Title	Adverse event management
SOP Code	2R2 SOP09_20Sep2021
Effective Date	

1.0 Purpose(s)

The objective of this standard operating procedure (SOP) is to define the methods of collection, documentation, investigation and assessment, as well as submission and follow-up, of adverse events that may occur in the course of the $2R^2$ clinical research study.
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 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)

Adverse Event (AE):

Any untoward medical occurrence in a research participant administered an intervention and which does not necessarily have a causal relationship with this intervention. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an intervention, whether or not related to the intervention (modified from ICH, E6 1.2)

Adverse drug reaction (ADR):

In this study the primary outcome is the rate of adverse events that result in permanent discontinuation of the study drug and are considered possibly or probably related to the study drug by the AE review panel. In GCP terminology - this is referred to as an adverse drug reaction. But we refer to this outcome in this documents, and in other documents as “drug-related adverse event”.

CTC: The site Clinical Trial Coordinator

ICH: International council for harmonisation 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.

Serious Adverse Event (SAE) (ICH, E6 1.50):

Any adverse event that:

- results in death,

- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

Serious Unexpected Adverse Drug Reaction (SUADR):
For this study, a serious unexpected adverse drug reaction, is considered a serious adverse event which is possibly or probably related to the study drug and that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

5.0 Procedures

5.1. Overview of procedures for adverse events reporting and management.

During treatment phase follow-up, participants are monitored for appearance of adverse events.

All events of grade 1 or 2 (including symptoms, signs, or laboratory results) occurring while participants are on treatment with study medication, which do not require treatment discontinuation for 48h or longer, are reported in the follow-up forms (CRF5), which are completed at each follow-up visit or patient encounter. For example: at first follow-up visit participants complain of nausea, medical team recommends taking study medication with light meal, participant is now able to tolerate treatment better and study medication is continued. This is reported in the CRF5 of the follow-up visit.

If an event is reportable, then it must be reported, as an Adverse Event in the specifically designed CRF9 (Initial report). This initial report must be completed and sent to the Coordinating Centre within 24h of becoming aware of the event. The CRF10 (Final report) is completed later, usually when the event has been investigated and managed.

The events which are reportable in this study are:

1. Events of any grading, which require, in treating physician's opinion the discontinuation of study treatment for 48h or longer;

2. All events of grade 3 or 4, regardless of whether they require discontinuation of study treatment or not;

3. All deaths in treatment phase.

5.2 Site Principal Investigator Responsibilities

The site Principal Investigator (or Qualified Investigator) is responsible for:

5.2.1. With respect to any AE, ensuring that appropriate medical treatment is provided to a participant during and after his/her participation in the study (ICH, E6 4.3.2);

5.2.2. Ensure that as Site PI, she/he is notified of AE within 24h, when they occur to study participants

5.2.3. Promptly (within 24 hours of being aware of the event) reporting to Coordinating centre all AEs of grade 3, 4 or 5 and events of all grades which require treatment discontinuation for 48h or longer (ICH, E6 4.11.2), using the appropriate forms.

5.2.4 In addition to the above, to report\ to the Institutional Research Board (IRB) any AE that is serious and unexpected (SUADR), as well as any new information that could adversely affect participants' safety or the conduct of the study (ICH, E6 3.3.8); The Coordinating Centre shall notify Health Canada of these SUADR events as well (as specified in SOP10).

5.2.5. In the case of a death, providing the Coordinating centre and IRB with all additional requested information (autopsy reports, medical reports, etc.) (ICH, E6 4.11.3);

5.2.6. Accurately and regularly documenting **all** AEs in the source documents and case report forms (CRFs).

5.2.7. Date and sign all Initial and Final AE reports for the site.

5.3. Management of adverse events

In this study follow-up during treatment is in line with standard practice, and conducted by the treating physicians and TB clinic staff. However, **if a reportable AE occurs, the study team must be directive and ensure appropriate management as outlined in the protocol** and **appendix 1**.

Related to AE management, the research team needs to ensure that:

- The treating team is informed of the possible adverse event (if not already aware of it) and the participant is followed with the care needed until resolution of the event.

- For each type of adverse event, the appropriate history, exam, tests and investigations are done. Please refer to appendix 1 for a list of requirements for each type of event.

- In case of permanent interruption of study medication, ask the participant to bring back the bottle with all remaining study medications, which will be returned to pharmacy for logging and final disposition (refer to **SOP04** "Dispensing and blinding of study medication" for procedures at your site).

Note: if the event does not meet the definition of a reportable event (i.e. mild symptoms (grade 1 or 2) for which study treatment does not need to be discontinued), study team at site needs to document the event in CRF5.

5.3. Data collection and reporting of adverse events

The primary outcome of this study is to compare the rates of study drug-related adverse event (AE) of grade 3 to 5 during treatment between participants randomized to the three study arms. The secondary outcome is to compare rate of grade 1 and 2 AEs between participants randomized to the three study arms. Data collection and reporting of AE is therefore an essential part of the study. The research team needs to be informed of a possible Grade 3-5 adverse event occurring to a study participant. It is therefore important that study participants are informed, at randomization and reminded during follow-up, how to contact the research staff if they think they may have an adverse event. Is also important that the treating team is aware of the need to inform the research staff if they learn of a possible adverse event.

The following procedures are specific to the collection of participant information to enable appropriate assessment of potential adverse events. Two case report forms (CRF) have been created for this component of the research study – "Adverse event initial evaluation Form (CRF9)" and "Adverse event final evaluation form (CRF10)".

Site research staff should notify the central coordinating center of reportable adverse event by entering the **initial form (CRF9)** in the study website. This form should be completed **within 24 hours of the decision to stop study medication** - permanently, or if planned for at least 48 hours OR **within 24 hours of site learning of a grade 3-5 event** (even if study medication is not stopped). Note that participants who stopped study medication for 48h or more, may eventually restart the study drug, but if it is stopped for more than 48 hours a CRF9 form should be completed.

To help readers understand, the following example scenarios are described:

1. Abnormal laboratory value detected that meets the criteria for a Grade 3 or 4 AE. **For all Grade 3-4 AEs the study drug must be stopped** permanently or for at least 48h. There may be circumstances when the study can be re-started if another reason for the AE is found.
    - *Example*: When reviewing the results of week 4 laboratory tests, the research staff realizes that AST value meets criteria for grade 3 AE. They notify the treating team, and the patient is advised immediately to stop the study drug.

2. The treating team decides to stop the study drug permanently (or for more than 48h) because of symptoms, drug interactions, or other clinical problem.
    - *Example*: Participant is having a rash and the treating physician decides to permanently stop the study drug. The treating team informs the research staff that the participant will not be able to continue with the study drug.

3. The treating team decides to stop therapy permanently or for more than 48 hours, after a temporary interruption of study drug.
    - *Example*: Participant reports nausea and vomiting. The treating team decides to hold the treatment for 1-2 days in order to see if treatment can be resumed after this brief interruption. After 2 days the treating team decides to prolong the interruption beyond 48h.
4. Research team learns of an adverse event or possible adverse event that already occurred and resulted in a permanent discontinuation (or one that lasted longer than 48 hours) of study medication. The drug may have been stopped by the participant, or by another provider.
    - *Example*: At a follow-up visit, the participant informs the treating team that because they had a rash, they consulted their family physician who advised them to stop the study treatment, two weeks earlier.

Note: Some participants may decide to stop the study drug because of non-specific symptoms such as fatigue or headache. They report this to their treating team, but the treating team does NOT believe this is a true adverse event, and instead advises the patient to restart the study drug. However the patient does not restart (refuses). This is NOT an adverse event, but rather patient decision to stop study drug early. CRF9 is not needed in this case. You need to report patients' symptoms in CRF5 and complete CRF 6 - End of treatment (See also **SOP05** regarding ascertaining and recording study drug taken during follow-up).

See **appendix 2** for details on data to be collected in CRF9. Complete CRF9 in paper version first and then enter it in the website. The narrative to include in CRF9 can be written in a word document and then printed to be attached to the paper CRF9 and copied and pasted in the website, when CRF9 is entered in the 2R2 website (see 5.3.1. below). **NOTE**: the paper version of CRF9 must be signed by the site PI.

Once entered in the website, the initial information about the participant's AE will be transmitted to the Coordinating centre.

5.3.1. Procedures for reporting CRF9:

- Log on to the website (http://2r2.crc.chus.qc.ca), go to "Add/select records" and choose the participant's study ID number. In the section "Adverse events" choose "Add a new AEI". Open the "AE Initial evaluation-CRF-9" in the menu of the left. 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 of the event by email and the event information should be entered into the website as soon as possible.
- Enter the appropriate study participant information from the CRF9 into the website and at the end of each section click on the "save/stay of page" button at the bottom of the screen and then on "save/go to next page". The data will be saved and can be modified. Record the event number given by the database on the paper CRF for future reference.
- At any point during data entry you may exit this section by choosing another page on the left menu. It is advisable to always press the "save/stay on page" key prior to this in order to save any data that has been entered. To return to the AE initial information, select the event number and then click on the "adverse event initial evaluation" choice on the left menu.
- Once all the initial evaluation information has been entered, and you consider the form completed, press the "save & exit" button to transmit the event information to the Coordinating centre. At this point no further modifications can be made to this data. If any further modifications are required this must be done through the Coordinating center (refer to Maintenance of Study data SOP). The coordinating center will be alerted by an email that an Adverse event form has been completed for that center. The CTC and PI of the center will be copied in the email. The email constitutes the record of "Notification to coordinating centre of adverse events" that needs to be kept in the Master binder at the study site. The final decision of AE panel will also be communicated to the center PI and CTC and will be part of the communications to be kept in the Master binder.

As soon as the event is resolved, the ADVERSE EVENT FINAL EVALUATION FORM CRF-10 must be filled out for each study participant (see appendix 2 for details on data to be collected).

Note: complete CRF10 in paper version first and then enter it in the website. The narrative to include in CRF10 can be written in a word document and then printed to be attached to the paper CRF10 and copied and pasted in the website, when CRF10 is entered in the 2R2 website (see 5.3.2. below). **NOTE**: the paper version of CRF10 must be signed by the site PI.

5.3.2. Procedures for reporting CRF10:

- The information from the CRF 10 must be promptly entered into the study website, once the event is resolved, in order for the final information about the participant's adverse event to be transmitted to the Coordinating centre.

- Log on to the website (http://2r2.crc.chus.qc.ca) go to “Add/select records” and choose the participant’s study ID number. In the “Adverse events” section, select the adverse event for which you would like to enter the final report. Then you can select the “Adverse event final evaluation- CRF10”, from the menu on the left. Note – after 20 minutes of inactivity users will be automatically logged off the website. If unable to log on to the site, the Coordinating centre should be notified that the final information is available and the event final information should be entered into the website as soon as possible.

- Enter the appropriate study participant information from the CRF into the website and at the end of each section click on the “save/stay on page” button at the bottom of the screen. The data will be saved and can be modified.

- At any point during data entry you may exit this section by choosing other pages in the left menu. It is advisable to always press the “save/stay on page” key prior to this in order to save any data that has been entered. To return to the AE final information, select the event number and then click on the “adverse event final evaluation” in the left menu.

- Once all the final evaluation information has been entered, press the “save & exit” button to transmit the event information to the Coordinating centre. At this point no further modifications can be made to this data. If any further modifications are required this must be done through the Coordinating center, (refer to Maintenance of Study data SOP).

5.4 Coordinating center responsibilities

Procedures that coordinating center should follow for adverse event reporting are described in detail in SOP10_AE Administration.

6.0 References

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

RI-MUHC SOP: SOP-CR-012_07 Serious Adverse Drug Reaction Reporting in Clinical Trials. 01 Sep 2018

Health Canada: GUIDANCE DOCUMENT For Clinical Trial Sponsors: Clinical Trial Applications. Revised Date: 2011/11/07; Effective Date: 2013/05/29.

APPENDIX 1 - ADVERSE EVENTS
RELATIONSHIP TO THERAPY, EVALUATION, GRADING AND MANAGEMENT

Source documents used to develop this appendix:
For all events: the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 & v4.02 & 5.0 (**https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50**);
For hepatotoxicity: ATS guidelines for hepato-toxicity (Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52. An official ATS statement: hepatotoxicity of antituberculosis therapy. Saukkonen JJ et al.).

Adverse event

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure.

Relationship to therapy

Relationship	Description
Unsure	Further information and follow-up is required.
None	Clear alternative explanation. Very unlikely related to study drug.
Unlikely	Improbable, temporal relationship and other explanations exist.
Possible	Reasonable temporal relationship although other explanations also exist.
Probable	Reasonable temporal relationship and unlikely to be any other explanation or cause.

General guidelines for grading the severity of an adverse event **

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to the adverse event.

**Not all Grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than five options for Grade selection.

Refer to the tables on the following pages for detailed information on the **evaluation, grading and management** for specific types of adverse events.

For all type of events: if study medication is **temporarily interrupted**, participant's therapy duration must be prolonged by the total number of days with no therapy.

Drug-drug interaction (DDI)

(see also Appendix 3 (A and B) for list of interactions)

Symptoms	• Various symptoms related to specific medications involved.
Medical History	• According to specific medications involved & symptoms. • Question re any new medications, including over the counter medications- Remember hormonal contraception! • Alcohol, recreational drugs.
Investigations	• According to specific medications involved & symptoms. Important to measure drug levels or assess drug effects.
Grading severity	**Grade 1**: Potential drug interaction noted but no change in therapy required and neither short- nor long-term effects detected. **Grade 2**: Potential drug interaction is noted and after an initial change in therapy no further problems. Participant does not suffer any untoward clinical effect. **OR** Drug interaction is noted and therapy has to be modified repeatedly but eventually is successful. Participant does not suffer any untoward clinical effect **OR** Participant visits emergency room or walk-in clinic, but is not hospitalized/stays less than 24 hours. **Grade 3**: Drug interaction noted. Care providers unable to adjust therapy successfully to achieve therapeutic effects. No other adverse effect. **OR** Participant requires immediate medical evaluation resulting in hospitalization **OR** There are Grade 3 abnormalities in laboratory tests done. **Grade 4**: Drug interaction causes serious health problems such as diabetes or hypertensive, or cardiac crisis or results in seizures **OR** Hospitalization is required
Management	• Grade 1-2: Continue monitoring; potentially adjust concomitant medication. • Grade 3 or 4: LTBI therapy must be discontinued.

Gastrointestinal intolerance

Symptoms	• Nausea, Upset stomach, Vomiting • Loss of appetite • Abdominal pain • Diarrhea
Medical History	Participant must be questioned regarding • Alcohol • Possible exposure to other causes of GI upset - notably other persons with gastroenteritis, recent travel, possible exposure to 'food poisoning' • Past history of other gastrointestinal (GI) problems particularly peptic ulcer or gallbladder disease. GI intolerance must be distinguished from other GI problems including gallbladder (cholecystitis), appendicitis, peptic ulcer, etc. • Use of other potentially causative medications. • Females of childbearing age should be questioned carefully to rule out pregnancy. Physical examination required • Vital signs: temperature, heart rate and blood pressure. • Abdominal exam for signs of peritoneal irritation, tenderness, or mass.
Investigations	• Liver function test (bilirubin, ALT, AST) • Amylase • CBC • Pregnancy test (women of childbearing age) • Abdominal/ Liver ultrasound or X-rays may be performed at discretion of treating team.
Grading severity	**Grade 1**: Some upset stomach with nausea and/or loss of appetite but no vomiting and no change in bowel habits. **Grade 2**: Nausea with some vomiting, or abdominal pain that is severe enough to disturb daily routine, or persistent diarrhea. **Grade 3**: Prolonged nausea and vomiting and/or severe abdominal pain that disrupts daily life (e.g. cannot sleep) severe diarrhea (5 or more/day).
Management	• Grade 1 and 2: 1)Try changing the hours of treatment; 2) Try taking the pills with light meal or a snack; 3) Split the dose in two, taken maximum 1h apart. 4) Take one or two days off study medication and then try to take study medication again. • Grade 3: Stop stud drug AND examine participant in person, AND check LFT: if all normal, consider rechallenge the medication after symptoms resolve. **If symptoms reappear, permanently stop study medication**.
Notes	• Use of antiemetic medications (in case of nausea and vomit) while still taking study medication is NOT recommended unless the cause of GI symptoms have been established and it is clearly NOT the study medication. • If study medication is interrupted, then antiemetic medications can be given.

Hematologic

Symptoms	• Usually no symptoms, picked up by measuring hematologic parameters.
Medical History	• As necessary, question regarding other medications and diet (particularly if iron deficiency is possible). For females of childbearing age, question regarding menstrual period (heaviness, frequency). • If anemia - question re possible blood loss • Also question regarding alcohol and use of other possible hematologic suppressants.
Investigations	• B12, folate and iron studies • CBC & differential • Other investigations may be needed
Grading severity	See table below
Management	• Grade 1-2: Continue monitoring. • Grade 3 or 4: Review with treating team, evaluate other causes. If no other cause is found and not corrected with B12, folate or iron, discontinue therapy.

Test	Grade 1	Grade2	Grade 3	Grade 4
Neutrophils	≥ 1500/mm^3 and < LLN (OR ≥ 1.5 x 10e9 /L and < LLN)	≥ 1000 and <1500/mm^3 (OR ≥ 1.0 and <1.5 x 10e9 /L)	≥ 500 and <1000/mm^3 (OR ≥ 0.5 and <1.0 x 10e9 /L)	<500/mm^3 (OR <0.5 x 10e9/L)
White blood cells	≥3000/mm^3 and <LLN (OR >3.0 x 10e9/L and <LLN)	≥2000 and <3000/mm^3 (OR ≥2.0 and <3.0 x 10e9/L);	≥1000 and < 2000 /mm^3 (OR ≥1.0 and <2.0 x 10e9/L);	<1000 (OR <1.0 x 10e9/L)
Platelets	≥ 75,000/mm^3 and < LLN (OR ≥ 75.0 x 10e9/L and < LLN)	≥ 50,000 and <75,000/mm^3 (OR ≥ 50.0 and <75.0 x 10e9 /L)	<50,000 and ≥25,000/mm^3 (OR < 50.0 and ≥ 25.0 x 10e9 /L)	< 25,000/mm^3 (OR < 25.0 x 10e9/L)
Hemoglobin (Hgb)	≥10.0 g/dL and <LLN; (OR ≥ 100 g/L and <LLN; OR ≥6.2 mmol/L and <LLN);	<10.0 - 8.0 g/dL; OR <100 - 80g/L; OR <6.2 - 4.9 mmol/L;	<8.0 g/dL; OR <80 g/L; OR <4.9 mmol/L; transfusion indicated	Transfusion indicated, Life-threatening consequences; urgent intervention indicated.

Abbreviations: LLN: Lower Limit of Normal

Hepatotoxicity**

Symptoms	• Anorexia, loss of appetite • Fatigue • Nausea and vomiting • Right upper quadrant pain • Jaundice, dark urine, pale stools • Itching • May have easy bruising, leg edema or abdominal swelling
Medical History	Study participant must be questioned regarding • Alcohol • Use of recreational drugs, prescription, non-prescription drugs & herbal remedies • Past history of liver disease • Injection drug use, transfusions and other risk factors for liver disease • Recent travel Physical examination • Assess the presence of jaundice. • Examine liver for tenderness, enlargement and signs of liver failure (bruising, bleeding, edema and ascites).
Investigations	• Liver function test (bilirubin, ALT, AST) • CBC, INR • HIV, Hepatitis A, B and C serology (unless known positive) • Abdominal / Liver ultrasound may be performed at discretion of treating team
Grading severity *(ALT is more specific for liver injury, but If both AST and ALT are done, use the higher value to classify the event)*	**Grade 1-2**: ALT/AST 1 to ≤ 3 times upper limit of normal (ULN) plus symptoms, **OR** ALT/AST 1 to ≤ 5 times ULN with no symptoms, **Grade 3**: ALT/ AST 3 to ≤ 10 times ULN plus symptoms **OR** ALT/ AST 3 to ≤ 10 times plus bilirubin ≥2 times ULN, regardless of symptoms **OR** ALT/AST 5 to ≤ 10 ULN and no symptoms**,** **Grade 4**: ALT or AST > 10 times ULN
Management	• Grade 1-2: Therapy should be continued, LFT's should be repeated in 2 weeks. • Grade 3 or 4: Therapy should be discontinued permanently unless there is another explanation for the hepatotoxicity. Follow-up should include ALT and AST approximately weekly until the values return to normal (at least 3 LFT's).

****Adapted from ATS guidelines for hepato-toxicity (**Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52. An official ATS statement: hepatotoxicity of antituberculosis therapy. Saukkonen JJ et al.)

Hyperbilurubinemia

1) Rifampin can cause asymptomatic unconjugated hyperbilirubinemia. This is called isolated hyperbirubinemia, and is defined as bilirubin above normal, but there are NO symptoms AND ALT/AST are normal.
This does not require interruption of Rifampin. In case Rifampin is stopped this hyperbilirubinemia will resolve spontaneously.
If participants have isolated asymptomatic hyperbirubinemia, it is not necessary to repeat the LFT to monitor it, unless symptoms develop. This isolated lab abnormality does not need to be Graded. Please refer to UpToDate® (https://www.uptodate.com/contents/search) and to Saukkonen et al. 2006, for further information.

2) If participants have bilirubin that is more than double ULN, AND also ALT/AST that are more than three times ULN, with or without symptoms, **rifampin should be stopped**.
This is because if ALT/AST are elevated AND bilirubin is >2xULN, in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding represents a signal of potential drug induced hepatotoxicity (Hy's Law). Treatment with rifampin should be stopped (reference: US-FDA 2009).

References:
Saukkonen JJ et al., An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52.
US-FDA, Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation)

"Other" category

(reminder: if choosing "Others" specify type of event as precisely as possible)

Symptoms	Examples: • Weakness, malaise, generalized pain • Headache • Abnormal blood pressure (but not a drug-drug interaction -DDI) • Abnormal glycemia (but not a DDI) • Abnormal biochemistry • Cardiovascular events NOTE: if participant is taking concomitant medications which could be causing their symptoms, DDI should be considered as diagnosis, unless it has been demonstrated otherwise
Medical History	Participant must be questioned regarding • Alcohol and recreational drugs use. • Exposure to viral infectious illnesses (Flu, etc) • Use of other potentially causative medications. • Use of other medications with possible side effects (including over the counter). • Possible other causes (depending on the symptoms) • Previous occurrence of similar symptoms Physical examination required • Vital signs: temperature, heart rate and blood pressure. • Exam to exclude a specific diagnosis (guided by clinical picture)
Investigations	• Based on symptoms and differential diagnosis: may include: o Liver function test (bilirubin, ALT, AST) o Amylase o CBC o Biochemistry o Imagining exams -at discretion of treating team.
Grading severity	**Grade 1**: Some discomfort (pain, weakness, ect) but participant can continue activities as usual. **Grade 2**: Symptoms are severe and/or prolonged enough to disturb daily routine. Medical evaluation may be required, but it does not result in hospitalization and, if observation in ER is required, it last less than 24h; AND there is no Grade3-4 abnormality in laboratory tests (if done). **Grade 3**: Symptoms are prolonged and/or severe enough to disrupt daily life (e.g. cannot sleep, cannot work, cannot attend school) **OR** Severe or medically significant but not immediately life-threatening. **OR** Participant visits emergency room which results in hospitalization or observation in ER for more than 24h **OR** Hospitalization or prolongation of existing hospitalization indicated **OR** Grade 3 Abnormalities of laboratory tests (if done). **Grade 4**: Potential Life-threatening consequences **OR** Urgent intervention and hospitalization indicated, **OR** Grade 4 Abnormalities of laboratory tests (if done).

Management	• Grade 1: Try to change time and modality in which treatment is taken, adjust concomitant medications (if present). • Grade 2: Stop study therapy for 1-2 days (max 2 days) and then try again. • Grade 3: Interrupt treatment for 1-2 days, give symptomatic treatment as needed, exclude other possible diagnosis, try to restart therapy. If symptoms reappear, permanently stop medication.

Abbreviations: DDI, drug-dug interaction.

Pregnancy

Symptoms	• Nausea, upset stomach, vomiting • Loss of appetite
Medical History	Participant must be questioned regarding • Sexual activity and contraceptive use. Especially hormonal contraception • Date of last menstrual period
Investigations	• Pregnancy test (blood test)
Grading severity	• Grade 3: an unintended pregnancy is considered a grade 3 adverse event
Management	• Stop study drug and re-evaluate restarting therapy following completion of the pregnancy. If in standard arm (i.e. rifampin 10mg/kg/day): may consider to continue the study medication during pregnancy.

Rash

Symptoms	• Itching, rash or hives • Location – may be generalized or localized. Check if: - does it affect limbs, trunk, or face? - is it discrete spots or confluent? - what percentage of total body area is affected? • May cause low blood pressure and weakness, dizziness, or fever. • May cause painful mouth ulcers, eye irritation, wheezing/shortness of breath.
Medical History	Participant must be questioned regarding • Use of drugs including non-prescription drugs, herbal remedies and recreational drugs. • The relationship of the rash to timing of the when medication is taken. • Exposure to other potential allergens, especially food. • Past history of allergies and family history of allergies. • Possible viral illnesses, including contact with children with rash/viral illness.
Physical examination	Do physical examination (TAKE PICTURES of affected areas (not the face), if participant agrees. Check: • Location of the rash: face, trunk (back, stomach, or chest), and limbs. • Appearance of the rash: color (red, purplish, etc.), markings (small spots or large patches), palpable, hives or purpura? • Vital signs: blood pressure and heart rate, and temperature. • Mucus membranes and respiratory system must be examined carefully.
Investigations	• CBC and differential with specific count of eosinophils • Flow rates (if wheezing is present).
Grading severity	**Grade 1**: Macules/papules covering <10% body surface area with or without symptoms (e.g., Itching, burning, tightness). Vital signs, mucosal and conjuntiva- are all normal. **Grade 2**: Macules/papules covering 10 - 30% body surface area and symptoms (e.g., pruritus, burning, tightness), if present, are not severe OR limiting instrumental activities of daily living (IADL), as shopping, cooking, doing housework, etc. In all cases: vital signs, mucosa and conjuntiva- are all normal. **Grade 3**: Rash affects >30% of body surface area (even if no other symptoms), OR mucus membranes or conjunctiva are affected; OR vital signs are abnormal (fever or low blood pressure) OR there is wheezing OR it is limiting self-care activities of daily living (ADL), as eating, dressing, taking shower, etc.

Management	• If other cause suspected - may continue study drug, but watch carefully • Grade 1: May continue therapy and may give antihistamines, BUT close follow-up required (daily or every other day). If the rash worsens: permanently stop study medication (and DO NOT use rifamycin-containing regimens* as alternative treatment). • Grade 2: Stop therapy. Give antihistamines. Close follow-up. May re-challenge BUT only under close monitoring (after the 1st dose and then daily or every other day). If rash reappears permanently stop study medication (and DO NOT use rifamycin-containing regimens* as alternative treatment) • Grade 3: Permanent discontinuation of therapy. Give antihistamines. May need steroids. Follow-up until resolved. **DO NOT re-challenge with study treatment, DO NOT use rifamycin-containing regimens* as alternative treatment**.
Notes	• Use of corticosteroids should be reserved only to severe rash after stopping study medication.

Note* Examples of rifamycin-containing regimens are: 4R, 3HR, 3HP

Definitions: **ADL** (activities of daily living) are basic daily activities for self-care, as eating, dressing, getting into or out of a bed or chair, taking a bath or shower, and using the toilet.; **IADL** (Instrumental activities of daily living) are activities related to independent living (as cooking, shopping, doing housework, using a phone, managing money).

APPENDIX 2 – ADVERSE INITIAL & FINAL EVALUATION FORMS

The following is a list of explanations for specific fields on the ADVERSE EVENT INITIAL & FINAL EVALUATION FORMS. It does not cover all fields, only those that may require further descriptions or qualifications. For some of the dates, if the study participant is uncertain about the exact date, you can indicate on the form: "exact date is unknown, study participant's best guess is".

Research staff information –this data is captured through the user ID when logging into the website.

Why was study medication stopped? If stopped due to intolerance or if treating team feels they should not stop (the last two options for this question) – do not continue with this form. Also, the participant is now in the follow-up post treatment phase, (refer to SOP06 End of treatment and SOP07 Study Participant Follow-up Post Treatment).

Most important reason for stopping study medication:

- The cause of adverse event may not be clear at the time of the initial report. Tick all reasons which are still in the differential diagnosis process, in the initial report. In the final report, the cause of event should have been clarified and only one can be chosen.
- Active TB is not an AE it is an outcome and will be investigated separately, (refer to Active TB & Follow-up Post Treatment SOPs, i.e. SOP07 and SOP08).
- If pregnancy is the reason for stopping the study medication, the study participant should be contacted approximately every 3 months (using the adverse event final report form to collect information and the adverse event remains open) until after the birth and the study participant restarts treatment or a decision is made not to restart treatment.
- For participants in standard arm (i.e. taking 10mg/kg/day of rifampin) the treating team can decide with participant, if the benefit of LTBI therapy justify the continuation of therapy during the pregnancy. In that case, even if there is not interruption of therapy, pregnancy will still have to be reported as an adverse event, by completing CRF9 and CRF10.

Date of resolution of adverse event: This is the date of the clinic visit during which the event is considered "over" and either the study drug is safely restarted, or an alternate management plan is begun. Note it may be that the complete resolution happens after the last visit is done for the adverse event management and is communicated to the treating team or the research staff by phone by participant. In that case write the date of the complete resolution as reported by the participant during the call, not the last visit date. For all cases in which there is no follow-up call, the date of resolution will remain the date of last visit.

Total number of visits the study participant had for the adverse event: include the visit done for the first evaluation for the adverse event and the last resolution of this adverse event.

Initial impression or treating team: the grading of the severity and the relationship to the therapy are assessed based on ATS guidelines for hepato-toxicity, or the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 and v4.02 and v5,0 (at http://ctep.info.nih.gov/reporting/ctc.html) for all others,(refer to appendix 1 to for details).

Investigations & treatment plan

- All investigations reported as mandatory in CRF9, must be performed for the particular type of AE.
- For hepatotoxicity: do not need to redo HIV tests if they were done at baseline or within 3 months from the event.
- For pregnancy: determine number of weeks pregnant and if on birth control at the time of conception. Report this information in the final evaluation **narrative description** (question AF15). Refer to site specific guidelines for whether or not participant is put back on medication following completion of pregnancy.

After an adverse event: if participant has study medication restarted successfully, participant returns to follow-up during treatment phase of the study (refer to SOP05 Study Follow-up During Treatment).
If study medication is permanently discontinued, participant will then be in the follow-up post treatment phase, (refer to SOP06 End of treatment and SOP07 Follow-up Post Treatment).

Narrative of the event:

For both CRF9 and CRF10, please starts the narrative by including the following sentence:

A <*gender*> participant, <*age*> years old, with <*co-morbidities/no co-morbidities*>, and taking <*concomitant medications/no concomitant medications*>, <*smoking…/day or not smoking*>, <*drinking quantity of alcohol/ not drinking*> started study medication on <*date start*>. Indication for LTBI treatment was <*indication*>. She/he took approximately <number>% of total doses of study medication , with <*reported/or measured by pill counts*> <*good/poor/etc*> adherence.

> Example: A female participant, 45 years old, with no comorbidities and taking no concomitant medications, no smoking, reporting alcohol intake of 1 drink per week, started study mediation on October 1st . LTBI treatment was started because she is a close contact of patient with active pulmonary TB. After taking about 25% of total study doses, with reported good adherence, then she had two episodes of …

Then describe the event as follows:

For CRF9 (Initial adverse event report): write a brief narrative of the actions taken so far. The important points to include are:

1. Which is the type of adverse event (at the best of knowledge at this point of the event management);
2. Is this event expected or unexpected;
3. Event severity.

For initial AE report provide as much information as available at the time of the report (for example if some tests have been requested but results have not been received yet, write that the results are pending).

The final AE report (CRF10) should be prepared once the event is resolved; and it should be as comprehensive as possible.

For CRF 10, please include all of the following:

1. Date treatment started and indication for LTBI treatment (note: details regarding history of exposure and TST/PPD status are not necessary).

2. Date of onset of AE including initial symptoms, and/or lab results. Specify both time at which drug is taken and time of onset of symptoms.
3. Description of severity of the adverse event (please report the characteristics which would help grading the severity: for example for a gastrointestinal event, report frequency of vomiting and bowel movements; if participant was able to eat/drink; if could continue daily activities, etc.
4. What were the results of initial evaluation of the AE: report medical history of other possible causes (as food taken, other drugs, alcohol etc.), symptoms check done (a part for the symptoms reported by the participant, which other symptoms were asked about?), physical exam, lab tests, results of other specialists' consultations.
5. When was the study drug held (date and time of last drug intake) and by who (participant, treating team, other doctors, etc).
6. What happened after initial evaluation- provide sequence of events, especially: hospitalization, consultation of other clinic, resolution of abnormalities (symptoms or lab tests) – note in case of resolution, specify the time between last dose intake and symptoms or lab test abnormality resolution; re-challenge made with the study drug; alternative therapy given.

Important information to include in the report:
How long, in hours, passed between study dose and initial presentation of signs and symptoms?
Did the participant present with signs and symptoms similar to those reported in this AE report, but of lower toxicity grade, prior to this AE?
Was participant seen by an MD, urgent care or ER staff **(including study staff)**?
If applicable, list the medications that were prescribed to treat the AE, including doses and frequency:

Ensure that enough information is provided so that the adverse event panel members are able to determine the relationship to therapy and grading of the adverse event. Please make sure the above points 1-6 are mentioned in the narrative of CRF10. If some information are not known or not done, write so.

For both CRF9 and CRF10, narrative report should be as concise as possible and NOT include the planned duration of the study medication or any reference which would identify in which arm participants are.

Never include in the narrative the following:

- Names of anyone (participant, family members, doctors, etc)
- Planned duration and dosage of the study medication
- Time intervals that will "give away" which study medication the study participant was on – instead use percentages – i.e. study participant had taken 50% of required therapy.
- Abbreviations (always spell them out especially over the counter medications, and lab test)

Appendix 3: Potentially important drug interactions for rifampin.

NOTE ***These lists are not exhaustive. If you are unsure about a specific medication, please contact the coordinating center.***

3A: Potentially important drug interactions with RIF

Group	Drug class	Drug name	Effects	Recommendations
Antiacids	Aluminum hydroxide gel, Magnesium hydroxide gel		Antacid reduces RIF absorption	RIF should be taken 1 hour before or 2 hours after antacid
Antiarrhythmics	Amiodarone, Digoxin	Aceyldigoxin, Amiodarone, Disopyramide, Mexiletine, Quinidine, Tocainide	RIF decreases levels of antiarrhythmics	Follow and adjust levels
Antibiotics		Chloramphenicol, Clarithromycin, Doxycycline, Dapsone	RIF decreases levels of antibiotics	Follow and adjust levels
Antibiotics		Clarithromycin, Erythromycin	These antibiotics increase levels of RIF	Follow and adjust levels
Anticoagulants		Anisindone, Dicoumarol, Nicoumalone, Warfarine	RIF decreases levels of anticoagulants	Follow PT, INR
Anticonvulsants	Barbiturates, Benzodiazepines, Phenytoin	Diazepam, Lorazepam, etc	RIF decreases levels of anticonvulsants	Follow and adjust levels
Antidepressants	Tricylciques	Amitiptyline, Amoxapine,	RIF decreases levels of antidepressants	Follow and adjust levels
Antifungal		Fluconazole, Itraconazole, Ketoconazole	RIF decreases levels of antifungals, Ketoconazole reduces RIF absorption	Follow and adjust levels, separate ketoconazole and RIF dose by 12 hours
Antihypertensive		B-blockers (Metoprolol), Calcium-channel blockers (Amlodipine, Verapamil, Diltiazem.)	RIF decreases levels of antihypertensives	Follow and adjust levels
Antimalarials	Quinine		RIF decreases levels of Quinine	Follow and adjust levels
Antipsychotic	Haloperidol		RIF decreases levels of Haloperidol	Follow and adjust levels
Bronchodilatators	Theophyllines	Aminophylline, Diprophylline, Dyphylline, Oxtriphylline, Theophylline,	RIF decreases levels of Theophylline	Follow and adjust levels of theophylline

Group	Drug class	Drug name	Effects	Recommendations
Erectile dysfunction	Sildenafil	Viagra	RIF decreases levels of Sildenafil	Follow and adjust levels
General anaesthetics			RIF decreases levels of General anaesthetics	Follow and adjust levels
Hormonal contraceptives			RIF decreases levels of hormonal contraceptives	Additional barrier method of contraception should be used
Immunosuppressive medications		Cyclosporine, Tacrolimus, Corticosteroids (prednisone)	RIF decreases levels of immunosuppressive medications	Follow and adjust levels
Lipid lowering		Clofibrate	RIF decreases levels of Clofibrate	Follow and adjust levels
Oral hypoglycemic agents		Sulfonylureas, Chlorpropamide, Glimepiride, Glyburide, Glypizide, Tolazanamide, Tolbutamide, Regaglinide	RIF decreases levels of oral hypoglycemic agents	Follow blood sugars and adjust medication
Thyroid hormone		Levothyroxine	RIF decreases levels of thyroid hormone	Follow and adjust levels
Uricosurics	Probenecid			Follow and adjust levels

3B. Potentially important drug interactions with RIF and HIV medication.

Note that for all patients placed on RIF, close monitoring is required, including CD4 counts, and virologic response

Adapted from: AIDS info- **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV;** Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/284/pi-drug-interactions

Last Updated: December 18, 2019; Access date for this document: March 15, 2020.

Antiretrovirals	Recommendations for use with Rifampin	Dose adjustment needed (for ART or RIF) and recommendations	Additional information on effect on Antiretrovirals and/or Rifampin Drug Concentrations
PIs			
All PIs	**Do not use with RIF**	NA	↓ PI concentration by >75% Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. Increasing the COBI dose is not recommended.
NNRTIs			
DOR	**Do not use with RIF**	NA	DOR AUC ↓ 88%
EFV	**Can use with Rifampin**	EFV dose should be 600mg/day Do not use EFV 400 mg with rifampin.	EFV AUC ↓ 26%

Antiretrovirals	Recommendations for use with Rifampin	Dose adjustment needed (for ART or RIF) and recommendations	Additional information on effect on Antiretrovirals and/or Rifampin Drug Concentrations
ETR	**Do not use with RIF**	NA	Significant ↓ ETR possible
NVP	**Do not use with RIF**	NA	NVP ↓ 20% to 58%
RPV	**Do not use with RIF**	NA	RPV AUC ↓ 80%
NRTI			
TAF	**Do not use with RIF , unless benefits outweigh risks.**	If coadministered, monitor virologic response.	Intracellular TFV-DP levels are higher when TAF is coadministered with rifampin compared to TDF administered alone, but clinical outcomes have not been studied. **TAF with Rifampin Compared with TDF Alone:** • TFV-DP AUC ↑ 4.2-fold **TAF with Rifampin Compared with TAF Alone:** • TAF AUC ↓ 55% • TFV-DP AUC ↓ 36% **TAF 25 mg Twice Daily with Rifampin Compared with TAF Once Daily Alone:** • TAF AUC ↓ 14% • TFV-DP AUC ↓ 24%
TDF	**Can use with Rifampin**	No dose adjustment needed.	↔ AUC TFV

Antiretrovirals	Recommendations for use with Rifampin	Dose adjustment needed (for ART or RIF) and recommendations	Additional information on effect on Antiretrovirals and/or Rifampin Drug Concentrations
ISTI			
BIC	**Do not use with RIF.**		BIC AUC ↓ 75%
DTG	**Can use with Rifampin-** in patients without suspected or documented INSTI-associated resistance mutations **Do not use with RIF** in patients with certain suspected or documented INSTI-associated resistance mutations.	Use DTG 50 mg twice daily (instead of DTG 50 mg once daily).	**Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Twice Daily Alone:** • DTG AUC ↓ 54% and C_{min} ↓ 72% **Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Once Daily Alone:** • DTG AUC ↑ 33% and C_{min} ↑ 22%
EVG/c	**Do not use with RIF.**	NA	Significant ↓ EVG and COBI expected

Antiretrovirals	Recommendations for use with Rifampin	Dose adjustment needed (for ART or RIF) and recommendations	Additional information on effect on Antiretrovirals and/or Rifampin Drug Concentrations
RAL	**Can use with Rifampin**	Use RAL 800 mg twice daily instead of 400 mg twice daily. **DO NOT USE RAL 1,200 mg once daily with rifampin** Monitor closely for virologic response	**RAL 400 mg:** • RAL AUC ↓ 40% and C_{min} ↓ 61% **Rifampin with RAL 800 mg Twice Daily Compared to RAL 400 mg Twice Daily Alone:** • RAL AUC ↑ 27% and C_{min} ↓ 53%
CCR5 Antagonist			
MVC	**Can use with Rifampin if Without a Strong CYP3A Inhibitor*** **Do not use with Rifampin If Used With a Strong CYP3A Inhibitor***	MVC 600 mg twice daily	MVC AUC ↓ 63%

Notes: * examples of CYP3A inhibitors are: EVG/c, All Pis, EFV (reference: Table 20. Mechanisms of Antiretroviral-Associated Drug Interactions; available at: https://aidsinfo.nih.gov/guidelines/htmltables/1/7346)

Abbreviations: BIC: bictegravir; **COBI** or **/c:** cobicistat; **DOR**: doravirine; **DTG** :dolutegravir; **EFV**: efavirenz ; **ETR**: etravirine; **EVG**: elvitegravir; **MVC**: maraviroc; **NVP**: nevirapine; **RAL**: raltegravir; **RPV**: rilpivirine; **TAF**: tenofovir alafenamide; **TDF**: tenofovir disoproxil fumarate

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP09_16Jan2020	16 January 2020	NA (original version)
SOP09_06Jul2020	06 July 2020	- Added signature of site PI for CRF9 - CRF10 (pages 4 and 5) - Grading for white blood cells added in Appendix 1 (pg. 10) - More specifications added in section on hepatotoxicity and on hyperbilirubinemia, Appendix 1 (pg 11-12); - Table of interactions added in appendix 3 (pg 18-24).
SOP09_20Sep2021		- Clarifications on reportable AE (pages 2-4) -Appendix 1 (pag 7); -Tables for grading and management of DDI (pg8), GI intolerance (pg9); Rash (pages 16-17); - New table added for "other" events (pg 13-14); - Changed layout of table for hematologic events (pag 10).