Title	Active TB initial and final evaluation
SOP Code	2R2 SOP08_25Nov2019
Effective Date	

1.0 Purpose(s)

The objective of this standard operating procedure (SOP) is to ensure appropriate follow-up and reporting of study participants who develop active TB during the trial.

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 affected

This SOP concerns the site 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 this SOP.

4.0 Definition(s)

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

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

ICF: Informed consent form.

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

IRB: Institutional Review Board

5.0. Procedures

5.1. Principal Investigator Responsibilities

The site Principal Investigator is responsible for:

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

5.1.2. **In the case of a death, providing the coordinating centre and IRB if applicable, with all additional requested information (autopsy reports, medical reports, etc.)** (ICH, E6 4.11.3);

5.1.3. **Reporting to the Coordinating centre all cases of active TB within 48h after the event** is known (ICH, E6 4.11.2);

5.1.4. Accurately and regularly documenting **all** cases of active TB in the source documents and CRF11 and CRF12.

5.2 Coordinating Centre Responsibilities

5.2.1 It is the responsibility of the Administrator at the Coordinating Centre to review all cases of active TB for comprehension and completeness. The Administrator will correspond with the site study team member responsible for the active TB report to ensure the case of active TB is properly reported on the website.

5.2.2 Once the case of active TB is properly reported, it is the responsibility of the Administrator at the Coordinating Centre to notify the Active TB Panel members (ATB panel) of the case of clinical diagnosis of active TB. The Administrator will correspond with the TB panel members to ensure the case of active TB is properly evaluated on the website. Once the report of active TB (CRF11 and CRF12) has been sent to the panel, it can not be modified (unless more information are required by the panel).

5.2.3 It is the responsibility of the ATB panel members to provide an independent evaluation of each case of active TB.

5.3 Active TB – Management and Data collection

General information

Active TB is one of the secondary objectives of the study; detailed information on active TB occurring during the duration of the study, in treatment and post-treatment phases, is necessary to ensure participants safety and study outcome collection.

Management

5.3.1. Any patients with symptoms suggestive of active TB must be evaluated following a standardized protocol, including x-rays, sputum AFB smears and cultures. Study staff at each site has to work with treating team to ensure that these investigations take place. If the site investigator or coordinating centre think that the investigations are not sufficient, this should be discussed with treating team and appropriate investigations implemented in order for the research staff to collect all the information needed for ATB reporting in the trial. If participants are diagnosed with active TB elsewhere than the study site, information must be collected regarding date and method of diagnosis, date and type of treatment, treating physician, and health facility. Permission must be sought to obtain clinical, laboratory, and treatment information, and copies of relevant x-rays from the treating physician.

5.3.2 Diagnosis: both chest x-ray and TB cultures are essential at Time of active TB diagnosis. At least 2 sputum samples for AFB smears and TB culture must be done. All positive mycobacterial cultures from participants who develop active TB within 26 months post randomization must be sent to reference TB laboratories for identification and **drug susceptibility testing**.

5.3.3 Treatment for active TB should follow National TB program and/or WHO guidelines.

5.3.4. A Chest-x ray is essential at End of treatment (i.e. within one month from end of treatment) to document treatment outcome.

Data collection

5.3.5. Two worksheets have been created to collect information on active TB: ACTIVE TB INITIAL EVALUATION FORM (CRF11) and ACTIVE TB FINAL EVALUATION FORM (CRF12). The ACTIVE TB INITIAL EVALUATION FORM (CRF11) must be filled out by the site research team for each study participant that has suspected active TB, within 48hrs of being informed of the suspected TB. The coordinating centre will contact the site PI and research staff promptly to review the clinical information, and verify that all necessary investigations have been performed or are underway.

5.3.6. Once a study participant, who has been diagnosed with active TB, has completed active TB treatment or, if a participant dies of possible TB, all information regarding investigation, diagnosis, treatment and response to the treatment must be collected using the ACTIVE TB FINAL EVALUATION FORM (CRF-12). **Note**: if after initial evaluation of suspected TB, an alternative diagnosis is done, this will be reported in CRF-12, and the event will be classified as "not TB".

5.3.7. For both CRF1 and CRF12: in the narrative section avoid providing any information that will reveal the study arm of participant (i.e. planned duration of treatment and dose of rifampin), because the Active TB Panel must be blinded to the study arm in order to make an impartial judgement.

5.3.8. Make sure that a copy of Chest x-rays at time of diagnosis, at time of end of treatment and at time of randomization is available in participant medical file, so that the copy can be sent via 2R2 website to the study coordinating center (see point 5.4.5 below).

5.4. Data entry into website

5.4.1. The active TB information must be entered into the study website in order for this information to be transmitted to the Coordinating centre. (The Active TB report acts as a notification mechanism to the coordinating centre). CRF11 must be entered in the website within 48h from knowing of the suspected TB.

5.4.2. Log on to the website (http://2r2.crc.chus.qc.ca) choose "Add/select records", select the participant among the randomized participants, and then press "Active TB initial form" in the left menu. (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.

5.4.3. Once all the ACTIVE TB Initial evaluation form information has been entered press the "save and exit " button to transmit the event information to the coordinating centre. At this point, an automated email will be sent to the Administrator who will then review the information. If information is missing or the report is not clear an email with questions/requesting clarifications/explanations will be sent to the site study team member responsible for the report. The requested information should be included in the ACTIVE TB Final evaluation report (CRF12).

5.4.4. To enter CRF12 in the website: log on to the website (http://2r2.crc.chus.qc.ca) and choose "Add/select records", select the participant among the randomized participants, and then press "Active TB Final form" in the left menu. (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 that the follow-up information is available and the follow-up information should be entered into the website as soon as possible. **Note** that CRF12 in the website cannot be completed if CRF11 Initial Active TB report has not been closed first.

5.4.5. Enter the appropriate study participant information from paper CRF12 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. **Note** that to complete the entry of CRF12 you need also to upload in 2R2 website a copy of : i) chest-x ray done at diagnosis, ii) chest x ray at the end of treatment and iii) chest x ray that was done at randomization. This is done because the TB clinical panel will need to review copies of the three chest x-rays. The copies have to be made non-nominal before uploading (i.e. remove the participant's name and date of birth).

5.4.6. At any point during data entry you may exit this section by selecting "Home" on the 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.

5.4.7. Once all the final information has been entered, press the "save and exit" button to transmit this information to the coordinating centre. At this point, an automated email will be sent to the Administrator who will then review the information. If information is missing or the report is not clear an email with questions/requesting clarifications/explanations will be sent to the site study team member responsible for the report. This email does not require a response, the requested information should be included in the ACTIVE TB FINAL EVALUATION CRF12.

Note: In order to be considered a study outcome the date of diagnosis of active TB must fall during the 26 months post randomization. This date will be determined during the analysis based on how the diagnosis was made. There is no data entry for this date.

6.0. References

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

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP08_25Nov2019	25 November 2019	NA (original version)