Title	**Procedures for Adverse Event reporting and evaluation**
SOP Code	2R2 SOP10_20Sep2021
Effective Date	

1.0 Purpose(s)

The objective of this standard operating procedure (SOP) is to ensure all reports of adverse events (AE) for the study 2R^2: *Higher dose Rifampin for 2 months vs Standard dose Rifampin for Latent TB: a 3-arm randomized trial*:

1. Are reviewed for appropriateness, completeness, and clarity prior to submitting them to the Adverse Event (AE) panel members.
2. Are reviewed by AE panel members following the protocol procedures (i.e. blind to study arm and independently)
3. Are reported to ethic committees and regulatory authority (Health Canada), if Serious Unexpected Adverse Drug Reactions
4. Have a final evaluation performed by the AE panel, which is complete and concordant.

This will ensure:

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

2.0 Scope: Persons/Areas affected

This SOP concerns the coordinating center, the AE administrator and the AE evaluation panel for the study entitled 2R^2: *Higher dose Rifampin for 2 months vs Standard dose Rifampin for Latent TB: a 3-arm randomized trial.*

This SOP is also distributed to sites, for knowledge of the overall reporting process.

3.0 Responsibilities.

The trial coordinating center is responsible for developing and maintaining this SOP and for making it available to all people who are involved in adverse event reporting and evaluations.

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 events administrator (AE administrator): person designated by the study PI, to be in charge of overseeing the reporting evaluation and management of AE in the study from all sites.

Adverse events panel: A panel of three physicians with expertise in clinical aspects of TB. In this study the members of the AE panel are also the members of the Data and Safety Monitoring Board (DSMB).

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".

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).

DSMB: Data and Safety Monitoring Board

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 (it can be called also Ethic Committee or Research Ethic Board)

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

Sections 5.1 to 5.3 describe the AE reporting process and are meant for all users of this SOP; section 5.4 is more technical and is meant to give instructions for use of 2R2 website to AE administrator.

5.1. Overview of process of AE reporting and evaluation in 2R2 study

In this study adverse events are reported as follows:

1. Mild events (i.e. grade 1 or 2), which **do not** require, in treating physician's opinion, study treatment discontinuation, are reported in the case report forms used for regular follow-up visits during treatment (CRF5). Treating team will provide medical care required for these events including necessary follow-up . The coordinating center will not be alerted by these reports. **Note**: given the ICH, E6 1.50 definition of Serious Adverse Event, and the Health Canada definition of Suspected Unexpected Serious Adverse Drug Reaction, the mild events we refer to in this category, CANNOT be a Serious Adverse Event nor a SUSADR (as either SAE or SUADR are NOT grade 1 or 2 events that can be managed without interruption of study medication).

2. Events of any grading, which requires, in treating physician's opinion the discontinuation of study treatment: these are reported in forms specifically designed for reporting of adverse events (Initial and final AE reporting forms, CRF9-CRF10). The coordinating center will be alerted by these reports and the reporting process will continue as described below.

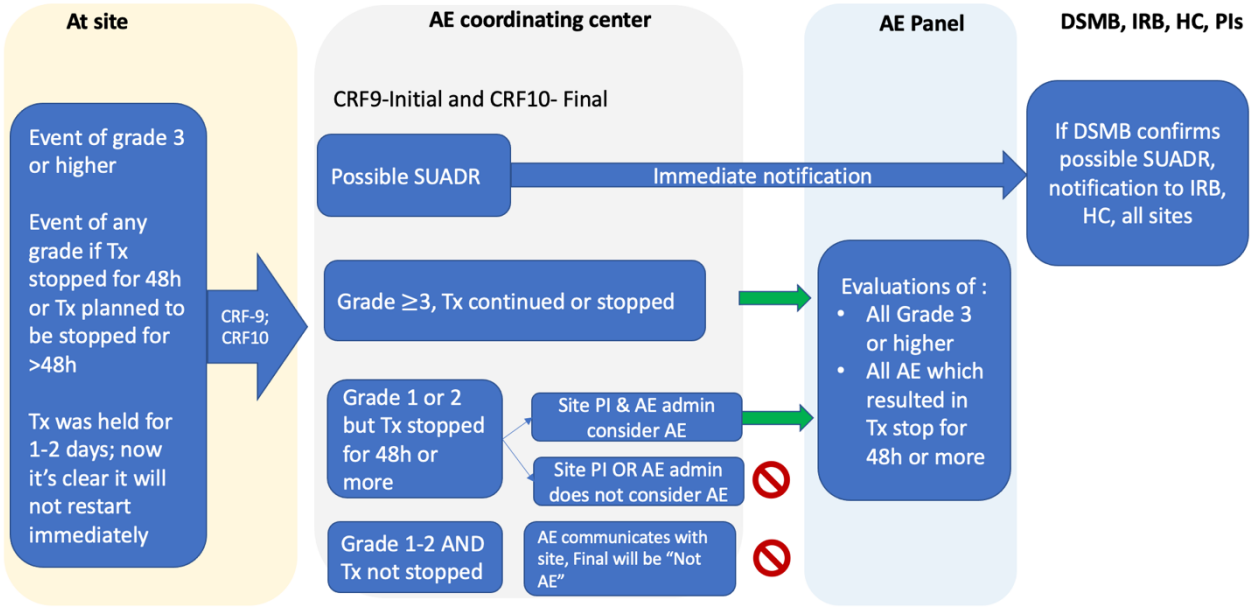
3. All events of grade 3 or 4, regardless of if they require discontinuation of study treatment or not are reported in AE report forms (CRF9-CRF10). The coordinating center will be alerted by these reports and the reporting process will continue as described below.

4. All deaths (regardless of apparent cause) during treatment phase are reported in AE report forms (CRF9-CRF10). The coordinating center will be alerted by these reports and the reporting process will continue as described below.

In 2R2 study, adverse events meeting definitions in section 2-4 above are reported by site investigators to the coordinating center, within 24 hours of AE being detected (i.e. site being aware). Note: the Site PI must be made aware and an Initial report is filed on website, thereby alerting the Coordinating center.

The AE reports are reviewed within 24 hours by the AE administrator, who will immediately notify the study PI of all deaths, and any AE that may meet the definition of a SUADR. Once the final AE reports are complete, they are evaluated by a 3-member independent and blinded AE panel (figure 1). Details on reporting of AE from sites are in SOP09 AE reporting and management.

Fig 1: Summary of process of AE reporting in 2R2 study.



Abbreviations: **AE**: adverse event; **AE Admin**: AE administrator; **DSMB**: Data and Safety Monitoring Board; **HC**: Health Canada; **SUADR**: Serious Unexpected Adverse Drug Reaction; **Tx**: treatment.

5.1.1. Initial AE report.

Study sites must **promptly** report all AE (using CRF9 "Initial AE report") that :

1) Result in drug discontinuation for 48 hours or more. Note: all adverse events of any Grade (i.e. grade 1 to 5) must be reported if they result in discontinuation of the study for 48 hours or longer.

2) Are of grade 3 or higher, even if not resulting in treatment discontinuation. Note: This is unusual as the protocol states that study drug must be stopped if associated with any Grade3-4 events. However, this situation can occur in certain circumstances for example, with hospitalizations due to other diseases, in which case the study treatment can be continued.

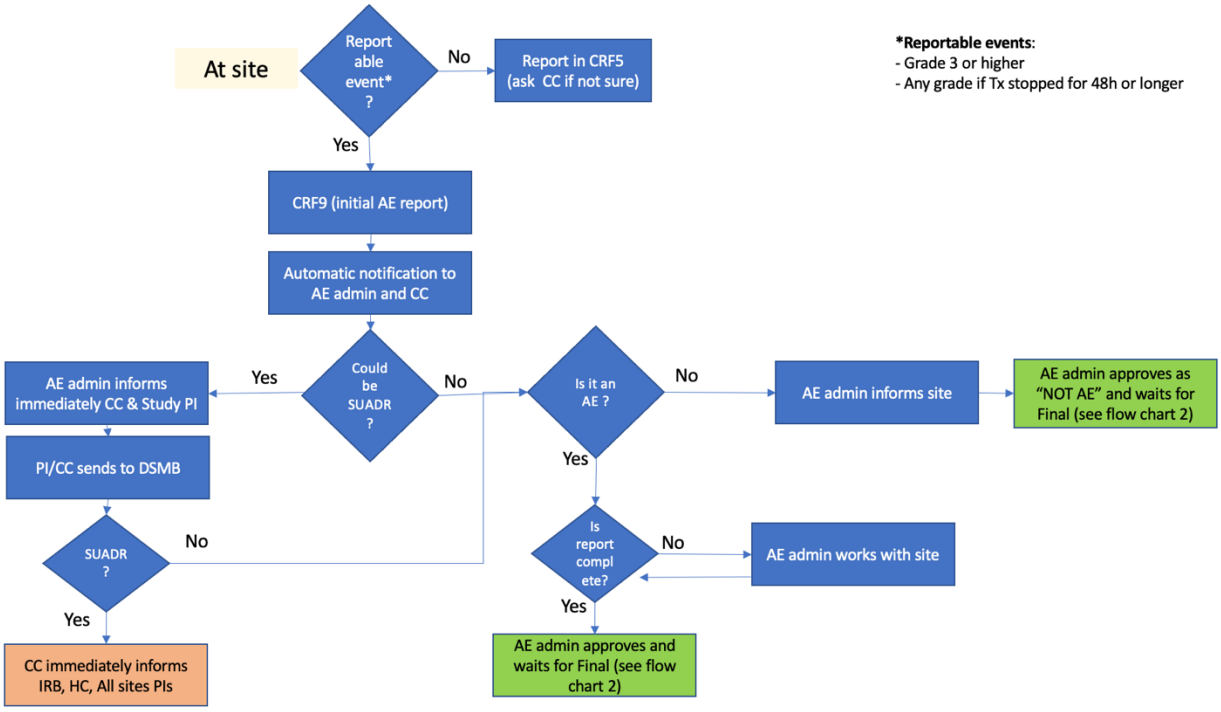
Promptly means within 24h of deciding to stop the drug, or of learning about the event.

Reports are sent by the site PI to the coordinating center via the study website using CRF9 and CRF10. If there is any issue with the website functioning, the paper CRF9 need to be scanned and sent by email to the coordinating center with subject INITIAL AE REPORT. The e-CRF9 can be completed online as soon as website is available again.

The site PI may delegate a research coordinator to submit the AE report, but the site PI must be notified promptly of all such adverse events and remains responsible for AE reporting.

The initial AE report is used as a **notification mechanism** to the coordinating centre, as they receive immediately an automatic email as soon as an initial AE report (CRF9) is submitted (**Figure 2**)

Figure 2. Flow-chart for initial AE report



Note: Potential SAE and SUADR are included in the category of reportable events as all Serious Events (as per ICH definition) are NOT events of grade 1 or 2 that can be managed continuing the study medication.

Abbreviations: **AE**: adverse event; **AE Admin**: AE administrator; **CC**: coordinating center; **DSMB**: Data and Safety Monitoring Board; **SUADR**: Serious Unexpected Adverse Drug Reaction;

Legend: Green boxes represent final stages for AE initial reports; Orange box represents the situation in which a Serious And Unexpected Adverse Drug Reaction is communicated to IRBs and regulatory authorities.

When an initial AE report is received at the coordinating center, it is screened promptly by the AE administrator. If a severe and Unexpected Adverse drug reaction is suspected, the coordinating center is informed and immediately sends the report to DSMB for them to judge: if DSMB concludes the AE meets the definition of a Severe and Unexpected Adverse Drug Reaction, the initial report is submitted to ethic committee of coordinating center, to Health Canada and all sites' PIs for them to submit to their local ethic committees. Note: submission of Severe and Unexpected Adverse Drug Reaction will be done using CIOMS form and respecting the Health Canada prescribed timing: 7 days of coordinating center awareness for SUADR which are life threatening or death; 15 days of coordinating center awareness for other SUADR.

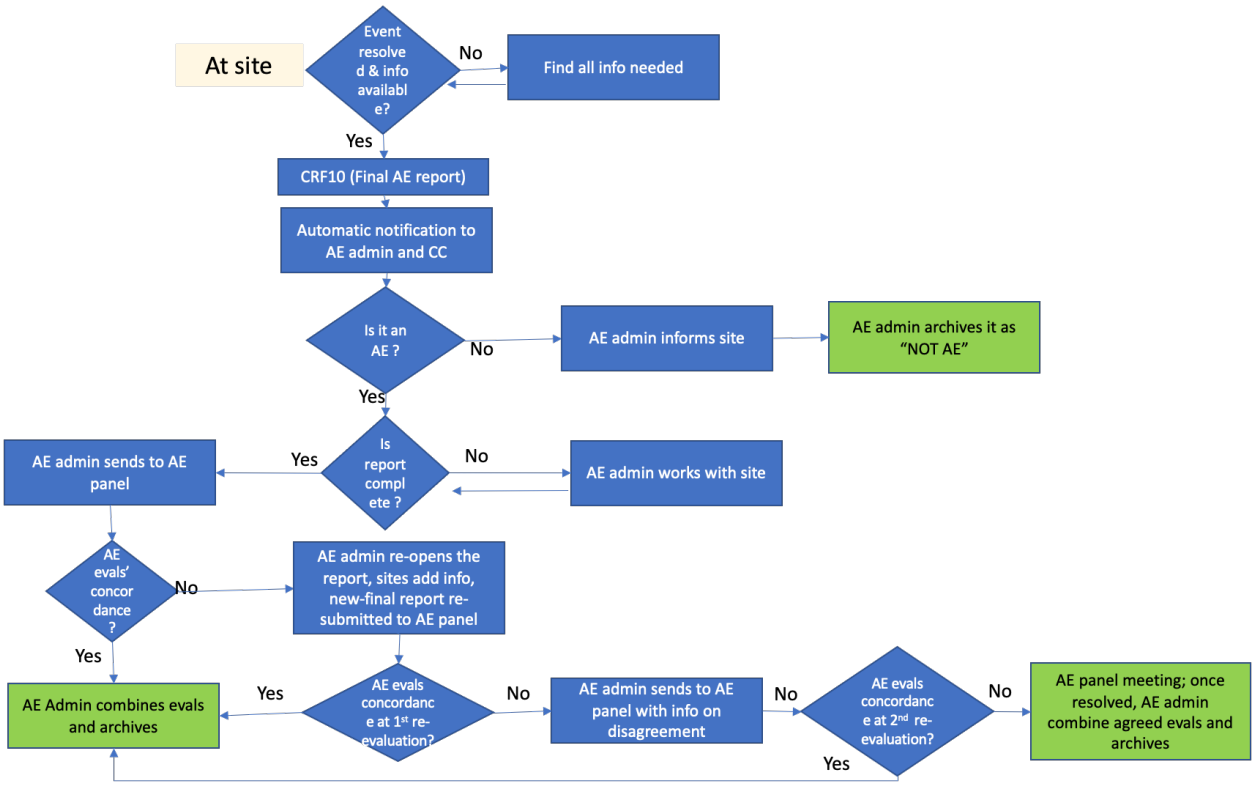
If initial AE is not suspected to be a Serious And Unexpected Adverse Drug Reaction, AE administrator makes sure the report is complete and blinding is maintained; approves it, and waits for final report.

If AE administrator thinks the AE reported does not meet the protocol definition of an AE, they communicate this to the site and classify the report as "NOT an AE".

5.1.2. Final AE report.

Once the event is resolved and all the relevant information about the AE become available, study sites complete and submit a final AE report (CRF10 "Final AE report") to the coordinating center by entering CRF10 in the study website (**Figure 3**).

Figure 3. Flow-chart for Final AE report



Abbreviations: **AE**: adverse event; **AE Admin**: AE administrator; **AE evals**: AE evaluations done by AE panel; **CC**: coordinating center.

Legend: Green boxes represent final stages for AE Final reports

Once CRF10 is submitted, the coordinating center and the AE administrator are automatically notified; AE administrator checks the final report for completeness and blinding (re study arms). Once the final AE report is completed, the AE administrator submits it for review to the AE panel members, via 2R2 website. If the report is not complete, AE administrator works with the study site until is finalized. Occasionally it may happen that an AE does not meet the definition of Serious and Unexpected Adverse Drug Reactions initially, but as the adverse event evolves it comes to meet this definition. If this happens, as soon as the AE administrator becomes aware of this, he/she will notify the study PI, and the event will be reported as described above for Serious and Unexpected Adverse Drug Reactions.

Once reports of AEs are complete and checked, they are sent to AE panel are evaluated independently by the three members, who are blind to study arm. The AE administrator combines their evaluations once all are completed into a final evaluation, which is then archived. In case of disagreement between panel members: if two out of three panel members agree - then simple majority wins. If all three are different, the AE administrator will re-open the final AE report, for sites to add/clarify information and sends the finalized report to AE panel again. If after this first re-evaluation there is still disagreement: AE administrator re-sent the report to AE panel, disclosing which is the disagreement. If after a second re-evaluation there is still disagreement, the AE panel is invited to meet and discuss the report (see session 5.4.6 below for detailed instructions). Once consensus is achieved, AE administrator records the final consensus evaluation and archives the report.

If the AE administrator or the study PI judges that the event was not an AE, the final report is classified as a "NOT an AE" and archived. This can happen in the following situations:

1.Study medication was not stopped AND event was grade 1 or 2. Note: if an event is of grade 3 or higher, even if treatment is not stopped, it is reported as an AE and sent to AE panel for review.

2. Treating team judges this was not an AE- and AE administrator agrees- and treating team would restart treatment. Note: treatment can either be restarted or not in these cases, depending on participant's choice. If participant decides not to restart, this will be classified as a participant's decision to permanently stop the treatment and not an AE.

5.2. Role and duties of AE administrator

5.2.1. It is the responsibility of the AE Administrator to review for clarity and completeness all AEs sent through the 2R2 website. The AE Administrator will also check that AE reports ensure that the Adverse Events panel remains blind to study arm. After reviewing the initial AE report, the AE Administrator can judge the report to be: 1) Completed and appropriate; 2) Incomplete ; or 3) Not an AE.

5.2.2. For all initial reports which are judged to be AE reports: the AE administrator screens them for severity: if an event is grade 3 or higher, the coordinating center is informed and event report is sent to Study PI. Study PI will judge if these events are possibly Serious and Unexpected Adverse Drug Reaction. In doubt, the initial report, is sent immediately by study PI, to DSMB for them to assess whether this is a potential Serious And Unexpected Adverse Drug Reaction or not. If all three members, or two of the three thinks it is a potential Serious And Unexpected Adverse Drug Reaction, then the AE is reported immediately to the coordinating center research ethics committee, and to Health Canada. As well the report is sent to ALL sites' PIs for them to submit to their local ethic committees. For all other events, that are not a Serious And Unexpected Adverse Drug Reaction, AE will work with sites to finalize the initial report, if needed, and then will approve the initial report and wait for the final report to be submitted.

5.2.3. If an AE is reported in a language other than English, the AE Administrator will contact the coordinating centre, who will ask site to translate the report. Translations will be added to the original narratives in the AE reports on the website.

5.2.4. The handling of AE reports should be prioritized according to their grading severities (priority will be given to those with severities of 3 and greater).

5.2.5. Once event is resolved, and all appropriate information are available at the site, site submits a final AE (i.e. CRF10 is completed in the website). The final reports are reviewed by AE Administrator, who can judge them to be 1) Complete; 2) Incomplete; 3) Not an AE. Incomplete

reports are re-opened, and site is informed on which are the missing information. Once report is final, AE administrator will approve it.

5.2.6. The Adverse Events panel must review all reports of events which are considered an adverse event by the treating team and AE administrator (or study PI). These may have resulted in temporary or permanent discontinuation of the study drug. The panel must also review AE of Grade 3 or higher, even if the study drug is continued. They review the AE initial and final reports **blinded to study arm.** The AE Administrator will forward to the AE panel via 2R2 website, initial and final reports of each event, once the final report (CRF10) is complete and approved. Panel members are notified with an automatic email once the final report is approved by the AE administrator.

5.2.7. Each AE panel member must provide an **independent evaluation** in regard to **Type of event**, **Grading of severity** and **Relationship to study drug**, of each AE. The AE administrator will send a reminder to AE panel member(s) who did not complete the evaluation, until all three evaluations are in.

5.2.8. All AE panel evaluations must be reviewed by the AE administrator for completeness-in case of incomplete evaluation, AE administrator will write to the panel member(s) to ask to complete it.

5.2.9. Consensus should be obtained within the AE panel as to their AE evaluations, specifically for the **Relationship to therapy, Type of event** and the **Grading severity** components**.** If the evaluations do not concur, it is the responsibility of the AE Administrator to guide the AE members to consensus. Refer to point 5.4.6 below for details.

5.2.10. For guidance pertaining to the coding of the **Relationship to therapy** or **Grading severity** refer to the **SOP09** on Adverse event management and reporting.

5.3. Role and duties of the coordinating center:

The coordinating center will:

5.3.1. Review periodically with the AE Administrator the list of AE reports received and submitted to the AE panel.

5.3.2. Liaise with sites to ensure correct investigation and management of all possibly drug-related Grade3-5 AE.

5.3.3. Communicated immediately Serious And Unexpected Adverse Drug Reaction, occurring inside or outside Canada, to the trial DSMB, the REB of RI-MUHC and to Health Canada, as per Health Canada procedures and to all site PIs.

5.3.4. Conduct the protocol specified interim safety analyses, which will be reviewed by DSMB, and sent reports of these analysis to IRB, HC and ALL sites PIs, for them to send to IRBs of participating sites.

5.4. Use 2R2 website for Adverse Event Reporting and Evaluation.

5.4.1. **Access to AE reports in 2R2 website for AE administrator**

To use the functions related to AE reports management, log on to the website https://2r2.ltb.cred.ca using the AE Administrative User ID and Password. (Note – after 20 minutes of inactivity users will be

automatically logged off of the website.) If unable to log on to the site, contact the coordinating center (Federica.Fregonese@affiliate.mcgill.ca).

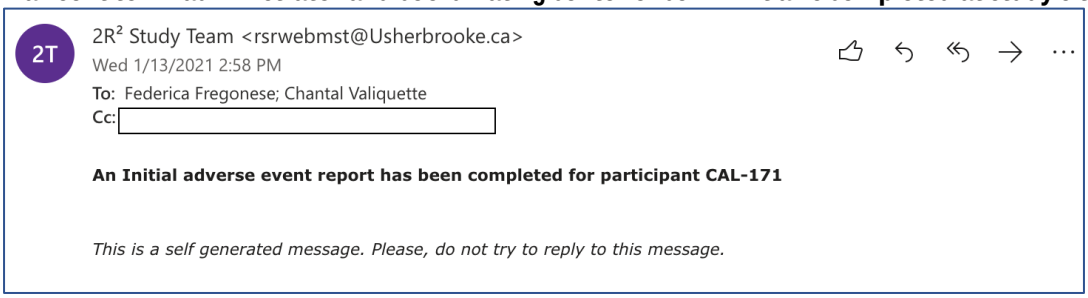
From the left menu, choose **Dashboard** and then open the **Adverse Event Management** window. This section contains three subsections:

1) **List of AE PANEL evaluation of adverse events** (see section 5.4.5. below)
2) **Adverse event management** (see sections 5.4.2. to 5.4.4. below)
3) **List of completed adverse event/evaluation** (see section 5.4.5. below)

5.4.2. Review of INITIAL AE reports by AE administrator

If an initial AE report has been completed by site investigator, AE administrator and coordinating center have received an automatic email (see example in figure 4).

Fig 4. Email sent to AE administrator and coordinating center once AE initial is completed at study site

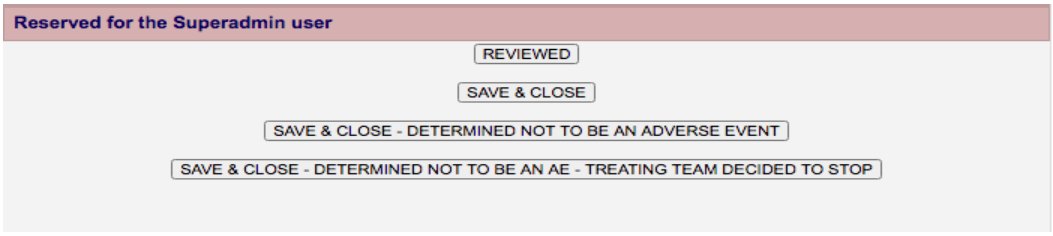


To go check the initial report, go to the session "**Adverse event management"** in Dashboard, as specified at 5.4.1., there is a list of AE report, with a status for each initial and final report.

The AEs awaiting review are identified with a status of **PENDING** in the **Status Initial** and **Status Final** columns of this list. To access a specific AE for review, click on **PENDING**. (Note – whenever an AE report will be modified by the site coordinator responsible for the AE, the status will return to **PENDING** and the AE must be reviewed again by the AE Administrator).

The initial/final AE report may be read by scrolling through the screen. Please refer to **SOP09** for the information required in an AE report narrative.

Four options are available at the end of the initial report screen for the AE Administrator:



- Choose "**REVIEWED"** if feedback should be sent to the site about the AE report. This will update the status of the AE on the list to **"REVIEWED"** and an automatic email informing that the AE report needs more information will be sent to the site coordinator responsible for the AE with a copy to the AE Administrator. By clicking on "**REVIEWED"**, the initial AE report is saved without submitting any information to AE panel.

This option is also to be chosen if it is the Administrator who directly modifies any of the AE data (**Note** – it is preferable thought to have the site modify the AE data to ensure data accuracy and agreement on what is reported in the AE report). If the data are modified by the AE Administrator the REVIEW option should be used and the AE Administrator should contact the study coordinator responsible for the AE to discuss these modifications. For record, the modifications should be reported at AI49:

AI49	Comments:

- Choose **"SAVE** & **CLOSE"** if report is completed. This is done once no more feedback from site is required. Choosing this option, will update the status of the AE on the list to COMPLETED.
  Note: it is important that AE administrator choose this option as soon as an initial report is judged as completed, because the final AE report for an event cannot be entered until the initial AE report has been formally approved by clicking on "SAVE & CLOSE" by AE administrator).

- Choose **SAVE&CLOSE – determined not to be an AE** - If AE Administrator determines that the event is not an AE. Write the reason why this is not considered an AE on AI49:

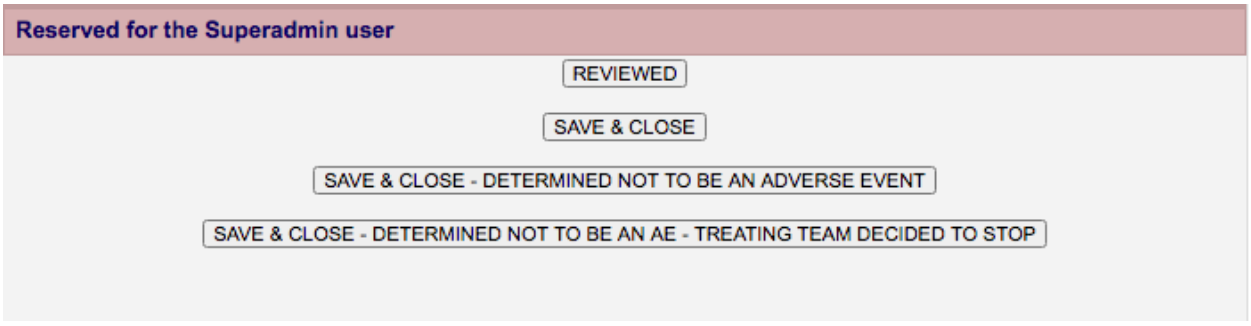
AI49	Comments:

If in doubt, discuss with coordinating center.
Once you click on **"SAVE&CLOSE** – determined not to be an AE" this will remove the AE from the list of "**Adverse event management"** and move it to the **"List of AE PANEL evaluation of adverse events"**. The coordinating center will inform the site of this decision.

- Choose **SAVE&CLOSE – determined not to be an AE- Treating team decided to stop:** If the treating team has decided to stop treatment but the event does not meet protocol definition of an AE as determined by the AE Administrator (and/or study PI), click on the "**SAVE&CLOSE"** – determined not to be an AE- Treating team decided to stop. Once you click on " **SAVE&CLOSE**" – determined not to be an AE- Treating team decided to stop" this will remove the AE from the list of "**Adverse event management"** and move it to the **"List of AE PANEL evaluation of adverse events"** and an email containing this decision will be sent to the site coordinator responsible for the AE submission with a copy to the AE Administrator. These cases need to be discussed with site PIs and coordinating center.

5.4.3. REVIEW OF FINAL ADVERSE EVENT REPORTS by AE administrator

Four options are available at the end of the final report screen for AE administrator:



- Choose **REVIEWED** if feedback should be sent to the site about the AE report and ask them by email the information needed. This will update the status of the AE on the list to **"REVIEWED"** and an email informing that the AE report need more information will be sent to the site coordinator responsible for the AE submission with a copy to the AE Administrator. By clicking on **"REVIEWED",** the final AE report is saved without submitting any information to AE panel.
  This option is also to be chosen if it is the Administrator who modifies directly any of the AE data (**Note** – it is preferable thought to have the site modify the AE data to ensure data accuracy and agreement on what is written in the AE report). If the data are modified by the AE Administrator the REVIEW option should be used and the AE Administrator should contact the study coordinator responsible for the AE to discuss these modifications.

- Choose **SAVE & CLOSE** – If no more feedback is required, AE Administrator clicks on the **"SAVE & CLOSE"** box. This will move the AE to the **"List of AE PANEL evaluation of adverse events"** for the AE administrator. An automatic notification email will be sent to all AE panel members that an AE is now ready for their review. The report will be in the **list of AEs for each AE panel member's.** Once an AE has been sent to the AE panel no modifications can be made to the AE reports. NOTE: be sure to choose this option once the report is finalized, clear and has been checked for blindness, as the AE panel has access to reports that have been approved by clicking on "SAVE & CLOSE".

- Choose **SAVE&CLOSE – determined not to be an AE** - If it is determined that the event is not an AE, click on the "**SAVE&CLOSE – determined not to be an AE**". Add at the end of the Narrative (AF15) the reasons why this was not considered an AE.
  Once you click on **" SAVE&CLOSE – determined not to be an AE**" this will remove the AE from the list and an email containing this decision will be sent to the site coordinator responsible for the AE with a copy to the AE Administrator. The report will be placed in the list of "List of completed adverse event/evaluation". Opening the report in this list will allow to add a comment explaining why this event was considered not an adverse event and save the report as final.

- Choose "**SAVE&CLOSE – determined not to be an AE- Treating team decided to stop":** If the treating team has decided to stop treatment but the event is determined not an AE, click on the **"SAVE&CLOSE – determined not to be an AE- Treating team decided to stop**". Once you click on " **SAVE&CLOSE – determined not to be an AE- Treating team decided to stop**" this will remove the AE from the list and an email containing this decision will be sent to the site coordinator responsible for the AE with a copy to the AE Administrator. The report will be placed in the list of "List of completed adverse event/evaluation". The AE administrator will have to open the report in this list and add a comment explaining why this event was considered not an adverse event and save the report as final. <u>These cases need to be discussed with site PIs and coordinating center.</u>

5.4.4. **Delays in filing FINAL ADVERSE EVENT REPORTS.**

If a study site has not entered a final AE report in the website, once an initial report has been **SAVED&CLOSED**, OUTSTANDING will appear in the **STATUS FINAL** column of the Adverse Event Management screen for the AE.

It is normal that site will take time to collect information and to wait for event to be resolved before filing the final report. However, if a final AE report has not been entered in the website <u>1 month after the initial AE report</u> was SAVED&CLOSED, "DUE" will appear in the Email Reminder column of the Adverse Event Management screen for the AE. An automatic reminder email can be sent to the site coordinator responsible for the AE by clicking on DUE. "SENT" and the date sent will then appear in the Email Reminder

column of the Adverse Event Management screen for the AE. Note: DUE will reappear in this column if the final AE report is still not entered after another month.

5.4.5. AE Administrator management of AE Panel's Evaluations

From the **Dashboard** (see 5.4.1.) click on the **Adverse Events Management** box to enter the **List of AE PANEL Evaluations of AEs** screen. This section contains a list of AE PANEL evaluations of AEs.

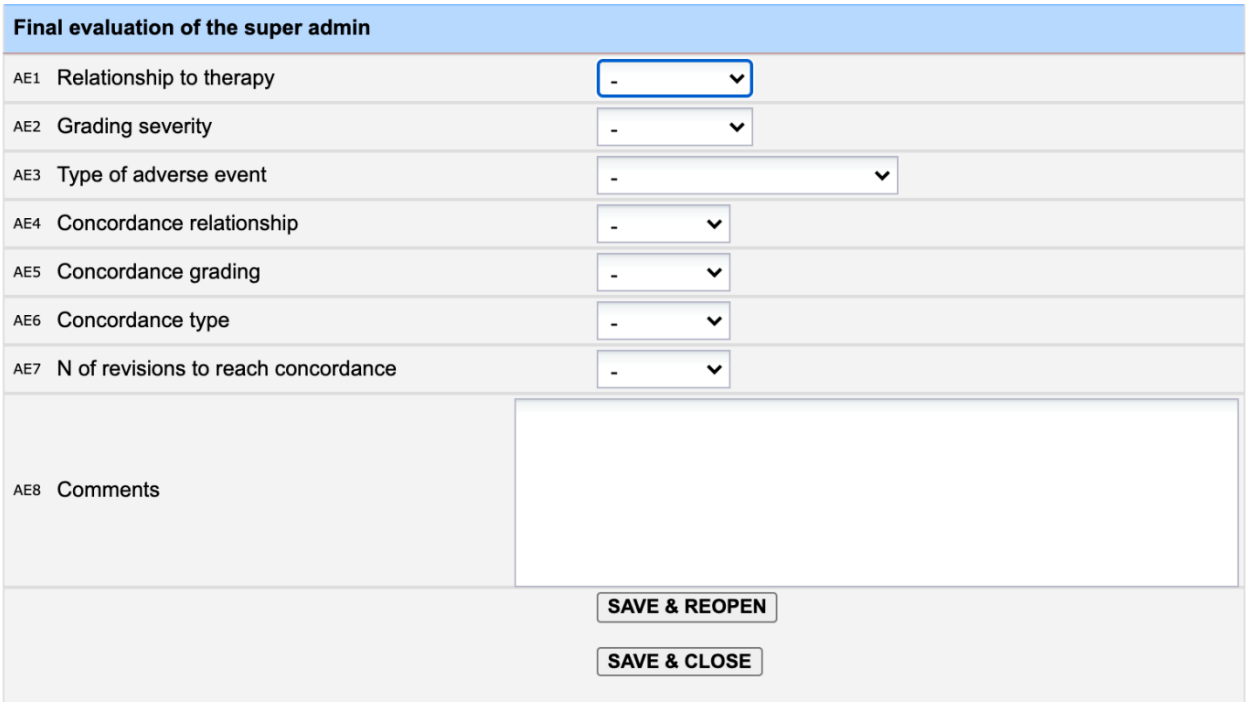
The evaluations awaiting review are identified with a status of **PENDING** in the **Adverse event evaluation status** columns (one column for each AE PANEL member) of this list. If an evaluation has been done by the AE PANEL member, the evaluation is classified as **COMPLETED** in the "Adverse event evaluation status" column for that reviewer and AE administration is notified by an email.
If an evaluation of an AE report has not been entered by the AE PANEL member, the evaluation is classified as **OUTSTANDING** in the "Adverse event evaluation status" column.

The AE administrator will follow-up on evaluations being completed. If needed, AE administrator will send by email a reminder to AE panel member(s) who did not complete the evaluation, until all three evaluations are in.

Once evaluations are **COMPLETED** for all three AE PANEL member in the "Adverse event evaluation status" column, the AE Administrator must review all 3 AE PANEL evaluations for each AE. To do so, click on FINAL (in the column Final).

The AE PANEL Adverse Event evaluation information pertaining to the **Relationship to therapy**, **Grading severity**, and **Type of adverse event** and **Comments** (additional relevant information, or questions from the AE PANEL member) are displayed for each panel member.

At the bottom of the screen there is the session for the AE administrator.



AE administrator will complete this session by combining the evaluation of the three members, and specifying the level of concordance for Type, Relationship and Grade. Note: If there is concordance, the N of revisions to reach concordance is 0. Refer to session 5.4.6 below, for situations in which there is no concordance.

If concordance was reached, choose **SAVE & CLOSE** at the end of this session. This will update the status of the report and move it to the session "List of completed adverse events evaluations".
It is important that reports are not **"SAVE & CLOSE"** until consensus has been reached between all 3 members of the AE PANEL).

5.4.6. AE administrator management of AE Panel's Evaluations when all three evaluations are discordant

General guidelines for evaluating "consensus" by AE administrator:

(a) **Consult with Principal Investigator** is required for all disagreements, before having a new evaluation redone, as it can be a judgment call based upon the specifics of the event. The PI MUST REMAIN BLINDED TO STUDY DRUG AT AL TIMES WHEN REVIEWING AE REPORTS OR JUDGEMENTS.

(b) **Grading**: Differences of 1 level are generally acceptable, with the exception of disagreements between grade 2 and 3. Death (grade 5) should not have any disagreement. Grades need to be within the 1 or 2 range OR within the 3 or 4 range, as AE will eventually be classified, for analysis, of Grade 1 or 2 vs of grade 3 or 4. Support material for grading are the tables in appendix of SOP09 for the most frequent event types. These tables have been shared with AE panel members by coordinating center.

(c) **Relationship to therapy**: there are only three possible choices for the AE panel members (Unlikely, Possible, Probable), so there should be agreement in most cases. For events of Grade 1 or 2, relationships which are close but not identical are acceptable, specifically: possible and probable. With Grade 3 to 5 a complete agreement between the 3 members is needed.

(d) **Type of event**: Small disagreements can be combined by AE administrator after discussion with study PI, if type expressed by 2 or 3 members is close but not identical (example: rash vs pruritus); designation of AE type for events of grade 3 and higher should have complete agreement.

After having discussed disagreements with study PI, Choose **SAVE & REOPEN** –If there is no concordance among the three AE panel members. In this case, the final AE report is "reopened" and it will need to be finalized and then re-evaluated. Contact by email the study site asking for more detailed or clearer information if needed.
Write also an email to the AE PANEL members to explain that re-evaluation is needed as there was no consensus (Note - feedback to AE PANEL members must never unblind them to the study medication).

At first re-evaluation, Panel members know only that there is no consensus, without any other information on the evaluations of other panel members. The AE administration will make sure that final report is clear and complete, asking sites to add information if were needed and then re-submit the final report to AE panel (as per session 5.4.3. above). The report becomes again "Pending" in the list of AE PANEL members.

If after this first re- evaluation, AE members' evaluations still do not concur, choose "SAVE & REOPEN". Check to see if changes can be done to the final report to improve it, then approve the final report ("SAVE & CLOSE") and write an email to AE panel members, to inform them about the persisting disagreement. For the 2nd re-evaluation AE panel members should be informed fully about the disagreement (i.e. which

were the types, grades or relationships to study medication expressed by the 3 members, without disclosing which member said what, and without unblinding). AE Administrator will ask them to re-evaluate.

If agreement cannot be found at this 3rd round of evaluation, AE administrator will ask panel members to meet and discuss evaluations, until an agreement is found. Members are still blind to study arm, but they know evaluations of other members.

Note: The AE Administrator cannot modify the AE evaluations done by AE Panel members. As well the AE PANEL members can only modify their respective evaluations, before final evaluation is saved and closed, and not the contents of the particular AE report.

The list of COMPLETED AEs, including AE members evaluations and final evaluation, is in "List of completed adverse events evaluations". Click on final to see the final evaluations. Note: if an event is classified by the AE administrator as NOT an AE, this will appear in the "List of completed adverse events evaluations", all evaluations will be blank, and the comment will explain why this was deemed not an adverse event.

6.0 References

Health Canada Guidance for Industry. Good Clinical Practice: Consolidated Guideline. ICH Topic E6

RI-MUHC Standard Operating Procedure SOP-CR-001_07, Administrative Management by Network of Networks, 01-Sept-2018.

7.0. SOP Revision history

SOP code	Effective date	Summary of changes
SOP10_15Mar2021	15 March 2021	NA (original version)
SOP10_21Jun2021		-Expanded the section on overview of reporting process. -Added flow charts to describe process;