Study sites monitoring visits

Title	**Study sites monitoring visits**
SOP Code	2R2 SOP13_06Jul2020
Effective Date	06 July 2020

1.0 Objective(s)

The objectives of this standard operating procedure (SOP) are to describe:

- The responsibility of the coordinating center to monitor quality of all aspects of the trial
- The responsibilities of the site principal investigator to allow and facilitate monitoring
- How monitoring can ensure that the study is conducted, and data generated, documented (recorded), and reported in compliance with the protocol, and GCP.

2.0 Scope: Persons/Areas affected

This SOP concerns the co-investigators (and their respective research teams) involved in conducting research with human participant 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 qualified investigator is responsible for adoption of the processes described in the SOP.

4.0 Definition(s)

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

II. **Monitor:** Research staff form coordinating center will conduct site visit to direct assess compliance with the protocol and applicable regulations and guidelines.

III. **Site Investigator**: A person responsible for the conduct of the research study at a study site. If a study is conducted by a team of investigators at the same study site, the Site Investigator is the responsible leader of the team.

IV. **Case report form (CRF):** A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each participant in a clinical research study.

V. **Good clinical practice (GCP):** An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human participant.

5.0 Procedures

5.1 General information

The regular study monitoring site visit is conduct by the monitor or by the principal investigator from the coordinating center in Montreal, Canada.

The monitor will perform periodic monitoring visit to each participating center, to directly assess compliance with the protocol and applicable regulations and guidelines. In particular, the purpose of study monitoring is to verify that:

- The rights and well-being of human participant are protected;
- Reported study data are accurate, complete, and verifiable from source documents;
- The study is conducted in compliance with GCP and the currently approved protocol.

5.2 Monitor role

The monitor should visit the study site frequently enough to assure that:

- The facilities used continue to be acceptable for purposes of the study;
- The study protocol or investigational plan is being followed;
- Changes to the protocol have been approved by the local IRB;
- Accurate, complete, and current records are being maintained;
- The site investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

5.2.1 Monitor preparation before performing the regular study monitoring site visit

The monitor will contact the site investigators to have availabilities of the site to conduct a visit. Once dates are fixed and before the visit the monitor will:

- Review relevant study site data using 2R2 website programs for data monitoring to identify any issue with the data. Also look for any unusual trends in the data;
- Review prior monitoring report and identify any outstanding issues;
- Ensure all Note-To-Files have been completed;
- Review emails from study site for any outstanding issues;
- Review adverse events, active TB cases and death to identify any outstanding issues;

Based on the points above, the monitor will decide on objectives of visit and data to be reviewed then will send an email at least 2 weeks before the regular study monitoring site visit (see **Appendix 1** for essential points to be included in the email), and a draft agenda for the visit (see **Appendix 2** for example of visit's agenda).

5.2.2 What the monitor accomplishes during a regular study monitoring site visit

- Meet with the study team, review and adjust the agenda, and discuss any issues;
- Verify all consent forms for study participant enrolled since last visit;
- Verify that all study participant records, data and source documents identified to be reviewed during the monitoring visit are complete and accurate;
- Verify any adverse events, active TB cases and death to make sure all information needed was obtained.
- If needed, take pictures of the CXRs of enrolment, active TB diagnosis, active TB resolution as required (i.e. if site; doesn't have digital CXR or if it was not possible to upload the pictures to 2R2 website, etc) - Note: the CXR will be de-identified before taking the picture.

- Verify that essential documentation (master binder) of the study, required by the monitoring visit, is complete (i.e. recent correspondence, participant screening log, participant identification code lists, up-to-date medical and nursing licenses/diploma, task delegation of responsibilities form, etc);
- Verify the storage and documentation of samples for population PK;
- Verify that the study drugs inventories are accurate and study drugs are stored appropriately;
- Verify that all study documents are kept in a secure, confidential manner;
- Ensure Monitoring site Visit Log (see log example in **SOP12**-Appendix 6 "Initiation site monitoring visit") is signed by monitor and all relevant study personnel;
- Meet with the study team at the end of the monitoring site visit to summarize and discuss findings and recommendations.

5.3 Monitoring site visits timeline

5.3.1.Visit timeline for 2R^2 during 22 months period of enrolment and treatment completion:

Visit #	Type of visit	Timing	Role of the visit
1	Initiation visit- in person	Before study starts	Assure trial can start at the site- See SOP12 for details on Initiation visit
2	Virtual (i.e. call/video-conference) regular monitoring	1 to 2 months after the study initiation	Check that procedures for screening and enrolment are followed and that enrolment proceeds as planned
3	Virtual or in person regular monitoring	3 months after the study initiation?	Ensuring GCP and SOP are followed for every study components, check quality of data collected.
4, 5, 6,7	In person regular monitoring	6 months after the previous regular study site monitoring visit and every 6 months thereafter	Ensuring GCP and SOP are followed for every study components, check quality of data collected.
…	Virtual or in person exceptional visit prompted by site or coordinating center	At any time if needed	Respond to specific needs raised by site research team; act on any change emerged at site (as protocol violation) or issued by the coordinating center (as implementation of an amendment, etc).

5.3.2.Visit timeline for 2R^2 during the 22 months from the last treatment permanent discontinuation (post-treatment follow-up):

Visit #	Type of visit	Time	Role of the visit
1,2	In person (or virtual)	12 months after last monitoring visit at the end of enrolment period	Ensuring GCP and SOP are followed for every study components during post-treatment follow-up, check quality of data collected
--	Virtual or in person exceptional visit prompted by site of coordinating center	At any time if needed	Respond to specific needs raised by site research team; act on any change emerged at site (as protocol violation) or issued by the coordinating center (as implementation of an amendment, etc).
3	Study closure	At the end of study	See **SOP17** for information on study site closure

5.4 Study site role

5.4.1. Preparation for regular study monitoring site visit from study sites includes:

- Ensuring that documentation (paper and electronic) is kept up to date;
- Completing the applicable case report forms (CRFs), on a regular basis;
- Performing any outstanding CRF corrections, additions or deflections, including explanations (if necessary);
- Ensuring that the master binder, including essential documents, is up to date;
- Ensuring that appropriate access to electronic records is arranged for the monitors (if required). Organize and document training for monitor for electronic health record system or obtain documentation of same;
- Having all paper and/or electronic records available for review, along with the corresponding source documents;
- Ensuring that research staff follow all institutional requirements for permitting third parties onto site, e.g., security pass, escorting monitors.

5.4.2 Facilitating the monitoring site visit

The site coordinator, under the supervision of site PI, has to be prepared to provide or verify the following during regular study monitoring site visits, as applicable:

- Investigator qualifications, resources, and site facilities (e.g. laboratories, equipment, staff) remain adequate to safely and properly conduct the trial;
- Current list of study personnel and task delegation of responsibilities form;
- Conduct of the trial is in compliance with the currently approved protocol/amendments, GCP, applicable regulatory requirement/s(s), and site SOPs;
- Signed informed consent was obtained for each participant before participation in the trial, and only eligible participant have been enrolled;
- Signed re-consent forms were obtained, as applicable;
- Participant enrolment logs and original recruitment targets and timelines;
- Source documents, other trial records, and essential documents are accurate, complete, up-to-date and filed appropriately;
- All required Research Ethics Board (REB) documents;
- All serious adverse event (SAEs), active TB and death have been reported within the time periods required by GCP, protocol, REB, as required; and
- Action has been taken to prevent the recurrence of deviations (if any) from the protocol, SOPs, GCP, or applicable regulations.

5.5 Regular study monitoring site visit report

The monitor will prepare a monitoring site visit report detailing monitoring findings **(Appendix 3)**. The report should include a statement of the findings, conclusions and any actions required to correct any deficiencies noted during the visit. The inventory supplies, agenda and the check list for the monitoring site visit should be added as appendix in the report.

The monitor will send the draft of the report to the site investigator, who will give feedback. Once coordinating center and site investigator agree on the final version, the report can be classified as final and a copy must be kept in the master binder on site.

The monitor will follow-up with the study site, by email or phone calls, to ensure all corrective actions mentioned in the visit report have been taken. All corrections made will be reviewed and reported in the next regular study monitoring site visit report.

6.0. References

Research Institute of McGill University Health Center, "SOP-CR-013_07 Study Monitoring and Communication", 01-Sep-2018.

7.0 SOP Revision history

SOP code	Effective date	Summary of changes
SOP013_06July2020	06 July 2020	NA (original version)

APPENDIX 1
Essential points to include in the email to send to the site investigator for the regular study monitoring site visit

The email subject should state "Monitoring site visit for $2R^2$ trial".

The email should contain the following information:

1. Proposed dates for the visit
2. Who will be conducting the visit
3. Visit objectives (which can be one or more of the following):
    - Review and establish strategies to enhance recruitment
    - Review the screening and randomization process
    - Review the reporting and management of :
        - Study participants' follow-up during treatment
        - PK study
        - Adverse events
        - End of treatment
        - Study participants' follow-up post treatment
        - Cases of active TB
        - Death
    - Review data entry
    - Review and establish strategies to deal with any other problems the sites may be having
    - Additional training (as required for new staff or new functionalities)
4. That the visit will include:
    a. A review of site facilities
    b. Review of all informed consents signed since previous visit
    c. A regulatory review of any changes and updated to essential documents (for example annual review of local IRB/REB), if any
    d. Spot check of eligibility and data entered into the study website for specific participants (provide list of participants for whom checks are needed) as well as review their source documentation to ensure all data collected are verifiable
5. What has to be available during the visit:
    - Master binder (essential documents for regulatory review)
    - Signed informed consent forms (and list study participant recruited since previous visit)
    - Research files & source documents
6. There will be a meeting with the site PI at the beginning of the visit and a summary meeting at the end of the visit, to report on findings.
7. Arrangements needed: a desk/work area (for monitor to review the study charts), access to the internet (to verify the website data), assistance of site study coordinator (for any questions or to have access to any specific study documents)
8. Proposed agenda/schedule (to be finalized with site investigator).

APPENDIX 2

SAMPLE AGENDA/SCHEDULE FOR VISIT

Draft agenda has to be finalized with site PI.

Agenda contains dates, times and names of people involved in any visit activity. If the site has several clinics to be visited a list of the times & dates for each clinic visit should be included. The order of the agenda will be dependent upon availability of staff and timing of visit.

Activities that must be included are:

- Meeting with site investigator & site coordinator to
    - Review questions/issues at site
    - Follow-up on any major outstanding issues from previous visit
    - Discuss primary objective of visit
    - Review the agenda and plan the visit

- Review and establish strategies to deal with primary objective of visit
- Review Master binder (essential document for regulatory review as required)
- Facilities review (pharmacy, lab, clinic, etc)
- Inventory supplies/storage (medication supply)
- Review signed consents form
- Review study files – CRF, patient charts, website
- Review PK sub-study sample storage & documentation
- Summary meeting (findings, recommendation, what next, etc.)

APPENDIX 3
SAMPLE OF A MONITORING SITE VISIT REPORT

MONITORING SITE VISIT- INTERIM VISIT REPORT

[Site name and date of the visit]

Name of Clinical Site: **Date of report:**
Date(s) of visit: **Number enrolled since last visit:**
Conducted by: **Number enrolled since started:**

Clinical site personnel involved with the study:

Name	Title	Available during discussions

Summary of monitoring site visit:

The **primary objective** for this visit was to:

Methods, observations, recommendations of all the following:

- ADMINISTRATION (e.i. finance, contract, master binder, etc)
- FACILITIES
- SCREENING & ELIGIBILITY
- INFORMED CONSENT ADULT / ASSENT / PARENTAL
- RANDOMIZATION
- FOLLOW-UP DURING TREATMENT
- END OF TREATMENT
- FOLLOW-UP POST TREATMENT
- ADVERSE EVENT (AE)
- ACTIVE TB
- DEATH
- PK STUDY
- CONCLUSION

ANNEX 1 to MONITORING SITE VISIT REPORT: Agenda of the monitoring visit

[….]

ANNEX 2 to MONITORING SITE VISIT REPORT: Inventory of supplies

SUPPLIES	COMMENTS
Medications	**Rifampin for two experimental arms** (what is used, quantity and expiry dates) **Rifampin for standard arm** (what is used, quantity and expiry dates, if applicable)
Others_____	

ANNEX 3 to MONITORING SITE VISIT REPORT: Check-list for the monitoring site visit

STUDY TEAM MEETING

ITEMS	Y	N	N/A	COMMENTS
1. Review of site visit agenda with site investigator & study staff				
2. Review of previous site visit outstanding items				
3. Review of participant cumulation status & enrollment objectives				
4. Review of protocol and any amendments				

FACILITIES REVIEW

ITEMS	Y	N	N/A	COMMENTS
1. Tour of facilities (clinic, CXR, labs, pharmacy as appropriate)				
2. Ensure site has adequate supplies (meds, lab, etc)				
3. Ensure adequate resources to run study				

REGULATORY REVIEW (MASTER BINDER)

ITEMS	Y	N	N/A	COMMENTS
FROM COODINATING CENTER				
1. Revision history of protocol and amendment				
2. Original study protocol				
3. Original approved consent form and amendment				
4. Institutional Research Board (IRB) approval				
5. Regulatory agency documentation (Health Canada)				
FROM SITES				
6. Local IRB application				
7. Local IRB approvals				
8. Local IRB committee composition				
9. Informed consents/assent if translated				
10. Annual REB renewal of protocols if applicable				
11. Revision history of CRF and amendment				
12. Most recent version of CRFs				
13. Adverse Event & Serious Adverse Event Safety reports submitted to REB as per applicable regulations				
14. Annual summary of study progress submitted to REB				
15. Signature sheet / task delegation of responsibilities form				
16. Staff documents: CVs, medical licenses/diploma				
17. Training log				

REGULATORY REVIEW (MASTER BINDER)

ITEMS	Y	N	N/A	COMMENTS
18. Up-to-date copy of Monitoring Site Visit Log				
19. Monitoring site visit report				
20. Audit certificate if applicable				
21. Inter-institutional (contract) and transfer of funds agreement				
22. Copy of insurance if applicable				
23. Site laboratory certification up-to date				
24. Copy of normal range values for each laboratory used				

25. GCP training certificate				
26. GCP guidelines				
27. Separation of confidential medical records from CRFs				
28. Research records stored in a secure area				

SAFETY REVIEW

ITEMS	Y	N	N/A	COMMENTS
1. Review all informed consent forms (ICF)				
2. Review screening log				
3. Review list of participant identification codes				
4. Review participant enrolment log				
5. Review all adverse event, active TB and death data				
6. Review randomization processes				