that dispensed the medications. The pharmacy will be in charge of keeping the log of the bottles; and of final disposition of used bottles and of any remaining study medication at the end of treatment. Please refer to **SOP04** "Dispensing and blinding of study medications" for more information.

When follow-up is done at-distance (i.e. by phone), for COVID-19 related measures, ask the participant to count during the call how many pills are remaining in the bottle. Report the pills counted by participants are home, as "estimated" pills count in the CRF5. If the call is a video-call, and participant counts the pills in front of the camera, answer Yes to question *"G15. Did study participant bring their medication bottle?"* and report the pills as "remaining in the bottle". Ask participants to bring back the bottles in the next in person appointment, if there is one, otherwise to give back the empty bottles to the courier, if study medications are delivered at home, and if there is a next delivery. If neither is possible: 1) if at the end of treatment bottles are empty, ask participants to dispose them; 2) If, for any reasons, bottles still contain remaining medications once participant has permanently stopped study treatment (as after an AE or after participant's decision to stop): set up a system to pick back the remaining medications- as use of a courier or doing an home visit. NOTE: for Canadian sites: for participants in standard arm, ask participants to dispose the remaining rifampin at the pharmacy that dispensed it (either hospital pharmacy or local pharmacy); for participants in high dose arms, collect back the remaining pills.

D) Pills for the next period (until the next scheduled visit) must be dispensed. **Please write the total number of new pills dispensed at the visit** (i.e. if participant brings back 6 pills and you dispense 90 new pills **write 90 pills**).
Note: For participants who are randomized in the $2R_{20}$ or $2R_{30}$ arm, write both the number of pills dispensed and the number "daily doses".
For participants who are randomized to $4R_{10}$ count the number "daily doses" (for example if a participant is taking 1 pill of 150mg and 1 pill of 300mg rifampin per day, and is given 33 pills of 150mg and 33 pills of 300mg, count 33 daily doses of rifampin).
For all patients, write also the number of days for which the participants will have a supply of study medications. Please make sure that date of next appointment is taken so that participant has enough pills to cover a few days (about 3 days) extra in case appointment is missed. For example, if participant is given pills for 18 days, make sure appointment is in about 15 days.

E) If **monitoring of drug levels** for concomitant medication is required, research staff must ensure that the appropriate tests are done. Otherwise, all other information should be obtained from the participant's medical record.

5.1.2. At the first visit after randomization

Participants should start treatment as soon as possible after randomization (ideally next 1-2 days). Therefore, at the first visit after randomization, the date on which participant started the treatment has to be reported in CRF5. See point 5.3.1 below for more information.
Note: the first week after randomization should be the two weeks visit for participants in high dose arms and the four weeks visit for participants in standard arm.

5.1.3. At 2 weeks after randomization:

- for participants in the two high dose arms

For participants in high dose arms, there should be a visit, with blood draw for liver function tests and complete blood count. Results of all these tests are reported on the CRF-5 "Follow-up during treatment" (see section 5.4 for instructions on how to fill this form). Please refer to SOP09 (Adverse events) for more information on interpretation of lab results.

- for participants in standard dose arm

At 2 weeks after randomization there is not visit for participants in standard dose arm, but research assistants will call participants in standard dose arm to check how they are. If they are fine, and there is no symptom, this is NOT considered an official visit (therefore, no need to report the call in the CRF5). If any problems are found during the call, then this telephone visit is reported in CRF5, and the providing medical team is notified. Note: the time and day of this call should be scheduled with participants at enrolment.

5.1.4. At 4 weeks after randomization:

- for all participants (i.e. participants in the three arms).

At 4 weeks after randomization there is a visit for participants in all arms, in which blood draw for liver function tests, complete blood count, creatinine and BUN needs to be done. Results of all these tests are reported on the CRF-5 "Follow-up during treatment" (see section 5.4 for

instructions on how to fill this form). At week 4 visit, two blood samples are also taken for population pharmacokinetic sub-study therefore research assistant calls participants 5 days and 1 days prior to the 4 weeks visit, to remind PK procedures (see **SOP11**_PK "Population pharmacokinetic study").
Note: keep a log of calls done for each participant, to be sure all needed calls have been made.

Note: if PK study is on hold for specific reasons (as during COVID-19 related measures), PK sampling is not done, neither are the calls at 5 days prior and 1 day prior to the visit.

5.2 Visits schedule

5.2.1. Study participants who were randomized to $2R_{20}$ and $2R_{30}$ should come for follow-up visits at 2, 4 and 8 weeks after randomization (meaning 2,4, and 8 after they have started their treatment). Those who were randomized to $4R_{10}$ should come for follow-up visits at 4, 8 and 16 weeks after randomization (meaning 4,8 and 16 weeks after they have started their treatment). The timing of these visits is an approximation, but given the short duration of treatment for $2R_{20}$ and $2R_{30}$, there is not much possibility for schedule changes for participants randomized to these arms. More flexibility is possible for the $4R_{10}$ regimen (see table 1 below).
The following table provides acceptable time frames for the required follow-up visits. If the treating team wants to see the study participant more often (i.e. more frequent follow-ups) this is not a problem. For all participants: the last visit should always be within 2 weeks of the projected end of treatment (to allow for symptoms screening during all the period in which participant is on treatment; to allow for the last pill count).

Table 1.Time frames for required follow-up visits. All intervals are from the date of randomization - assuming participant will start study treatment right away.

Arm	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4*	Additional follow-up
$2R_{20}$ or $2R_{30}$					
Preferred	**2 weeks**	**4 weeks**	**8 weeks**		as needed
Possible alternatives	+/-3 days	+/- 3 days	+/- 1 week		
$4R_{10}$					
Preferred	**4 weeks**	**8 weeks**	**16 weeks**		as needed
Possible alternatives	+/- 1 week	+/- 1 week	+/- 2 weeks		
Possible alternatives	4 weeks	8 weeks	12 weeks	16 weeks	as needed
	2 weeks	4 weeks	8-10 weeks	16 weeks	as needed
	4 weeks	8 weeks	14-15 weeks		as needed

*__Note__: A 4th visit is not systematically required per protocol, but it is necessary if a participant has been seen already 3 times, per decision of the treating team, and the last visit was more than 2 weeks prior to end of treatment (as for example at weeks w4, w8, w12).

Special situations for visit scheduling:

Situation #1. If participants delay the start of treatment by more than 4 days after randomization, base the date of the subsequent follow-up appointments on the date of start of the treatment. Please note that, in this case, the dates of appointments will be different from the suggested dates generated by the website (as these are based on date of randomization).

Situation #2. For study participants who do not complete their treatment within the allowed time per protocol (i.e. 144 days for $4R_{10}$ and 72 for $4R_{20}$ or $4R_{30}$) additional follow-up visits should be scheduled, after discussion with the treating team.

Each site will have to develop a system to manage their follow-ups. If required, support from the coordinating center will be provided.

5.2.2. In conformity with principle 4.12 of the ICH E6, if the study is abandoned or terminated prematurely for any reason, the Principal Investigator should inform the participants taking part in the study promptly and ensure that suitable treatment and follow-up are provided to them.

5.2.3. Participants may not come to a scheduled follow-up visit (**no-shows**). See detailed information on no-show in section 5.3 below.

5.2.4 Participants who wish to stop the study medication (or never start) should be encouraged to take it, but **the decision to take (start or continue) the study treatment is the participants'**. This means they must be allowed not to take treatment, or to stop it, if that is their wish. However, it is even more important to continue to follow the participant for active TB (since they are at greater risk than if they finish the study treatment). It is important to advise them of the need for continued follow up in the study, to alert them about symptoms of TB that may arise, and inform what to do if such symptoms occur. Information regarding the end of treatment must be recorded in End of Treatment form (CRF-6) (see **SOP06**-"End of Treatment" for instructions). Once participants permanently stop the study drug (for any reason), the post-treatment follow up will start (see **SOP07**-"Post treatment follow-up" for instructions).

5.2.5. It is imperative that patients are not 'lost to follow-up' while on study treatment. **Every effort must be made not to lose all contact with participants during treatment phase** - for safety and ethical reasons. At enrollment documentation should include multiple possible ways to contact the participant (including emails, Facebook, WhatsApp, etc). The names and phone numbers for at least two other contact persons should also be collected at the time of initial enrolment. This is part of the essential documents collected in CRF-4.

5.2.6. It sometimes happens that a participant no longer wants to participate in the study and wants to completely **withdraw**. Note that this is a totally different situation from the participant wanting to stop the study drug, which is quite frequent, and should be allowed (see section 5.2.4 above). When a participant withdraws from a study, this usually indicates that the consent process was inadequate (meaning the participant did not really understand what the study involved), or a conflict has arisen with study staff. Naturally

this situation is to be prevented if at all possible, but if the participant withdraws, they should be informed where and how alternative treatments can be obtained. As well, the study coordinating centre must be informed of each withdrawal and the reasons for the withdrawal - as soon as possible. All follow-up with this person is stopped. They should be asked whether we can use their study data up to the time of withdrawal.

5.3. Procedures for handling of no-shows

5.3.1. Definitions and general principles:

In this study **a "no-show" is defined as** a participant who does not show-up at one appointment, without having taken the initiative to communicate the impossibility to attend the visit beforehand (for example: a 2-week visit is scheduled for Tuesday 24th, on Monday 23rd participant calls the clinic to inform they had an impediment to attend the visit and ask to change the date to Wednesday 25th: this IS NOT a case of no-show. If the same participant did just skip the appointment without asking to postpone it, it would be considered a no-show).

In case of visits planned to be done remotely, because of COVID-19 related measures, **a "no-show" is defined as:**
-for a visit of 2 weeks (for participants in high dose arms) or a visit of 4 weeks (for participants in all arms): there is no blood test done and/or cannot reach participant by phone at the scheduled (and agreed) time.
- for a visit at weeks 8 or 16 (for participants in all arms): it was not possible to reach participants by phone at the scheduled (and agreed) time.

Considering the follow-up principles (listed in 5.1.) and the schedule of follow up (in 5.2.) there are two types of actions to be taken when participants do not come for their scheduled treatment phase follow-up appointments: 1) Actions to ensure safety; and 2) Actions for routine follow-up.

In all sites, actions to ensure safety are performed by research staff (or research staff ensure the actions are completed). Routine follow-up actions are undertaken by the usual treating team.

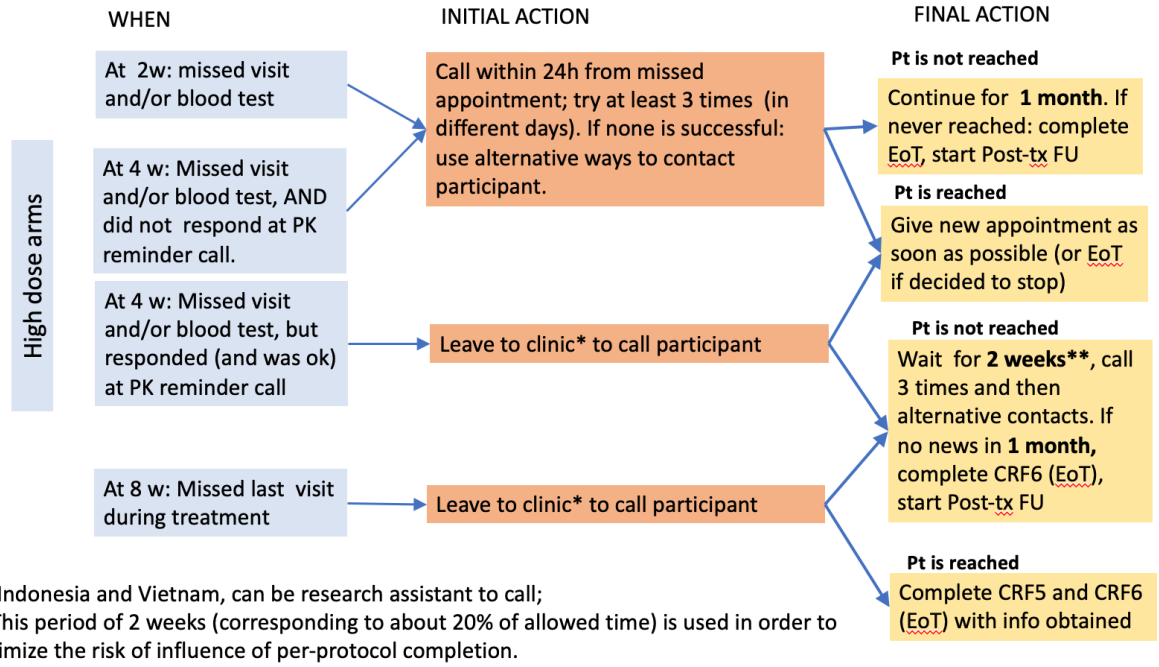
In sites were LTBI is managed by treating teams independently from the study (as in Canadian sites) this distinction is easy. In sites where the research staff may also be the routine care providers for LTBI management, as in Indonesia and Vietnam, the sites must develop a site-specific SOP for 'Routine actions for no-show for treatment phase appointments". This should be based on what is considered feasible and acceptable by the TB program ***and should not include more interventions than what is done now, routinely, for no-show during treatment phase follow-up of active TB patients***.

5.3.2. Instructions for actions to ensure safety and actions for routine follow-up in case of no-show.

1. At 2 weeks after treatment start:
    a. **If participants in high dose arms** do not show up at the 2 weeks visit, which includes a blood test for safety, research assistants must ensure that participant is called within 24h from the missed appointment (this is an action to ensure safety) (Figure 1)
    Notes:
    1) in Canadian sites the call can be made by the clinic staff, if they are the ones usually following up on missed appointments at the clinic. However, the research assistant should call, if it is not possible for the clinic staff to do the call within 24h.
    2) in Indonesia and Vietnam: the person in charge to call can be a member the research team.
    3) At all sites: if after at least 3 attempts to call participants (done at different times and in different days), participant still cannot be reached use alternative ways to contact (i.e. email, alternative contact, etc). Once participant is reached: a new appointment is given as soon as possible (or fill an End of Treatment form, if participant has decided to stop treatment). If participant is not reached, research assistant will try to contact him/her for one month and then consider participant has stopped treatment, fill an End of Treatment form (CRF6) and start the post-treatment follow-up. The Date of last dose (T4) will be the date of last visit to which participant attended. Report the attempts to contact participants in comment (T5).

    b. If **participants in standard dose arm** cannot be reached by phone by research assistants (who does the call at 2 weeks to check how they are), this is not considered a no-show (as there is no official visit at 2 weeks for standard arm), therefore no action is required at this time.

Figure 1. Procedures for participants in high dose arms



*In Indonesia and Vietnam, can be research assistant to call;
** This period of 2 weeks (corresponding to about 20% of allowed time) is used in order to minimize the risk of influence of per-protocol completion.
Abbreviations: **EoT**: End of Treatment; **FU**: follow-up; **pt**: Participant ; **w**: weeks.

2. At 4 weeks after treatment starts:

All participants (i.e. participants in high dose arms and **in standard dose arm)** have a visit which includes blood test (for safety) and PK sampling. As before this visit, research assistants call participants 5 days prior to the visit and 1 day prior to the visit to remind instructions for PK (see SOP11 "Population PK"), instructions for no-show are as follows (Figures 1 and 2):

1) If research assistant cannot reach participants 5 day prior to the visit, she/he should keep trying to reach the participant until either participant is reached by call or come to the 4 weeks appointment. If participant cannot be reached and does not come to the 4 weeks appointment, research assistant tries to call alternative numbers as well. If participant is reached a new appointment is given as soon as possible (or fill an End of Treatment form, if participant has decided to stop treatment). If participant is not reached, research assistant will try to contact him/her for one month and then consider participant has stopped treatment, fill an End of Treatment form and start the post-treatment follow-up. The Date of last dose will be the date of last visit to which participant attended. Report the attempts to contact participants in comment (T5).

2) If research assistant reaches the participant by telephone **5 day prior to the visit** AND participant reports symptoms at that time, a CRF5 (follow-up form) must be completed and clinic staff notified, so that visit or test can be arranged as needed;

3) If research assistant reaches the participant by telephone **5 day prior to the visit** AND, participant reports NO symptoms at that time and then (despite reminder of visit and PK procedure) does not show up at the visit, research assistant will: - **in Canadian sites** leave

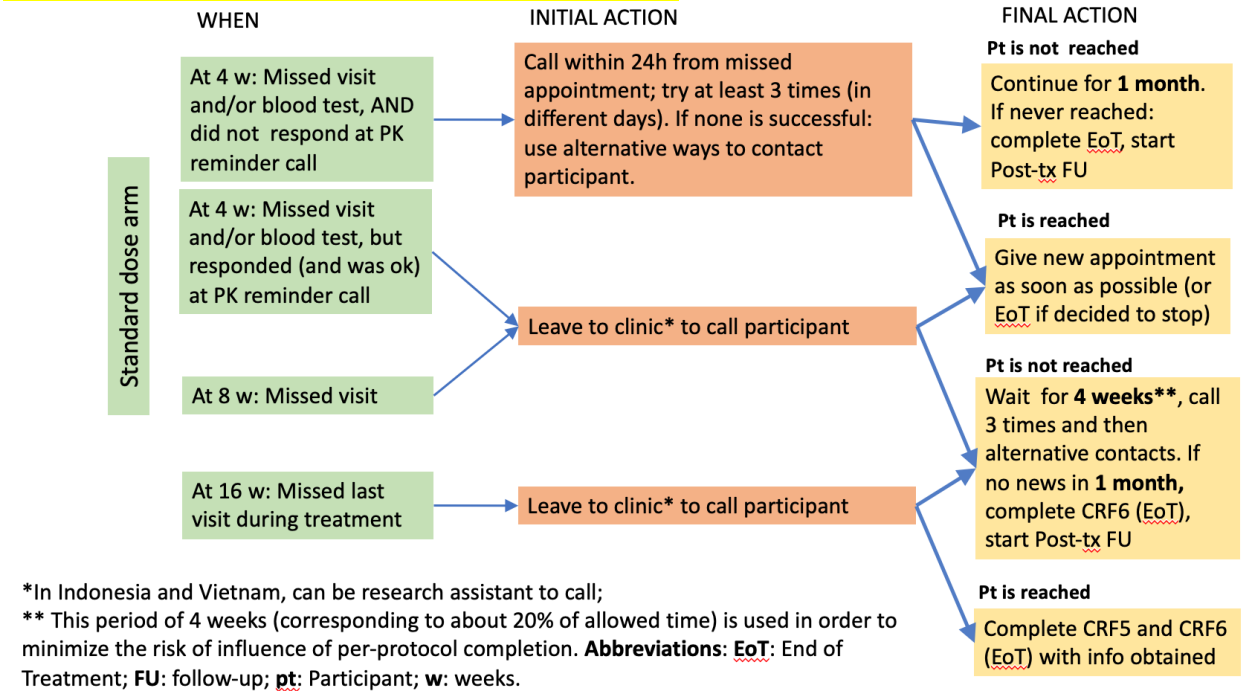
it up to the clinic staff to follow-up the no-show as per clinic routine procedure (without interference). **In Indonesia and Vietnam**: the person in charge to call can be a member the research team.

At all sites: if participant is reached, a new appointment should be given as soon as possible (or fill an End of Treatment form, in case participants decides to permanently stop study medication). If participant cannot be reached, the research assistant will wait until 2 weeks* after missed appointment for high dose and until 4 weeks* after missed appointment for standard dose and then call participant. If after at least 3 attempts to call participants (done at different times and in different days), participant still cannot be reached, use alternative ways to contact participant. If after one month, participant is still not reached, fill an End of treatment form and start post-treatment follow-up. The Date of last dose will be the date of last visit to which participant attended. Report the attempts to contact participants in comment (T5).

* This period of delay of 2 weeks for high dose or 4 weeks for standard dose (corresponding to about 20% of allowed time) is used to minimize the risk of influence of per-protocol completion.

Reminder: phone calls at 5 and 1 days prior to the PK visit, are recorded in a log (develop by site), to keep track of calls made.

Figure 2. Procedures for participants in standard dose arm



*In Indonesia and Vietnam, can be research assistant to call;
** This period of 4 weeks (corresponding to about 20% of allowed time) is used in order to minimize the risk of influence of per-protocol completion. **Abbreviations**: **EoT**: End of Treatment; **FU**: follow-up; **pt**: Participant; **w**: weeks.

3. At 8 weeks after treatment starts:

For participants in standard arm: at week 8 participants in standard arm are still on treatment. If participants in standard arm do not show up at this visit (Figure 2):

1) in Canadian sites research assistant will leave it up to the clinic to follow-up the no-show as per usual clinic routine procedure.
2) in Indonesia and Vietnam: the person in charge to call can be a member the research team.

In all sites: If participant can be reached, a new appointment should be given as soon as possible (or fill an End of Treatment form, if participant has decided to stop treatment). If participant cannot be reached, research assistant will wait for 4 weeks* and then contact participants and if no answer after at least 3 attempts (done at different times and in different days), contact alternative numbers. If after one month, participant is still not reached, fill an End of treatment form (CRF6) and start post-treatment follow-up. The Date of last dose will be the date of last visit to which participant attended. Report the attempts to contact participants in comment (T5).

* This period of delay of 4 weeks before starting to call (corresponding to about 20% of allowed time) is used in order to minimize the risk of influence of per-protocol completion.

4. At 8 weeks after treatment starts **for participants in high dose arms** and at 16 weeks after treatment starts **for participants in standard dose arm (Figures 1 and 2):**
This is the last visit during treatment If participants do not show up at this visit:
1) in Canadian sites research assistant will leave it up to the clinic to follow-up the no-show as per usual clinic routine procedure (without interference). If there is no procedure in place at the TB clinic for calls at the last visit during treatment, research assistant will call participant 3 times (in different days and time). If able to reach participant: write information for follow-up in CRF5 and for End of Treatment in CRF6.
In Indonesia and Vietnam: the person in charge to call can be a member the research team.

In All sites: If unable to reach participant after a missed last visit: wait 2 weeks* after missed appointment for high dose arms and 4 weeks* after missed appointment for standard arm, then try to reach participant. If after at least 3 attempts to call participants, done at different times and in different days, participant still cannot be reached, use alternative ways to contact participant). If after one month of trying, participant could still not be reached and no information on participant could be obtained, we consider as a permanent discontinuation of treatment. Fill an End of Treatment form (CRF6), report the attempts in comment (T5) and report "patient decision" as reason to stop. The Date of Last dose (T4), will be the date of the last appointment to which participant attended. Participant is now in post-treatment follow-up.

* This period of delay of 2 weeks for high dose or 4 weeks for standard dose (corresponding to about 20% of allowed time) is used to minimize the risk of influence of per-protocol completion.

Note for Canadian sites: each TB clinic has its own protocol for handling no-shows. The protocol in place for reaching patients who miss appointments at the clinic should be reviewed carefully with the clinic manager and documented. This written protocol must be reviewed by the site PI and coordinating center. If they feel that the currently used protocol for handling missing appointments is not adequate for follow-up in this trial, then the site PI should discuss with clinic manager and treating team, about implementing added measures in a 'missed appointment' protocol. Once established, this protocol should be followed carefully and applied equally to all study participants. An example of a 'missed appointment' protocol is as follows:

"Participants who miss a treatment phase follow-up visit should be contacted later the same day, or, at latest, the next working day, to re-schedule their appointment as soon as possible. At the same time, they can be asked if they have any new symptoms or problems. If the participant cannot be reached by phone, then a second and third attempt to contact them by phone should be made within the next 4 working days. If it is impossible to reach the participant by phone, then after one week a letter should be sent to the participant, giving a date for a next appointment."

5.4. Data collection for follow-up of study participant during treatment

General information

The following procedures are specific to the collection of participant information to enable appropriate follow-up during the treatment phase of the study. A worksheet has been created for this component of the research study – ROUTINE FOLLOW-UP VISIT DURING TREATMENT FORM (CRF-5).

If a study participant does not come for the visit, there are three possible circumstances for partial follow-up:

1) Participant was reached by phone: The treating team or research team spoke to participant by phone but did not see them. Questions about current symptoms can be asked by phone. The sections "General Information", "Current symptoms and physical exam", and "Other medications", "Action regarding study medication" can be completed, at least in part, but sections on "Adherence to treatment" and "Investigations" will not be completed. Participant should be rescheduled to come back to clinic as soon as possible.

Note: if the visit is done by phone because of COVID-19 related measures, complete all the parts of the CRF5, using information from e-chart when needed (for Investigations, for example). For Adherence, see part C of 5.1.1. Specify in "Comment G5" of CRF5 that the reason for having the visit done by phone was "COVID-19 related measures"

2) Participant seen during a home visit: All parts of the CRF5, except Investigations, can be completed. Pill counts can be done, and pills dispensed. Participant can come to the next study scheduled appointment (unless laboratory testing is needed earlier).

3) Participant sent another person to get study medication: Participant was not seen but sent someone else (family member) to collect study medication. In this case fill the section regarding

study medication and drugs dispensed. Ask the person about symptoms and report them in the CRF5. Participant should be rescheduled to come to clinic as soon as possible.

In all three situations –except if it is a virtual visit due to COVID-19 related measures- the CRF-5 should be completed partially, and these alternate methods of contact, plus reasons for not coming to the clinic, specified in the "General information" section of CRF5.
In case of virtual visit due to COVID-19 related measures, complete all the CRF5 and specify the reason as "COVID-19 measures"

5.4.1. Date treatment started: this information is provided only at the time of the 1st follow-up visit. If at the time of this 1st follow-up visit the study participant has not yet started treatment but says they will start: leave this blank, you will add the date at the time of a subsequent follow-up visit, ONLY when you know the date the participant started. If participant decides that they will never start (i.e. refuses treatment), leave this blank and complete the End of Treatment form CRF-6.
If the study participant never came back to any follow-up visits, the research staff needs to verify whether they have at least taken 1 dose. In these cases, this information should be written in the End of treatment form (CRF-6) and not in CRF5. For unused medications: see section 5.1.1. part C.

5.4.2 Symptoms, Physical exam.
If participants has any symptoms that could be due to side effect of study medication or to TB, a physical examination must be done and, if deemed necessary, the appropriate laboratory tests. In case symptoms, exam or laboratory tests suggest this could be an adverse event, an adverse event report (CRF-9) must be completed and entered in the 2R2 website. This will alert the coordinating center who will assist in preparing the report. Participants have to be followed until adverse event is resolved (see instruction for adverse event reporting in **SOP09**).

5.4.3. Routine laboratory test at visit of week 2 and 4.
If routine tests done at weeks 2 or 4 are abnormal, results must be discussed with treating team and plan for a follow-up must be done, which may include repeating the test, stopping the drug, and reporting an adverse event, depending on the test result and on participants condition. See SOP09 on Adverse event for more information.

5.4.4. Concomitant medications.
At each visit, report ANY new concomitant medication the participant is taking, including medication over the counter. Always try to use the generic term, if possible. Please write down the name of the medications, and the ingredients, or, if this is not available, write what the drug is used for (for example" 'cold remedy" or 'for upset stomach" or "vitamins").
If study participant starts taking any new medications that may have clinically important interactions with the study drug and the treating team believes these are not manageable, the participant should be proposed alternative treatment, if possible, and moved into the follow-up post treatment phase of the study. In this case an adverse event form (CRF-9) and an end of treatment form (CRF-6) must be completed.

5.4.5. Action regarding study medication:
For participants randomized to 2 months high dose rifampin, the last visit during treatment has to be done close to 8 weeks after treatment starts.
For participants randomized to 4 months of standard dose rifampin ($4R_{10}$), the last visit during treatment could happen, instead of week 16, also at week 14 or 15 (therefore before the treatment is completed). In these cases, in which participants are still taking study medication, choose option *"Study medication continued as per protocol at same dose"* and do not complete and End of treatment (CRF-6) yet, as exact date of stop is not yet known. Call the participant just after the date the treatment is supposed to stop (this call will be recorded in a CRF-5, as "participant was reached by phone" type of encounter) and ask the date of the last dose intake. With this information complete the End of treatment form (refer to SOP06 "End of treatment").

If study participants interrupt their treatment and then are ready to resume treatment (and the treating team is convinced that the study participant will actually complete treatment), simply carry on with the remaining doses regardless of the length of the interruption was or how long the study participant was on treatment prior to the interruption.

5.4.6 Source documents
The following source documents are required to back up information collected in CRF5 and need to be kept with paper version of CRF-5, after nominal information has been deleted.

- Laboratory results (for the results reported in CRF5);

Note that if physical exam is done and reported in CRF5, must be documented in patient file.

5.4 Data entry into website

5.4.1. The ROUTINE FOLLOW-UP VISIT DURING TREATMENT FORM (CRF-5) must be filled out for each study participant at each follow-up visit. The CRF-5 is divided in 4 sections: "General information", "Symptoms and physical exam", "Investigations during follow-up" and "Treatment plan". (See section 5.4, for details on data to be collected).

5.4.2. The follow-up information must be entered into the study website in order for it to be available to the Coordinating Centre.

5.4.3. Log on to the website (https://2r2.ltb.cred.ca) and go to "Add/Select records", select the participant for whom you want to enter a follow-up form and then choose "follow-up during treatment" among the options appearing under the participant selection section. (Note – after 20 minutes of inactivity users will be automatically logged off of the website). If unable to log on to the site, the Coordinating centre should be notified and the information should be entered into the website when it becomes available.

5.4.4. Enter the follow-up information into the website and at the end of each section click on the "Save/go to next page" button at the bottom of the screen. The data will be saved

and can be modified as required. Note: each follow-up visit form is classified and stored in the website by the visit date.

5.4.5. At any point during data entry you may exit this section by clicking on the menu on the left of the screen or "home" key. It is advisable to always click on the "save/stay on page" key prior to this in order to save any data that has been entered or modified.

5.4.6 To return to the follow-up information to complete the data entry or to modify previously entered data, choose the participant's study ID number (Add/select record) and then click on "Select participant", choose the appropriate date of the visit (Select which visit you want to update) and then click on "Select visit" and then on the section you want to update ("General information", or "Symptoms and physical exam", etc). Enter or modify the appropriate information and click on the "save" button at the bottom of the screen.

5.4.7. Refer to the SOP20 "User manual for study website" for detailed explanation on how to fill follow-up for in the website and on the final approval by coordinating center.

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 RI-MUHC ADDENDUM_Subject Recruitment and Screening_01Sep18 - Research Institute of the McGill University Health Centre

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP05_25Nov2019	25 November 2019	NA (original version)
SOP05_06Jul2020	06 July 2020	- addition of blood test at 2 weeks for high doses arms (sections 5.1.2-5.1.4. and 5.3.3) - specifications added re data entry (section 5.4)
SOP05_03Oct2021	__/___/ 2021	- More details on Follow-up principles (page2); - Virtual follow-up procedures in case of COVID-19 related measures (page 3, 12-13); -Procedures to recuperate unused study medications (page 3). - Calls at 2 weeks follow-up added for participants in standard arms (page 4); - Procedures for no-shows in all arms (pages 7-10) ;

Appendix 1: Instructions to fill in CRF5

Instructions appears in *italic*.

G0. Research staff completing the form_____

Complete this in the paper format of CRF5, when entering the information in the website this response will appear automatically as it is linked to the user ID of the first person entering the form on-line.

GENERAL INFORMATION

G1. Date of this visit c c c c c c c c
D D M M M Y Y Y Y
Date in which this visit took place.

G1.1 How was this visit conducted? (choose one):
- c In person visit
- c Remote visit (i.e. by phone)
- c Home visit
- c Participant sent another person to get study medication
- c Other, G.1.2. If Other, specify_____

This question has been added since, to comply with measures in place to control COVID-19 epidemic, some visits could be done at distance (i.e. by phone). Please chose "remote visit": if this patients contact was done by phone (for COVID-19 measures or for other causes). If this visit is not captured by any of the given choices, choose "Other" and specify what encounter was this.

G1.3 This visit was (choose one):
- c A routine follow-up visit (Go to question 1.5)

*For all visits required by protocol (i.e. 2 weeks, 4 weeks and 8 weeks for **high dose arms** and 4 weeks, 8 weeks and 16 weeks for **standard arm**) choose "A routine follow-up visit".*

- c An additional visit, requested by research team or treating team (Go to question G1.4.)

  Choose this option if the visit has been added to the follow up schedule by the medical team or by research team (for example: medical team thought closer follow-up was necessary, an extra monitoring is needed as per clinic standard, etc). In this case specify reason below (at G1.4)

- c An additional visit requested by participant (Go to question G1.4)

  Choose this option if the visit has been added to follow up by the participant (for example, participant calls to express concerns and ask to be seen). In this case specify reason below (at G1.4).

  Note: all these types of visits can be either in person or by phone. This has been specified in G1.1.

  G1.4 If additional visit, please specify the reasons: _____

G1.5 If this was a routine follow-up visit, was this visit within the recommended schedule?

c visit done within recommended schedule (go to G6)

c visit done outside of recommended schedule for treating team or research team decision (Go to G1.6)

c visit done outside of recommended schedule for participant decision (Go to G1.6)

G1.6 If done outside of recommended schedule, please specify reasons_____

Choose option "visit done within recommended schedule" if a routine follow-up visit was done within the following ranges of time:

***In high dose arms**:*

1st visit: 2 weeks +/- 3 days after treatment begins;
2nd visit: 4 weeks +/- 3 days after treatment begins;
3rd visit: 8 weeks +/- 1 week after treatment begins.

***In standard arm**:*

1st visit: 4 weeks +/- 1 week after treatment begins;
2nd visit: 8 weeks +/- 1 week after treatment begins;
3rd visit: 16 weeks +/- 2 weeks after treatment begins

G5. Comments

_____

_____

_____

Write: "due to COVID-19" if this was the reason for a remote visit.

G6. This visit is:

For each visit, please choose one of the 4 options below. This is needed, as there are some type of visits in which specific information are collected.

c The FIRST visit after participant started treatment

G7. If FIRST visit, please write the date on which participant took the first dose of treatment:

c c c c c c c c
D D M M M Y Y Y Y

Choose this option if this is the first contact with participant after randomization and participant did start treatment. Ask participant the exact date in which they started therapy and report it here (G7).

In the rare events in which participants have they first follow-up visit BEFORE having started the therapy, as for example, if they had specific issues for which they could not start treatment yet and they needed another assessment, do not choose this option, but option 3 ("Any other visit during treatment"), as treatment has not started yet.

Note: during COVID-19 measures this visit could be done remotely or in person (as specified at point G1.1). If done remotely, the blood work needed for this visit has anyway to be done, reviewed and entered in CRF5.

c The LAST visit during treatment

G8. If LAST visit during treatment and the participant is HIV+: Viral load _____copies/ml

This viral load does not need to be done for 2R² study, it can be taken from patient's record in the health facility where participant is followed for HIV treatment. If there is no recent or routinely done viral load in the HIV service, please contact the coordinating center to decide how to proceed (if this was not already discussed).

G8.1. Date of viral load c c c c c c c c
D D M M M Y Y Y Y

G9. Was the antiretroviral therapy changed during LTBI therapy because of possible interactions with rifampin?

c Yes c No c N/A (participant is not on antiretroviral treatment)

c Any OTHER visit during treatment (i.e. nor FIRST nor LAST)

Choose this option if this is not the first visit after participant started treatment (therefore the date of treatment start has been already reported in a previous CRF5), and this is not the last visit for the treatment follow-up of this participant. Routinely, this should be the case for visits at week 4 for high dose arms and at week 8 for standard arm. It can happen that there are more of these visits, in case participant has to come to clinic more often than the 3 schedules visits per protocol. Please specify above (at G1.3) if this was a routine scheduled visit or not.

G10. Has contact information changed? c No c Yes **(If YES, update information on CRF-4)**

(IMPORTANT NOTE: review contact information at each visit)

ADHERENCE TO TREATMENT

G11. The participant was randomized to: (automatically generated by the website)

Information on which is the participant's arm will appear in the website, for you to double check randomization of this participant is correct.

G12. c **4 month** 10mg/day Rifampin, with c c c mg/day dose per day

G13. c **2 months** high dose, with randomization code c c and G14. c number of pills per day

Choose the appropriate option and complete with the correct dose (or code and number of pills per day): this is to double check the randomization is correct.

G15. Did study participant bring their medication bottle? c YES c NO

G16. If YES, and **is randomized to 2 months high dose,** number of pills of study medication remaining in medication

bottle is c c c pills

G17. **If YES**, and **is randomized to 4 months standard dose,** number of daily doses of study medication remaining in medication bottle is c c c doses (Days)

G18. **If NO**, and is **randomized to 2 months high dose**, number of pills of study medication remaining by participant's estimate is c c c pills

G19. **If NO**, and is **randomized to 4 months standard dose**, number of daily doses of study medication remaining by participant's estimate is c c c doses (Days)

For visits done by phone (as during COVID-19 measures), ask participants to count the remaining pills during the call and report them as estimated pills (G18) or doses (G19) depending on participant's arm.

G24. Comments _____

CURRENT SYMPTOMS & PHYSICAL EXAM

Does the study participant have any of the following symptoms TODAY?

Y1. Fever/Night sweats? c NO c YES, (Y2) specify _____

Y3. Weight loss without dieting? c NO c YES, (Y4) specify _____

Y5. Cough? c NO c YES, (Y6) specify _____

Y7. Sputum production? c NO c YES, (Y8) specify _____

Y9. Skin problems? c NO c YES, (Y10) specify _____
(i.e. acne, itchiness, skin rash, etc.)

Y11. Gastrointestinal problems? c NO c YES, (Y12) specify _____
(i.e. abdominal pain, loss of appetite, nausea, vomiting, etc.)

Y13. Neurological problems? c NO c YES, (Y14) specify _____
(i.e. blurred vision, numbness, paresthesis, irritability, etc)

Y15. Other? c NO c YES, (Y16) specify _____
(i.e. fatigue, joint or muscular pain, headache etc.)

Y17. Physical exam is (Reminder: Exam must be done if any symptoms reported)

c NOT NECESSARY c NORMAL c ABNORMAL

Y18. If ABNORMAL, describe_____

If Yes to any of Y1-Y15, specify on symptoms. If not enough space, write "more info in N7" and add all specification needed on N7

INVESTIGATIONS

Note: at the 4 weeks FOLLOW-UP VISIT, the following ARE REQUIRED, otherwise as clinically indicated

F1. Date tests were performed c c c c c c c c c c
DD MMM YYYY

F2. Alanine transaminase (ALT) c c c c . c U/L

F3. Aspartate aminotransferase (AST) c c c c . c U/L

F4. Total bilirubin c c c . c umol/L

F5. Creatinine c c c . c mg/dL

F6. BUN (blood urea nitrogen) c c c . c mg/dL

F7. Hemoglobin c c c c . c g/L

F8. Hematocrit c . c c c L/L

F9. White blood cells c c c . c 10^9/L

F10. Platelets c c c . c 10^9/L

F11. Other investigations_____

For all lab results: remind to check the units they are reported on is the correct one. If your lab uses other units for the same tests, please do a conversion. If uncertain on the conversion, discuss it with site PI and, if needed, with coordinating center.

F12. Does study participant require monitoring of other medications being taken? c Yes c NO (If NO, go to section "Treatment plan")

F13. If Yes, how was the monitoring done? (tick one) c DRUG LEVELS c BLOOD TEST c CLINICAL

F14. If Yes, was the monitoring of other medication satisfactory? c YES c NO

F15. If No to F14, comments (Report drug levels OR blood test results OR clinical effects. Describe actions taken for unsatisfactory results_____

F16. If this is the 4 weeks FOLLOW_UP VISIT: were sample for PK taken?

c YES c NO, because participant refused c NO for other reason (F17), Specify _____

TREATMENT PLAN

OTHER MEDICATIONS

N1. Is the study participant taking any NEW medications prescribed by a doctor? c YES c NO **(If NO, go to N5)**

N2. If YES, list the names of all new medications being taken _____

N3. Do any of these medications have potential drug interactions with Rifampin? c YES c NO
(see drug interaction list, contact pharmacist)

N4. If YES, can treating team manage interactions & participant continues on study medication?
c YES c NO **(if NO: study medication must be stopped permanently; complete an End of Treatment form- CRF 6)**

N4.1. Comments **-**

_____

ACTION REGARDING STUDY MEDICATION

N5. Plan (tick one)

c Study medication continued as per protocol at same dose

c Study medication stopped for a possible adverse event **(REPORT Initial Adverse Event – CRF 9)**

c Study medication stopped permanently **(IF STOPPED permanently, complete an End of Treatment form- CRF 6)**

Study medication dispensed today (fill one only):

N5.1. c c c **pills** of study medication were dispensed today for participant who is in **2 months** high dose arm

N5.2. c c c **daily doses** of study medication were dispensed today for participant who is in **4 months** standard treatment arm

N5.3. How many days will the pills dispensed today be for? c c c days

N6. Suggested date for next visit is c c c c c c c c c
D D M M M Y Y Y Y
(auto generated depending on date of randomization)

Note : if participants started medications more than 4 days after randomization, the suggested dates given by the website would not apply (as they are based on randomization date), therefore decide the schedule of appointments based on start date of therapy, without using the suggested dates given by website. (see Table 1 in section 5.2 of this SOP for recommended visit range).

N7. General comments:

_____

_____