**III. POST – APPROVAL REVIEW**

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**3.10 Management of the DSMC/ DSMB/ IDMC Reports**

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| --- | --- |
| Supersedes | Standard Operating Procedure Version 4 |
| Version | 5.0 |
| Authored By | Dr. Narcisa Sonia Comia  Dr. Mary Warren Ilaga  Dr. Von Andre Medina |
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| Approved By | **Dr. Robert Magsino**  President and CEO |
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**3.1. OBJECTIVES/SCOPE/RESPONSIBILITIES**

**3.1.1 Objectives**

This SOP describes how the MMMC-RERC processes post-approval submissions by the Principal Investigators. Depending on the nature of the submissions, they may be processed by either expedited or full board review. This chapter describes submission procedures, required forms, documentation of committee action, communication of committee action to the PI, and filing of documents.

**3.1.2. Scope**

This SOP applies to all study protocol-related submissions after approval has been issued for the study protocol and study protocol-related documents. These submissions include study progress report, final report, study protocol amendments, continuing review application, non-compliance (deviation or violation) reports, early study termination report, queries from stakeholders, serious adverse event reports (SAEs)/ suspected unexpected serious adverse reaction reports (SUSARs), and DSMB/DSMC/ISMB reports.

**3.1.3. Responsibilities**

It is the responsibility of the PI to comply with post-approval review requirements, including the submission of required reports listed in ***MMMC RERC F-4-B: APPROVAL LETTER form.***

The Administrative Staff is responsible for receiving and processing all submissions, including inquiries or complaints from research participants and other stakeholders. Original primary reviewers are responsible for reviewing these post-approval submissions.

**3.2 POST APPROVAL REVIEW WORKFLOW**

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| **ACTIVITY** | **RESPONSIBILITY** |
| Receives and manages documents submission | Administrative Staff |
| |  | | --- | | Submits documents to the MMMC-RERC Chair/ Member-Secretary to determine classification of review as expedited or full board | | Administrative Staff |
| Chair/ Primary reviewers review submissions classified as expedited review. Primary reviewers review submissions classified as full board review | Chair/ Primary Reviewers/ Members |
| Review full board study protocols in meeting | Members |
| Communicates results to PI | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.3 REVIEW OF PROGRESS REPORTS**

**3.3.1. Objective/Scope/Responsibilities**

The objective of this SOP is to describe review procedures of progress reports submitted to MMMC-RERC.

This SOP provides instructions for the review of progress reports that are required by MMMC-RERC to be submitted by the PI to monitor the safety of participants enrolled in a study. The progress report becomes the basis for continuing review of protocols whose approval needs to be renewed.

This SOP applies to conducting any continuing review of study protocols involving human subjects at intervals appropriate to the degree of risk but not less than once a year. Depending upon the degree of risk to the participants, the nature of the study, the vulnerability of the study participants, and duration of the study, MMMC-RERC may choose to review or monitor the protocols more frequently.

This SOP describes the follow up of Progress Reports by the MMMC-RERC administrative staff and the review of such reports submitted by the PI by designated members of MMMC-RERC in compliance with ICH-GCP requirements.

It is the responsibility of MMMC-RERC administrative staff to remind investigators to submit the progress report before due date, to forward the report to the primary reviewers for review comments, and to communicate with the investigators if there is need for further information or action.

It is the responsibility of the primary reviewers to review the reports to check completeness of information and ensure that the data are in accordance with the protocols and other related documents approved by the MMMC-RERC.

**3.3.2 Progress Report Submission Workflow**

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| **ACTIVITY** | **RESPONSILITY** |
| Remind the PIs to submit the progress report one month before the due date using the *MMMC-RERC F-3-A: Reminder Letter for Progress Report* | Administrative Staff |
| Submit progress report on or before due date | Principal Investigator |
| Check the completeness of information in the report and forward to the primary reviewers for assessments/comments. | Administrative Staff |
| Review the progress report if it is in accordance with the approved protocol and related documents | Primary Reviewers |
| Report approval/other recommendations to full board | Administrative Staff |
| Discuss at full board and make a decision | Primary Reviewers |
| Communicate RERC decision to PI | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.3.3. Detailed Instructions**

**3.3.3.1 Submission and Management of Progress Report**

1. The Primary Investigator should provide the MMMC-RERC with a summary of the progress of the study depending on the foreseeable risk of the study to the participants. The frequency may be quarterly, biannual, or once a year.
2. The administrative staff checks the Study Protocol Database and tracks due dates of progress reports of Study Protocols approved by the MMMC-RERC.
3. The administrative staff prepares and sends reminder letter addressed to the PI using ***MMMC RERC F-3-A: REMINDER LETTER FOR CONTINUING REVIEW, PROGRESS REPORT/ FINAL REPORT*** and keeps a receiving copy of the communication. The reminder letter is sent to the PI one month before the due date of the report.
4. The progress report is facilitated through the submission of data using ***MMMC RERC F-3-B: PROGRESS REPORT FORM,*** together with documents deemed relevant by the investigator to clarify information indicated in the report.
5. The Administrative Staff checks the submission for completeness and gives a receiving copy of ***MMMC RERC F-3-B: PROGRESS REPORT FORM*** to the PI or his/her representative.
6. The Administrative Staff logs the date of submission on the ***MMMC-RERC F-5-H: SUBMISSIONS LOG*** and ***GENERAL SUBMISSION LOGBOOK.***

**3.3.3.2** **Classification of Review by the RERC Chair**

1. The RERC Chair/Member Secretary classifies the submission as either for full board or expedited review.
2. Generally, classification of review of progress report as expedited or full board is based on the initial review classification (i.e. progress report of full board study protocols is done through full board review); unless otherwise indicated by the specificities of the submitted information.

**3.3.3.3** **Review by Primary Reviewers**

1. The Administrative Staff sends the progress report to the Primary Reviewers.
2. For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.
3. Progress report subject to full board review received within the cut-off period of **fifteen (15)** calendar days before the scheduled RERC full board meeting is sent to Primary Reviewers**.**
4. The Administrative Staff includes. The progress report submission on the agenda for the next RERC meeting.
5. The Primary Reviewers accomplish the review and return the signed ***MMMC RERC F-4-B: PROGRESS REPORT FORM*** to the Administrative Staff on the day of the RERC meeting.
6. The documents are presented to Members when progress reports are deliberated on. For detailed information on the conduct of full board review***, see SOP Chapter II.***

**3.3.3.4** **Communication of results**

1. The PI is notified of the RERC decision, noting action on the progress report through an action letter.
2. For submissions under full board review, the MMMC-RERC decision will be sent to the Principal Investigator within **fifteen (15)** calendar days after the MMMC-RERC board meeting.
3. For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.
4. The PI may be requested to provide additional information or submit additional documents.

**3.3.3.5 Files management**

1. The Administrative Staff stores the signed progress report documents in the study protocol file folder upon approval of the progress report.
2. The Administrative Staff enters relevant study protocol data into the Study Protocol Database.

**3.4 REVIEW OF FINAL REPORTS**

**3.4.1. Objective/Scope/Responsibilities**

The objective of this SOP is to describe review procedures of MMMC-RERC for final reports.

This SOP aims to provide instructions for the review of final reports that are submitted by the PI after completion of subject enrolment and all follow up procedures done by the Principal Investigators in compliance with ICH-GCP requirements.

It is the responsibility of the MMMC-RERC administrative staff to forward the final report submitted by the PI to the primary reviewers for review comments and to ensure that the data are in accordance with the protocol and other related documents approved by the MMMC-RERC.

**3.4.2 Final Report Submission Workflow**

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| **ACTIVITY** | **RESPONSILITY** |
| Remind the PIs to submit the final report one month before the due date using the *MMMC-RERC F-3-C: Reminder Letter for Final Report* | Administrative Staff |
| Submit final report on or before due date | Principal Investigator |
| Check the completeness of information in the report and forward to the primary reviewers for assessments/comments. | Administrative Staff |
| Review the final report if is in accordance with the approved protocol and related documents | Primary Reviewers |
| Report approval/other recommendations to full board | Administrative Staff |
| Discuss at full board and make a decision | Primary Reviewers |
| Communicate RERC decision to PI | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.4.3 Detailed Instructions**

**3.4.3.1. Management of the final report package upon submission**

a.Upon completion of the study, the investigator should provide the MMMC-RERC with a summary of the outcome of the study, especially of the human participants who were involved, in a form of an end of study report.

b.The Administrative Staff checks the Study Protocol Database and tracks due dates of Final Reports of Study Protocols approved by MMMC-RERC.

c. The Administrative Staff prepares and sends reminder letter/notice addressed to the PI using ***MMMC RERC F-3-A: REMINDER LETTER FOR CONTINUING REVIEW, PROGRESS REPORT/ FINAL REPORT*** one month before the due date of the report.**The** administrative staff keeps a receiving copy of the communication.

d. The end of study reporting is facilitated through the submission of data using ***MMMC RERC F-3-C: FINAL REPORT FORM*,** together with documents deemed relevant by the investigator to clarify information indicated in the final report. This comprises the final report package.

e. The Administrative Staff checks the submission for completeness and gives a receiving copy of ***MMMC RERC F-3-C: FINAL REPORT FORM*** to the PI or his/her representative.

f. The Administrative Staff logs the date of submission on the ***MMMC-RERC F-5-H: SUBMISSION LOG and GENERAL SUBMISSION LOGBOOK.***

**3.4.2. Classification of Review by the RERC Chair**

**a.** The RERC Chair classifies the submission as either through full board or expedited review.

b. Generally, classification of review of final report as expedited or full board is based on the initial review classification (i.e. final report of full board study protocols is done through full board review); unless otherwise indicated by the specificities of the submitted information.

**3.4.3**  **Review by Primary Reviewers**

**a.** The Administrative Staff sends the final report package together with a copy of the **s**tudy protocol to the Primary Reviewers.

b. For submissions under expedited review, action is finalized at the level of the Chair within **fifteen (15)** calendar days.

c. Final report packages subject to full board review received within the cut-off period of **fifteen (15)** days before the scheduled RERC full board meeting are sent to Primary Reviewers**.**

**d.** The Administrative Staff places the final report submission on the agenda for the next RERC meeting.

e. The Primary Reviewers accomplish the review and return the signed ***MMMC RERC F-3-C: FINAL REPORT FORM*** to the Secretariat Staff on the day of the RERC Meeting together with the final report package.

**3.4.4** **Full board review of final report**

**a.** The Administrative Staff distributes the following final report packages to Members which include ***MMMC RERC F-3-C: FINAL REPORT FORM*** and other relevant documents or attachments.

b.The primary reviewers present the documents to Members and are deliberated on. For detailed information on the conduct of full board review, see SOP chapter 2.

**3.4.5 Communication of results**

**a.** The PI is notified of the MMMC -RERC decision, noting action on the final report through an action letter.

b. **F**or submissions under full board review, the MMMC-RERC decision will be sent to the Principal Investigator within **fifteen (15)** calendar days after the MMMC-RERC board meeting.

c.For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.

d. The PI may be requested to provide additional information or submit additional documents, in which case the final report may be accepted, but action regarding archiving may be declared pending.

e. If the final report is approved, the PI is informed of the following:

* The study protocol is classified as inactive.
* Ethical clearance is expired effective on the day of the RERC meeting.
* Study protocol records will be made available for three (3) years in the archived file cabinet after the expiration date.

**3.4.6 Files management**

**a.** The Administrative Staff stores the signed final report documents in the study protocol file folder, upon approval of the final report, when no further action is expected from the PI.

b. The Administrative Staff enters relevant study protocol data into the Study Protocol Database to signify the end of study.

c. The Administrative Staff transfers the study protocol folder to the inactive files. See ***SOP 5.6: Archived (Inactive/Completed/Terminated) Files*** for management of inactive files.

**3.5. REVIEW OF STUDY PROTOCOL AMENDMENTS**

**3.5.1 Purpose/Scope/Responsibilities**

The purpose of this SOP is to describe MMMC-RERC review procedures of protocol amendments and related documents.

This SOP applies to previously approved study protocols and related documents that are being amended later and submitted for approval by MMMC-RERC prior to its implementation.

It is the responsibility of the administrative staff to manage protocol amendment packages submitted by the PI. It is the responsibility of the original Primary reviewers to review the amendments and recommend appropriate action. It is the responsibility of the MMMC-RERC chair to determine whether the amendment goes to expedited or full board review.

**3.5.2 Study Protocol Amendment Submission Workflow**

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| **ACTIVITY** | **RESPONSIBILITY** |
| Submit application for Amendment using ***MMMC-RERC F-3-D: STUDY PROTOCOL / INFORMED CONSENT AMENDMENT SUBMISSION FORM*** | Principal Investigator |
| Receives and manages Amendment packages | Administrative Staff |
| Refers amendment document to original primary reviewers | Administrative Staff |
| Review amendments and make a recommendation | Primary Reviewers |
| Review recommendations and determine if amendment should be referred to full board | Chair |
| Discuss at full Board, if necessary | Members |
| Informs Principal Investigator about RERC decision | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.5.3 Detailed Instructions**

**3.5.3.1** **Receipt and management of the Study Protocol Amendment package upon submission**

a.A study protocol amendment is a written description of a change/s to or formal clarification of a protocol and/or informed consent documents. Favorable opinion or approval should be obtained from the MMMC-RERC that issued the ethical clearance or approval prior to the implementation of an amendment.

b. A study protocol amendment is facilitated through the submission of documents using ***MMMC-RERC F-3-D: STUDY PROTOCOL / INFORMED CONSENT AMENDMENT SUBMISSION FORM*** with the amended study protocol or protocol-related documents by the principal investigator to the MMMC-RERC that issued the approval to the study protocol. This comprises the study protocol amendment package.

**c.** The Administrative Staff checks the submission for completeness and gives a receiving copy of ***MMMC RERC F-3-D: STUDY PROTOCOL /INFORMED CONSENT AMENDMENT SUBMISSION FORM*** to the PI or his/her representative.

**d.** Upon receipt of the study protocol amendment package, the Secretariat Staff logs the date of submission on the ***MMMC-RERC F-5-H: SUBMISSIONS LOG and GENERAL SUBMISSION LOGBOOK.***

e. The Administrative Staff ensures that sufficient copies for the Members have been submitted by the PI for full board submissions.

**3.5.3.2** **Classification of Review by the Chair**

**a.** The Administrative Staff sends the Study Protocol Submission Package to the RERC Chair immediately for classification of review as expedited or full board.

b. A full board review is necessary if the proposed study protocol amendment increases risk to study participants, as assessed by the RERC Chair which may include but is not limited to:

* Additional treatment or the deletion of treatments
* Any change in inclusion/exclusion criteria
* Change in method of dosage formulation, (e.g. oral changed to intravenous)
* Significant change in the number of subjects
* Significant decrease or increase in dosage amounts

**3.5.3.3** **Review by Chair and Primary Reviewers**

**a.** All study protocol amendment packages will be sent to the Primary Reviewers together, if necessary, with the originally approved protocol for the reviewer to determine whether the amendment will change the original risk-benefit assessment.

b. For submissions under expedited review, the action is finalized at the level of the Chair within **fifteen (15)** calendar days.

c. Study protocol amendment packages subject to full board review received within the cut-off period of **fifteen (15) days** before the scheduled full board meeting are sent to Primary Reviewers**.**

**d.** The Administrative Staff includes the study protocol amendment request on the agenda for the next RERC meeting.

e. The Primary Reviewers accomplish the review and return the signed ***MMMC RERC F-3-D: STUDY PROTOCOL /INFORMED CONSENT AMENDMENT SUBMISSION FORM*** on the day of the RERC Meeting together with the Study Protocol Amendment Package.

**3.5.3.4** **Full board review of Study Protocol Amendment Submission Package**

**a.** The Administrative Staff distributes the Study Protocol Amendment Package to RERC Members along with the meeting agenda which includes

* ***MMMC RERC F-3-D: STUDY PROTOCOL/INFORMED CONSENT AMENDMENT SUBMISSION FORM***
* Amended study protocol or protocol-related document; with amended section clearly indicated
* Other documents that have been affected by the revision

b. The documents are presented to MMMC-RERC Members and the submitted amendments are deliberated on. For detailed information on the conduct of full board review, see SOP chapter 2.

**3.5.3.5**  **Communication of results**

**a.** The PI is notified of the MMMC-RERC decision noting which amended documents are approved for use through an action letter.

b. For submissions under full board review, the MMMC-RERC decision will be sent to the Principal Investigator within **fifteen (15)** calendar days after the MMMC-RERC board meeting.

c. For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.

d. The PI may be required to modify the amendment, provide additional information, or submit additional documents.

e. If the amendment is approved, the PI is requested to submit an amended study protocol or protocol-related document with a new version number and date.

**3.5.3.6**  **Files management**

**a.** The Administrative Staff receives the amended study protocol or protocol-related document with a new version number and date and stamps it “APPROVED” with the approval date.

b. The newly approved documents will supersede previous versions of the study protocol or protocol-related document.

c. The Administrative Staff stores the signed and approved documents in the study protocol folder.

**3.6. CONTINUING REVIEW APPLICATION**

**3.6.1 Objectives/Scope/Responsibilities**

The objective of this SOP is to describe review procedures of MMMC-RERC for continuing review applications submitted by the PI.

This SOP provides instructions for the review of continuing review applications submitted by the PI prior to the end of the ethical clearance of the study protocol previously approved by MMMC-RERC. The progress report becomes the basis for continuing review of protocols whose approval needs to be renewed.

This SOP applies to conducting any continuing review of study protocols involving human subjects at intervals appropriate to the degree of risk but not less than once a year. Depending upon the degree of risk to the participants, the nature of the study, the vulnerability of the study participants, and duration of the study, MMMC-RERC may choose to review or monitor the protocols more frequently.

This SOP describes follow up of continuing review applications by the MMMC-RERC administrative staff and the review of such reports submitted by the PI by the Primary Reviewers in compliance with ICH-GCP requirements.

It is the responsibility of MMMC-RERC administrative staff to remind investigators to submit continuing review applications before due date, to forward the report to the primary reviewers for review comments, to communicate with the investigators if there is need for further information or action.

It is the responsibility of the primary reviewers to review the reports to check completeness of information and ensure that the data are in accordance with the protocols and other related documents approved by the MMMC-RERC.

**3.6.2 Continuing Review Submission Workflow**

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| **ACTIVITY** | **RESPONSILITY** |
| Remind the PIs to submit the Continuing Review report one month before the due date using the ***MMMC-RERC F-3-A: Reminder Letter for Continuing Review*** | Administrative Staff |
| Submit Continuing Review on or before due date | Principal Investigator |
| Check the completeness of information in the report and forward to the primary reviewers for assessments/comments. | Administrative Staff |
| Review the Continuing Review Documents if in accordance with the approved protocol and related documents | Primary Reviewers |
| Report approval/other recommendations to full board | Administrative Staff |
| Discuss at full board and make a decision | Primary Reviewers |
| Communicate RERC decision to PI | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.6.3 Detailed Instructions of Continuing Review Application**

**3.6.3.1** Receipt and Management of the Continuing Review Application Package

a. Ethical clearance or approval is typically granted for a period of one year. After approval, continuing review is required to be done at least once a year, depending on the risk assessment of the study protocol and determined during initial review. This is facilitated through the submission of data using ***MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM.***

**b.** The frequency of continuing review is indicated in ***MMMC RERC F-5-B: APPROVAL LETTER***, which is provided to the PI upon approval of the study.

**c.** For ethical clearance or approval approaching the one-year expiry date and requiring a renewal or extension, the PI is advised to submit ***MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM*** sixty (60) days prior to expiry date.

d. For long-term (three years or more) clinical research and clinical trials, the PI and study team are required to submit evidence of a **Good** **Clinical Practice (GCP) Update Training** together with the ***MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM*** for further extension of ethical clearance.

e. The Administrative Staff checks the Study Protocol Database for study protocols that are due for continuing review

f. The Administrative Staff prepares and sends a letter to the PI using ***MMMC-RERC F-3-A: Reminder Letter*** at least one month in advance of the due date of continuing review by fax, e-mail, or post and keeps a receiving copy of the communication.

g. The continuing review application is facilitated through the submission of ***MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM.***

**h.** The Administrative Staff checks the submission for completeness and gives a receiving copy ***of MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM*** to the PI or his/her representative.

i. The Secretariat Staff logs the date of submission on the ***MMMC-RERC F-5-H: SUBMISSIONS LOG and GENERAL SUBMISSION LOGBOOK.***

**j.** The Administrative Staff ensures that sufficient copies for the Members have been submitted by the PI for full board submissions.

**3.6.3.2** **Classification of Review by the RERC Chair**

a. The Chair classifies the submission as either for full board or expedited review.

b. Generally, the classification of continuing review as expedited or full board is based on the initial review classification (i.e. continuing review of full board study protocols is done through full board review); unless otherwise indicated by the specificities of the submitted information.

**3.6.3.3** **Review by RERC Chair and Primary Reviewers**

**a.** All continuing review application packages will be sent to the Primary Reviewers together with a copy of the originally approved protocol for the reviewer to determine if there is any change in the original risk-benefit assessment.

b. For submissions under expedited review, action is finalized at the level of the Chair within **fifteen** (**15**) calendar days.

c. Continuing review application packages subject to full board review received within the cut-off period of **fifteen** (**15**) days before the scheduled full board meeting are sent to Primary Reviewers**.**

**d.** The Administrative Staff places the continuing review application on the agenda for the next meeting.

e. The Primary Reviewers accomplish the review and return the signed ***MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM*** on the day of the RERC Meeting together with the continuing review application package.

**3.6.3.4** **Full board review of continuing review application**

**a.** The Administrative Staff distributes the following continuing review application package to RERC Members which include the following:

* Accomplished ***MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM***
* Study protocol synopsis
* Current informed consent documents

b. The documents are presented to RERC Members when continuing review applications are deliberated on. For detailed information on the conduct of full board review, ***see SOP Chapter 2.***

**3.6.3.5** **Communication of results**

1. The PI is notified of the decision noting RERC action on the continuing review application through an action letter.
2. For submissions under full board review, the MMMC-RERC decision will be sent to the Principal Investigator within fifteen **(15)** calendar days after the MMMC-RERC board meeting.

b. For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.

c. The PI may be requested to provide additional information or submit additional documents.

**3.6.3.6** **Files management**

a. The Administrative Staff stores the signed continuing review application documents in the study protocol file folder.

**3.7 REVIEW OF SAEs AND SUSARs**

**3.7.1 Objectives/Scope/Responsibilities:**

The objective of this SOP is to describe the MMMC-RERC review procedures for serious adverse events (SAEs) and Serious Unsuspected Severe Adverse Reactions (SUSARs).

This SOP applies to the review of SAEs and SUSARs reports submitted by the Investigators and sponsor to the MMMC-RERC in compliance with ICH GCP guidelines. The MMMC-RERC reviews such reports to determine appropriate action to protect the safety of participants in an approved study.

ICH-GCP E6 defines a serious adverse event (SAE) or a serious adverse drug reaction (ADR) as any untoward medical occurrence that:

1. Results in death,
2. Is life threatening,
3. Requires hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity, or
5. Results in a congenital anomaly or birth defect.

A suspected unexpected serious adverse reaction (SUSAR) is a serious event the nature and severity of which is not consistent with the applicable product information. In the case of an unapproved investigational product, the event is not consistent with the Investigator’s Brochure (IB). In the case of a licensed product, the event is not consistent with the approved package insert or summary of product characteristics.

It is the responsibility of the PI to report serious adverse advents occurring in a patient enrolled in the study approved by MMMC-RERC.

**3.7.2. Serious Adverse Event Reports Workflow**

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| **ACTIVITY** | | | | **RESPONSIBILITY** | |
| Ensures completeness and receive serious adverse event (SAE) report/s | | | | Administrative Staff | |
| Logs report/s on Submissions Log and SAE Database | | | | Administrative Staff | |
| Assigns primary reviewers | | | | RERC Chair/ Member-Secretary | |
| ONSITE  (SAE and SUSAR) | | OFFSITE  (SAE and SUSAR) | |  | |
| Forwards to Chair and Primary Reviewer within 48 hours after receipt of reports | | Forwards to chair and primary reviewer at least fifteen (15) calendar days before the RERC meeting | | Administrative Staff | |
| If the report needs immediate action, forwards review to RERC Chair for further assessment/recommendation |  | | Administrative Staff | |
| Presents review in the RERC meeting | | | | Administrative Staff | |
| Deliberation of board action on the report/s | | | | Primary Reviewers/ Chair/ Members | |
| Communicates results to principal investigator | | | | Administrative Staff | |
| **If no further action:** sends notification of decision to the PI  **If recommend further action:** sends notification with recommendations to the PI; processes response by full board review  **If request information**: Sends notification of requested information to the PI; processes response by full board review | | | | Administrative Staff | |
| Manages study protocol files | | | | Administrative Staff | |

**3.7.3 Detailed Instructions**

**3.7.3.1 On-site Serious Adverse Event/s (SAE) and Suspected, Unexpected, Serious Adverse Reaction (SUSAR) Reports**

1. The PI accomplishes the ***MMMC-RERC F-3-G: SERIOUS ADVERSE EVENTS REPORT form*** *and* ***MMMC-RERC F-3-H: SAE REPORT SUMMARY*** and submits to the administrative staff within **48 hours**. The Administrative Staff informs the Chair of the submission.
2. The Administrative Staff forwards the SAE Report Package comprised of the following documents to the Chair and to the primary reviewers within **48 hours** of receipt:
   * ***MMMC-RERC F-4-G: SERIOUS ADVERSE EVENTS REPORTS and/or CIOMS Form***
   * ***MMMC-RERC F-4-H: SAE REPORT SUMMARY***
   * Latest Investigator’s Brochure
   * Protocol Summary
   * Other supporting documents, if any

c. If the primary reviewers assess that the report/s need/s immediate action, he/she will forward the report/s and his/her recommendation to the Chair for further assessment. The Chair will assess the recommendations for an immediate action.

d. The Administrative Staff includes the SAE report/s on the agenda of the next meeting, provided that cut-off period for RERC meeting inclusion is **fifteen (15)** days prior, in which the primary reviewer is required to attend. Should the primary reviewer be unavailable for the RERC meeting, the primary reviewer should send his/her review **seven (7) days** after his/her receipt of the SAE report package. His/her review is forwarded to the Chair. The Chair will then present the review to the committee in the meeting.

e. Copies of the SERIOUS ADVERSE EVENT/S REPORT and SAE REPORT SUMMARY are distributed to each RERC member together with the agenda.

f. During the meeting, the Chair calls for a decision on the SAE report/s with respect to the recommendation/s of Chair or reviewer assigned to the concerned study as presented by the RERC Chair/Secretary/Primary Reviewer. The committee may require any of the following actions:

* *No further action*
* *Modification of participant inclusion or exclusion criteria to mitigate the newly identified risks or informed consent documents to include a description of newly recognized risks;*
* *Recommend implementation of additional procedures for protecting/ safeguarding participants;*
* *Suspension of enrollment of new participants or research procedures among participants who are currently enrolled (check consistency)*
* *Request information*
* *Recommend suspension of the entire study*

**3.7.3.2. Offsite Serious Adverse Event/s (SAE) and Suspected, Unexpected, Serious Adverse Reactions (SUSARs) Reports**

1. The PI must submit the offsite SAE and SUSAR report every **three (3)** months.
2. The Administrative Staff forwards the SAE Report Package to the primary reviewers and the chair which comprises of the following documents at least **Fifteen (15)** calendar days before the MMMC-RERC meeting:

* **MMMC-RERC F-3-I: SERIOUS ADVERSE EVENTS REPORTS and/or**
* **MMMC-RERC F-3-H: SERIOUS ADVERSE EVENTS SUMMARY (offsite)**
* Latest Investigator’s Brochure
* Other supporting documents, if any

**c.** The primary reviewers assigned to the particular study review and return the signed ***MMMC-RERC F-3-H: SERIOUS ADVERSE EVENTS REPORT SUMMARY (offsite)*** to the Secretariat together with the SAE report package. Should the primary reviewer assigned be unavailable for the monthly meeting, he/she will send his/her review at least **Seven** **(7)** calendar days before the meeting which will be deliberated by the committee members for approval.

d. The Chair and primary reviewers may recommend any of the following actions:

* + - * + *No action required, study to continue;*
        + *Modification of participant inclusion or exclusion criteria*

*to mitigate the newly identified risks or informed consent documents to include a description of newly recognized risks;*

* + - * + *Recommend implementation of additional procedures for*

*protecting/ safeguarding participants;*

* + - * + *Suspension of enrollment of new participants or research*

*procedures among participants who are currently enrolled (check consistency)*

e. The Chair submits the recommendations to the administrative staff for inclusion in the agenda of the next meeting.

**f.** The Administrative Staff t includes the SAE reports on the agenda.

**g.** Copies of the **SAE REPORT SUMMARY** are distributed to each RERC member together with the agenda.

**h.** During the meeting, the Chair calls for a decision on the SAE report with respect to the recommendations of the Chair and the primary reviewers. The RERC can recommend any of the following actions:

* + - * + *No further action*
        + *Recommend further action*
        + *Request information*

**3.7.4 Communication of results**

1. The PI is notified of the RERC decision, noting committee action on the Serious Adverse Event/s Report through an action letter.
2. Action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.
3. The PI may be requested to provide additional information, submit additional documents, or implement corrective action.

**3.7.5 Files management**

a. The Administrative Staff stores the signed serious adverse event/s report in the study protocol file folder.

b. Files are managed in accordance with ***SOP 5.5: Active Files*.**

**3.8 REVIEW OF PROTOCOL NON-COMPLIANCE/VIOLATIONS/DEVIATION REPORT**

**3.8.1 Purpose/Scope/Responsibilities**

The purpose of this SOP is to describe the MMMC-RERC review procedures for protocol violation/deviation.

This SOP provides instructions for taking action and maintaining records of various types of protocol deviation or violations which include any of the following:

1. Failure of the investigators to comply with the procedures in the approved protocol
2. Failure of the investigators to comply with national/international guidelines for the conduct of human research, including those who fail to respond to the requests of MMMC-RERC.
3. It also covers action taken by MMMC-RERC related to protocol violation/deviation reports submitted by the PI related to any event at the site that is not in compliance with the previously approved protocol documents.

It is the responsibility of the administrative staff of MMMC-RERC to receive protocol violation/deviation reports submitted. It is the responsibility of the board to take action related to the protocol violation/deviation.

**3.8.2 Protocol Non-Compliance/Violations/Deviations Workflow**

|  |  |
| --- | --- |
| **ACTIVITY** | **RESPONSIBILITY** |
| Receive protocol violation/deviation reports | Administrative staff |
| Discuss at Full Board and make a decision | Members |
| Notify the investigator | Administrative staff |
| Keeps records | Administrative staff |

**3.8.3 Detailed Instructions**

**3.8.3.1. Management of submitted protocol deviation/non-compliance reports**

1. The PI should document, explain, and report to the MMMC-RERC any non-compliance from the approved protocol, whether minor or major, at the soonest possible time.
2. The investigator may implement a deviation from the protocol to eliminate an immediate hazard(s) to study subjects without prior MMMC-RERC approval, but must submit as soon as possible, a report of deviation or change, the reasons for it, and, if appropriate, an appropriate study protocol amendment/s.
3. Reporting of study protocol noncompliance is facilitated through the submission of ***MMMC-RERC F-3-J: STUDY PROTOCOL NON-COMPLIANCE (DEVIATION OR VIOLATION) REPORT,*** together with documents deemed relevant by the investigator to clarify information indicated in the report. This comprises the study protocol non-compliance report package.
4. The Administrative Staff checks the submission for completeness and gives a receiving copy of ***MMMC-RERC F-3-J: STUDY PROTOCOL NON-COMPLIANCE (DEVIATION OR VIOLATION) REPORT*** to the PI or his/her representative.
5. The Administrative Staff logs the date of submission in the ***MMMC-RERC F-5-H: SUBMISSIONS LOG and GENERAL SUBMISSION LOGBOOK.***

**3.8.3.2. Classification of Review by the Chair**

**a.** The Chair/Member Secretary classifies the submission as either for full board or expedited review.

b. Minor or administrative deviations that do not affect the scientific soundness of the study protocol or compromise the rights, safety, or welfare of human participants in the study are classified under expedited review.

c. Major deviations or protocol violations that consist of persistent protocol noncompliance with potentially serious consequences that could critically affect data analysis or put patients’ safety at risk are classified under full board review.

**3.8.3.3Review by Chair and Primary Reviewers**

1. Study protocol non-compliance report packages subject to full board review received within the cut-off period of **fifteen (15)** days before the scheduled MMMC-RERC full board meeting are sent to Primary Reviewers.
2. For submissions under expedited review, action is finalized at the level of the Chair within **fifteen (15)** calendar days.
3. The Administrative Staff includes the study protocol noncompliance report on the agenda for the next RERC meeting.
4. The Primary Reviewers accomplish the review and return the signed ***MMMC-RERC F-3-J: STUDY PROTOCOL NON-COMPLIANCE (DEVIATION OR VIOLATION) REPORT*** to the Administrative Staff on the day of the RERC Meeting together with the study protocol non-compliance report package.

**3.8.3.4 Full board review of study protocol noncompliance report**

**a.** The Administrative Staff distributes the following Study Protocol Non-compliance Report /Package to Members along with the meeting agenda which include ***MMMC-RERC F-3-J: STUDY PROTOCOL NON-COMPLIANCE (DEVIATION OR VIOLATION) REPORT* and documents related to the deviation.**

**b.** The primary reviewers present the documents to MMMC-RERC members when study protocol non-compliance reports are deliberated on. The members deliberate on both the type and degree of non-compliance and take the appropriate action.

**c.** The MMMC-RERC can recommend any of the following:

* Continue Study But Will Monitor Compliance
* Request For Further Information
* For Site Visit
* Suspend The Study Until The Following Are Met:
* Additional information is made available
* MMMC-RERC recommendations are implemented by the Principal Investigator and considered satisfactory by the MMMC-RERC
* Terminate The Study On The Basis Of One Or More Of The Following:
* SAE reports indicate harm to participants
* Breach of a previously approved conduct of research.
* Major changes, deviations or amendments of the approved protocol without approval by the MMMC-RERC
* Revision in the Informed Consent form without approval by the MMMC-RERC.
* Fraud.

d. For detailed information on the conduct of full board review, see **SOP Chapter 2.**

**3.8.3.5** Communication **of results**

1. The PI is notified of the RERC decision, noting RERC action on the study protocol noncompliance report through an action letter.
2. For submissions under full board review, the MMMC-RERC decision will be sent to the PI within **fifteen (15)** calendar days after the MMMC-RERC board meeting.
3. For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.
4. The PI may be requested to provide additional information, submit additional documents, or implement corrective action.

**3.8.3.6** Files **management**

**a.** The Administrative Staff stores the signed study protocol non-compliance report documents in the study protocol file folder.

b. Files are managed in accordance with ***SOP 5.5: Active Files*.**

**3.9 REVIEW OF EARLY STUDY PROTOCOL TERMINATION**

**3.9.1 Objectives/Scope/Responsibilities**

The objective of this SOP is to describe the MMMC-RERC procedures related to early termination of protocol implementation.

This SOP describes how MMMC-RERC proceeds and manages the premature or early termination of a protocol when subject enrollment is discontinued before the scheduled end of the study. Protocols are usually terminated at the recommendation of the Data Safety Monitoring Board (DSMB), the Scientific Director, sponsor, PI, by MMMC-RERC itself or other authorized bodies.

It is the responsibility of MMMC-RERC to act on any early protocol termination application. It is also the responsibility of MMMC-RERC to withdraw approval for any previously approved protocol when the safety or benefit of the study participants is doubtful or at risk. All applications are reviewed at full board for appropriate action.

The administrative staff is responsible for the receipt and management of the termination documentation. The primary reviewers review the reasons for early termination and make a report to full board.

**3.9.2 Early Protocol Termination Workflow**

|  |  |
| --- | --- |
| **ACTIVITY** | **RESPONSILITY** |
| Receives early protocol termination report | Administrative Staff |
| Informs the Chair of submission of early protocol termination report | Administrative Staff |
| Checks the completeness of information in the report and forwards to the primary reviewers for assessments/comments | Administrative Staff |
| Review the reasons for the early termination of the study | Primary Reviewers |
| Reports early termination of study protocol | Administrative Staff |
| Discuss at full board and make a decision | Primary Reviewers |
| Communicates MMMC-RERC decision to PI | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.9.3 Detailed Instructions**

**3.9.3.1 Management of the early study termination application**

1. An application for early study termination is submitted when a study approved by the MMMC-RERC is being recommended for termination before its scheduled completion. This is done when the safety of the study participant is doubtful or at risk and also upon the request of the PI or the sponsor owing to the existence of unresolved valid complaints. It may also be because the benefits from the study drug have been established.
2. Early study termination is facilitated through the submission of ***MMMC RERC F-3-K: EARLY STUDY TERMINATION APPLICATION FORM*,** together with documents deemed relevant by the investigator to support or clarify information indicated in the application. This comprises the early study termination application package.
3. The Administrative Staff checks the submission for completeness and gives a receiving copy of ***MMMC RERC F-3-K: EARLY STUDY TERMINATION APPLICATION FORM*** to the PI or his/her representative.
4. The Administrative Staff logs the date of submission on the ***MMMC-RERC F-5-H: SUBMISSIONS LOG and GENERAL SUBMISSION LOGBOOK.***

**3.9.3.2 Classification of Review by Chair**

1. The Chair classifies the submission as full board.
2. Generally, classification of review of early study termination applications is by full board.

**3.9.3.3** **Review by Chair and Primary Reviewers**

1. For submissions under expedited review, action is finalized at the level of the Chair within **fifteen (15)** calendar days.
2. Early study termination application packages subject to full board review received within the cut-off period of **fifteen (15)** days before the scheduled RERC full board meeting are sent to Primary Reviewers.
3. The Administrative Staff includes the early study termination application on the agenda for the next RERC meeting.
4. The Primary Reviewers accomplish the review and return the signed ***MMMC-RERC F-3-K: EARLY STUDY TERMINATION APPLICATION FORM*** to the Secretariat on the day of the RERC Meeting together with the early study termination application package.

**3.9.3.4** **Full board review of early study termination application**

1. The Administrative Staff distributes the early study termination application package to Members which include ***MMMC-RERC F-3-K: EARLY STUDY TERMINATION APPLICATION FORM* and** documents related to the early study termination.
2. The MMMC-RERC deliberates on the implications of the application on the rights, safety, and welfare of the study participants, including adapting specific provisions for continued protection and dissemination of specific information to the study participants.
3. MMMC-RERC may request information from the PI or invite the PI for clarificatory interview.
4. For detailed information on full board review, ***see SOP Chapter 2***

**3.9.3.5 Communication of results**

1. The PI is notified of the RERC decision, noting MMMC-RERC action on the early study termination application through an action letter.
2. For submissions under full board review, the MMMC-RERC decision will be sent to the Principal Investigator within **fifteen (15)** calendar days after the MMMC-RERC board meeting.
3. For submissions under expedited review, action is finalized at the level of the RERC Chair within **fifteen (15)** calendar days.
4. The PI may be requested to provide additional information or submit additional documents.
5. If the application is approved, the PI is requested to accomplish ***MMMC-RERC F-4-C: FINAL REPORT FORM.***

**3.9.3.6**  **Files management**

**a.** The Administrative Staff stores the early study termination application documents in the study protocol file folder.

b. Files are managed in accordance with ***SOP 6.5: Active Files*.**

**3.10 MANAGEMENT OF DSMC/DSMB/IDMC REPORTS**

**3.10.1 Objectives/Scope/Responsibilities**

The objective of this SOP is to describe the MMMC-RERC procedures related to management of DSMC/DSMB/IDMC reports.

This SOP describes how MMMC-RERC manages DSMC/DSMB/IDMC reports submitted by the PI.

It is the responsibility of MMMC-RERC to withdraw approval for any previously approved protocol when the safety or benefit of the study participants is doubtful or at risk. All applications are reviewed at full board for appropriate action. The administrative staff is responsible for the receipt and management of DSMC/ DSMB/ IDMC submission.

It is the responsibility of the primary reviewers to review the DSMC/DSMB/IDMC reports and make their recommendations.

**3.10.2 Receipt and Management of the DSMC/ DSMB/ IDMC Workflow**

|  |  |
| --- | --- |
| **ACTIVITY** | **RESPONSILITY** |
| Submits DSMC/ DSMB/ IDMC report | Principal Investigator |
| Receives DSMC/ DSMB/ IDMC report | Administrative Staff |
| Informs the Chair of submission of DSMC/ DSMB/ IDMC report | Administrative Staff |
| Sends DSMC/ DSMB/ IDMC report to Primary Reviewers  Reviews DSMC/ DSMB/ IDMC report | Administrative Staff |
| Report approval/other recommendations to full board | Administrative Staff |
| Discuss at full board and make a decision | Primary Reviewers |
| Communicate RERC decision to PI | Administrative Staff |
| Files the properly coded submission in the Active Study File Cabinet and updates Protocol Database. | Administrative Staff |

**3.10.3 Detailed Instructions**

**3.10.3.1 Management of DSMC/DSMB/IDMC Reports**

1. Data Safety and Monitoring Committee (DSMC)/ Data Safety Monitoring Board (DSMB)/ Independent Data Monitoring Committee (IDMC) are independent group of experts who monitor patient safety and treatment efficacy data while a [clinical trial](https://en.wikipedia.org/wiki/Clinical_trial) is ongoing. The primary mandate of the DSMC/ DSMB/ IDMC is to protect patient safety. If the [adverse events](https://en.wikipedia.org/wiki/Adverse_event) are particularly serious then the DSMC/ DSMB/ IDMC may consider terminating the study. This evaluation has to be made in consideration of risk/benefit.
2. **The PI must submit 10 copies of** DSMC/ DSMB/ IDMC report/s to MMMC-RERC.
3. The RERC Secretariat Staff checks the submission for completeness.

**d.** The Administrative Staff logs the date of submission on the ***MMMC-RERC F-6-H: SUBMISSIONS LOG and GENERAL SUBMISSION LOGBOOK.***

**3.10.3.2 Processing of DSMC/ DSMB/ IDMC**

1. The PI submits the DSMC/ DSMB/ IDMC report/s to the Administrative Staff of MMMC-RERC upon receipt of the document.

b. The Administrative Staff forwards the document to the Chair and to the Primary Reviewer(s) along with the following documents:

* Latest Investigator’s Brochure
* Protocol Summary
* Other supporting documents, if any

c. If the primary reviewer assesses that the report/s needs immediate action, he/she will forward the report/s and his/her recommendation to the Chair for further assessment. The Chair will assess the recommendations for an immediate action.

d. The Administrative staff includes the DSMC/ DSMB/ IDMC report/s on the agenda of the next meeting, provided that cut-off period for the scheduled RERC full board meeting inclusion is **fifteen (15)** days prior, in which the primary reviewer is required to attend. Should the primary reviewer be unavailable for the RERC meeting, the primary reviewer should send his/her review **seven (7)** days after his/her receipt of the DSMC/ DSMB/ IDMC report/s. His/her review is forwarded to the Chair. The Chair will then present the review to the committee in the meeting.

e. Copies of the DSMC/ DSMB/ IDMC report/s are distributed to each RERC member.

f. During the meeting, the Chair calls for a decision on the DSMC/ DSMB/ IDMC report/s with respect to the recommendation/s of the primary reviewers assigned to the concerned study. The committee may require any of the following actions:

* *No further action*
* *Recommend further action*
* *Request information*

**3.10.3.3 Communication of results**

1. The PI is notified of the RERC decision, noting RERC action on the DSMC/ DSMB/ IDMC report/s through an action letter.
2. The MMMC-RERC decision will be sent to the Principal Investigator within **fifteen (15)** calendar days after the MMMC-RERC board meeting.
3. The PI may be requested to provide additional information or submit additional documents.

**3.10.3.4** **Files management**

**a.** The Administrative Staff stores the DSMC/ DSMB/ IDMC report/s documents in the study protocol file folder.

b. Files are managed in accordance with ***SOP 6.5: Active Files*.**

**RELEVANT FORMS**

**MMMC RERC F-3-A: REMINDER LETTER FOR CONTINUING REVIEW, PROGRESS REPORT/ FINAL REPORT**

**MMMC RERC F-3-B: PROGRESS REPORT FORM**

**MMMC RERC F-3-C: FINAL REPORT FORM**

**MMMC-RERC F-3D: STUDY PROTOCOL / INFORMED CONSENT AMENDMENT SUBMISSION FORM**

**MMMC RERC F-3-E: CONTINUING REVIEW APPLICATION FORM**

**MMMC-RERC F-3-G: SERIOUS ADVERSE EVENT/S REPORT**

**MMMC-RERC F-3-H: SAE REPORT SUMMARY (Onsite)**

**MMMC-RERC F-3-I: SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSARS) SUMMARY REPORT**

**MMMC-RERC –F-4-J: CHECKLIST FOR SAE/SUSARs REPORT**

**MMMC-RERC F-3-K: STUDY PROTOCOL NON-COMPLIANCE (DEVIATION OR VIOLATION) REPORT,**

**MMMC-RERC F-3-L: EARLY STUDY TERMINATION APPLICATION FORM**