Chapter III : Post Approval Monitoring	Document Code: **IRB-SOP-1120-PAM-003-06**	
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***REVIEW: This Standard Operating Procedure is reviewed every 3 years or earlier as indicated.**

Purpose

To describe the post approval activities of the Makati Medical Center Institutional Review Board (MMC IRB) to the events reported by the principal investigator to MMC IRB. Submissions are required by IRB during the conduct of the study. The period covered begins after approval has been granted by the MMC IRB until the completion of the study at the IRB approved site.

3.1 Serious Adverse Events

3.1.1 Purpose

To describe the IRB review procedures for serious adverse events

3.1.2 Scope

This SOP applies to the review of all adverse event reports (including Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction reports) submitted by investigators and sponsors to the Makati Medical Center IRB to comply with ICH GCP. The IRB reviews such reports to determine appropriate action to protect the safety of participants in an approved study. The terminology used for the reporting of adverse drug events is based on the Suspect Adverse Reaction Report Form (CIOMS Form I), FDA Philippines.

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

A. results in death,
B. is life threatening,
C. requires hospitalization or prolongation of existing hospitalization,
D. results in persistent or significant disability or incapacity, or
E. results in a congenital anomaly or birth defect.

A suspected unexpected serious adverse reaction (SUSAR) is a serious event wherein 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.

This SOP also discusses the role of Adverse Events subcommittee in reviewing the serious adverse events reported to MMC IRB.

3.1.3 Responsibilities

A. The primary responsibility of the Makati Medical Center Institutional Review Board is to conduct an appropriate review of adverse event reports to ensure oversight over the safety of participants enrolled in the study.
   1) Ensures that investigators are made aware of its policies and procedures concerning SAE reporting.
   2) Sets up the necessary mechanisms to receive adverse event reports from investigators of researches that it has approved. A link is provided per protocol to enable investigators to submit the SAE and SUSAR reports online.
   3) Receives and reviews adverse event reports from its own site and takes the necessary action to ensure the safety of participants in the study.
   4) Receives SAE and SUSAR reports from other sites within and outside the country. It is the responsibility of the Makati Medical Center IRB to be updated about safety issues related to studies that it has approved which are also being conducted in other centers/sites.

B. The Makati Medical Center IRB has the authority to suspend or terminate approval of research at its site when the safety of participants is no longer assured. When Makati Medical Center IRB takes such action, it is required to provide the reasons for its action and to promptly report such decision to the investigator.

C. The functions of the SAE subcommittee are as follows:
   1) Ensures completeness of the SAE review forms.
   2) Deliberates on the trending of onsite and off-site reports at least once a year and makes necessary recommendation to the Board for appropriate decision.
   3) Conducts a monthly reporting of the SAEs in the Medication Safety Subcommittee meeting (MSS).
   4) Conducts at least once a year SAE subcommittee meeting and reports to the Board.
   5) Recommends appropriate actions in response to the Adverse Event Reports (Eg. Site visit).
   6) Analyzes the history of the SAEs from previous SAE reports for each protocol to make appropriate recommendation to the Board.
   7) Summarizes onsite SAEs of each protocol every 6 months.

8) Provides substantial comments by referencing to the Investigator's Brochure, DSMB reports, checking onsite SAE history and trending offsite SAEs

3.1.4 Process Flow/Step

NO	ACTION	RESPONSIBILITY
1	Report Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs).	Investigator or Representative
2	Receive and distribute SAE/ SUSAR.	Secretariat Staff
3	Review SAE and SUSAR and make necessary recommendations.	AE Subcommittee
	Offsite / Onsite	AE Subcommittee
	Immediate Action	Chair
	Conduct AE Subcommittee meeting	AE Subcommittee
	Discussion and deliberation during Full Board Review.	IRB Members
4	Notify the principal investigator of the IRB decision.	Chair/ Secretariat Staff
5	File the SAE documents.	Secretariat Staff
6	Update the database, index and tracker.	Secretariat Staff

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Detailed Instructions

3.1.4.1 Upon release of the approval letter, MMC IRB informs the investigators of the requirement to report SAEs and SUSARs using Form 3.1A or online submission within a specific time. For ONSITE SAEs, online submission is within seven (7) days after recognition of the event. Printed copies of the online submission must be provided within seven (7) days after recognition of the event. For OFFSITE SAEs, reports are submitted along with the progress report.

Reporting Time Frame:

a. Fatal or life threatening unexpected ADRs occurring in clinical investigation qualify for very rapid reporting. Regulatory agencies should be notified reporting (e.g., by telephone, facsimile, e-mail) not later than seven (7) calendar days after the first knowledge by the sponsor of that case followed by complete written report within eight (8) calendar days.
b. All other SAEs, SUSARs that are not fatal or life threatening must be filed by the IRB Secretariat as soon as possible but not later that fifteen (15) calendar days after the first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.
c. All the other adverse events, SUSARs, and DSURs will be reported as part of the annual progress report.
d. All Adverse Events reports to the IRB should be reported to the appropriate entities of the hospital if applicable or necessary (e.g., Therapeutics Committee, Quality Management Division, Medication Safety Subcommittee, etc.).

3.1.4.2 MMC IRB Secretariat receives the SAEs and SUSARs, logs the date of submission and updates the database.

- MMC IRB secretariat should classify the SAE/ SUSAR reports according to their origin or sites where they happened: Off-site and on-site. An "**ONSITE STAMP**" will be used for Onsite SAE reports.
- The Secretariat distributes (via email or printed copy) a copy of the onsite SAE report to the primary reviewers and SAE Subcommittee members within 24 hours upon receipt of the report.

3.1.4.3 IRB adopts appropriate response depending on the site where the SAE/ SUSAR happened. SAE Subcommittee members are provided with copies of SAE within 24 hours upon receipt. The SAE Subcommittee members are given 7 calendar days to review and provide recommendation using Form

3.1A or online submission and Serious Adverse Event Report Reviewer's Recommendation Form **(Form 3.1B)**.

A. For SAEs that occurred onsite, the Adverse Event Subcommittee Chair analyzes the investigator/ sponsor assessment (serious, related, and unexpected) and informs the Chair of the recommended action to ensure safety of participants. All onsite SAEs are reported in the full board meeting for discussion.

   The AE Subcommittee reportings are:

   1) Assessment of the SAE is UNLIKELY or UNRELATED to the study drug or device – the report is forwarded to the AE subcommittee if the report undergoes expedited review.
   2) Assessment of SAE/ SUSAR is DEFINITELY, POSSIBLY or PROBABLY related to the study drug or device – the report is added to the regular agenda for discussion during the full board. If immediate action is necessary, the report with recommendations is forwarded to the chair.

B. For multicenter, national studies, note the nature (related or expected) of the SAE/ SUSAR and discuss during SAE subcommittee meeting for recommendation and reports to IRB full board for the final decision.
C. SAE and SUSAR are discussed and reviewed during Makati Medical Center IRB meetings for appropriate action as follows:
   1) Request an amendment to the protocol or consent form
   2) Request further information
   3) Suspension of:
      a. Enrollment of new research participants until further review of the IRB.
      b. All trial-related procedures (except those intended for safety and well-being of the participant) until further review by the IRB.
   4) Termination of the study
   5) Take note and continue monitoring
   6) Site Visit
D. For multicenter, international studies, note the trend of occurrence of SAE/ SUSAR in study sites in foreign countries and other local site.

3.1.4.4 Investigator is informed by secretariat, about the IRB decision and recommendation through notification of IRB decision **(Form 2.9E)**.

3.1.4.5 All comments related to SAE are documented and kept on file. Primary reviewers are updated.

3.1.4.6 Secretariat updates the database, index and tracker accordingly.

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3.2 Protocol Violation/ Protocol Deviation/ Non-Compliance

3.2.1 Purpose

To describe the IRB review procedures for protocol violation/ deviation
To describe the IRB process of erring investigators who fail to comply with the procedures set by Makati Medical Center Institutional Review Board (MMC IRB)

3.2.2 Scope

This SOP provides instructions for taking action and maintaining records of various types of protocol deviation or violations:

A. It includes investigators who fail to comply with the procedures in the approved protocol or to comply with national/ international guidelines for the conduct of human research, including those who fail to respond to the Makati Medical Center IRB's requests.
B. It also covers action taken by the IRB related to protocol violation/ deviation reports submitted by the principal investigator related to any event at the site that is not in compliance with the protocol documents previously approved by the IRB.

This SOP applies to all MMC-affiliated investigators with protocols conducted in and outside Makati Medical Center (MMC). This specifies appropriate actions to ensure compliance.

Initiation and/or implementation of any non-approved study protocol shall be considered a VIOLATION of the standard operating procedures of the MMC IRB.

Any ongoing non-registered or non-approved study shall be suspended until the study proponents fully comply with the IRB requirements.

3.2.3 Responsibility

It is the responsibility of the IRB Secretariat to receive protocol violation/ deviation reports submitted to the IRB.
It is the responsibility or the board members or designated members to take action related to protocol violation/ deviation.
The primary responsibility of the MMC IRB is to ensure all investigators comply with International Conference on Harmonization Good Clinical Practice (ICH GCP) and other standard guidelines in research.

3.2.4 Process Flow/Steps

NO.	ACTIVITY		RESPONSIBILITY
1	Receive the protocol violation/deviation reports **(Form 3.5)** and/or report of non-compliance with the MMC IRB SOP	Receive report of non-compliance with the MMC IRB SOP.	Secretariat
2	Review protocol deviation and violation		Primary reviewers
3	Discuss at full board and make a decision.	Call to order a special meeting to discuss the violation.	Members/ Chair
4		Recommend the appropriate sanction for the offense	Members
5		Give the final decision on the sanction	Chair
6	Notify the investigator of the decision		Secretariat/ Chair
7	Keep records in protocol folder and update the database		Secretariat
6	Follow up the recommended action after a reasonable time.		Secretariat

Detailed instructions

3.2.4.1 Secretariat or any IRB member may receive protocol violation/ deviation reports **(Form 3.5)** for any event in the site that is not in compliance with the previously IRB approved protocol and related documents from

investigators and other parties related. The Secretariat receives the report of non-compliance with the MMC IRB SOP and ensures the completeness of the information. The protocol deviation report is submitted within 2 months upon recognition by the principal investigator.

3.2.4.2 Protocol deviation and violation are forwarded to the primary reviewers for assessment and recommendation.

3.2.4.3 Issues as well as the details of non-compliance involving research investigators are included in the agenda of the IRB meeting for Board recommendation and decision.

Frequent deviations especially research team-related are assessed. Corrective actions and further monitoring are required.

Board Decision

A. Continue study and monitor compliance
B. Request for further information
C. For site visit
D. Amend protocol
E. Amend Informed Consent Form
F. Suspend the study*
   (NB. until the following are met:*
   1) Additional information is made available.
   2) *MMC IRB recommendations are implemented by the Principal Investigator and considered satisfactory by the MMC IRB.)*
G. Terminate approval of current study**
   *(NB** Termination is based on one or more of the following:*
   1. *SAE reports indicate harm to participants.*
   2. *Breach of a previously approved conduct of research.*
   3. *Major changes, deviations or amendments of the approved protocol without approval by the MMC IRB.*
   4. *Revisions in the informed consent form without approval by the MMC IRB.)*

Research proposal of an involved Principal Investigator or co-investigator are held in abeyance as determined by the Chair.

For reports of non-compliance to the SOP, the chair is informed of such report and calls for a special meeting to deliberate on the incident.

3.2.4.4 Board members discuss and recommend the appropriate sanction.

Criteria for Non-Compliance

If a non-registered study has been completed, the following sanction/s will be imposed:

A. For the 1st offense:
   1) Prohibition from citing MMC as the study location or institutional review center.
   2) Non-inclusion of the study in the investigator's list of reference or bibliography.
B. For the next offense:
   - Prohibition from participation of the investigator(s) in any other institutional research in MMC.

Criteria for Withdrawal of Approval

Approval may be withdrawn by the MMC IRB for the following reasons:

A. SAE directly or indirectly attributed to the research.
B. Breach of previously approved conduct of the research.
C. Major changes, deviation and amendments to the approved protocol without another approval by the MMC IRB
D. Failure to respond to MMC IRB's request for information/ action.

3.2.4.5 The Chair gives the final decision of the board.

3.2.4.6 Notification of the Makati Medical Center IRB's decision

A. For the protocol deviation/ violation, the IRB Secretariat/ members record the Makati Medical Center IRB decision and prepare four (4) copies of the notification letter. The investigator, the sponsor, relevant national authorities and institutions, and the IRB are provided a copy of the notification letter.
B. For the non-compliance report, the Secretariat prepares a letter to inform the investigator of the decision. The chair signs the notification.

3.2.4.7 All protocol deviation/violation and non-compliance records are filed and the IRB database is updated accordingly.

3.2.4.8 The secretariat staff follows up the action after a reasonable time as stipulated in the letter to the principal investigator.

3.3 Site Visits

3.3.1 Purpose

To describe the Makati Medical Center Institutional Review Board (MMC IRB) procedures related to the conduct of site visits.

3.3.2 Scope

This SOP applies to any visit made in any study site, on behalf of the MMC IRB, to check compliance with Good Clinical Practice and MMC IRB approved protocol and related documents.

3.3.3 Responsibility

It is the responsibility of the MMC IRB to perform or designate some members or qualified representatives to perform on its behalf on-site visit of the research projects it has approved.

The MMC IRB members or Secretariat in consultation with the Chair may initiate an on-site evaluation of a study site for cause or for a routine audit. The Site Visit team consists of the following:

A. A reviewer of the study
B. A member of the Adverse Event Subcommittee
C. An MMC IRB member assigned by the MMC IRB Chair

3.3.4 Process Flow/Steps

NO.	ACTIVITY	RESPONSIBILITY
1	Select the study sites and inform the principal investigator about the planned visit ⬇	Members and secretariat
2	Check the approval given by the IRB from the protocol files and collect relevant information about the study site ⬇	Members and/or IRB representative
3	Check the onsite documents and compare with the documents and compare with the documents in the protocol files; interview the principal investigator and/or research staff ⬇	Site Visit Team

4	Write a report and make a recommendation utilizing the Site Visit Report **(Form 3.7)**	Site Visit Team
5	Present the findings to the Full Board which adopts an appropriate action	Site Visit Team
6	Communicate the board decision to the Principal Investigator	Secretariat
7	Implement the board recommendation and reports the action to the board	Principal Investigator
8	File copies of the documents and update the database	Secretariat

Detailed Instructions:

3.3.4.1 Selection of study sites

The MMC IRB selects the study site according to the following criteria for site visit:

A. New study sites or new principal investigators
B. Reports of remarkable serious adverse events
C. High volume of studies carried out at the study site
D. Frequent protocol submission for MMC IRB review
E. Non-compliance or suspicious conduct
F. Frequent failure to submit progress reports
G. Frequent protocol violations
H. Or as determined by the Chair

3.3.4.2 Before the visit

MMC IRB Representatives have the following responsibilities:

A. Review the MMC IRB files for the study and site
    1) Contact the site to notify them about the site visit.
    2) Coordinate the date and time for the site evaluation visit.
    3) Make the appropriate travel arrangements.
B. Make appropriate notes, or
C. Copy some parts of the files for comparison with the site files.

3.3.4.3 During the visit

A. Use the Site visit checklist **(Form 3.7)**
B. The MMC IRB representatives may conduct one or all of the following:
   1) Review the informed consent document to make sure that the site is using the most recent version,
   2) Review randomly the subject files to ensure that subjects are signing the correct informed consent,
   3) Observe consent process, if possible.
   4) Check if the files are orderly and confidentiality is maintained
   5) Interview the members of the research team/ investigator.
   6) Debrief the principal investigator about site visit findings and comments.

3.3.4.4 After the visit

MMC IRB representative:

A. Writes a report/comment (**use Form 3.7**) within 1 week describing the findings during the audit.
B. Forwards a copy of the site visit to the Secretariat for inclusion in the next board meeting.
C. Sends a copy of the report to the site for their files, and
D. Places the report in the correct files.

3.3.4.5 Presentation of the site findings

A. Present the site visit report to Full Board.
B. Board makes a decision about appropriate action.

Board Decision:

A. Continue study and post approval monitoring
B. Amend protocol
C. Amend Informed Consent
D. Stop recruitment
E. Terminate study
F. Blacklist Principal Investigator/ Sponsor
G. Recommend other corrective measures (specify)
H. Others (specify)

3.3.4.6 Secretariat communicates the board decision to the principal investigator for appropriate action utilizing Notification of IRB Decision **(Form 2.9D)**.

3.3.4.7 Principal investigator follows board recommendation and secretariat reports the investigator's action and response to the IRB.

3.3.4.8 Secretariat keeps a copy of the files and updates IRB database accordingly.

3.4 Review of RNE Reports

3.4.1 Objective:

To describe the safety, dignity and well-being of participants and / or the study team and the integrity of data against Reportable Negative Events.

3.4.2 Extent of distribution:

Institutional Review Board, Principal Investigators, Sponsors

3.4.3 Scope:

This SOP applies to the review of Reportable Negative Events in non-drug-therapeutic studies (e.g., social science research) done by the researchers to safeguard the safety and welfare of human participants, research team, and integrity of data.

3.4.4 Definition of Terms:

Negative Events Report – A type of submission where a researcher will amend his/her protocol (e.g., changing of title, changing objectives or some part in the methodology, etc.) after the approval of the protocol.

Special Meeting – an assembly of the committee outside the regular schedule of IRB Meetings for a specific purpose, usually to decide an urgent matter like critical research problems that requires immediate action.

3.4.5 Policy:

The Institutional Review Board is responsible regarding the safety, dignity, and well being of participants and/or of the research team and the integrity of the data when a Reportable Negative Events occurs.

3.4.6 Process Flow Map

NO.	ACTIVITY	RESPONSIBILITY
1	Receive and document the Reportable Negative Event.	IRB Staff
	⬇	
2		

	Retrieve the protocol file for identification and documentation.	IRB Staff
3	Send the Reportable Negative Event to the IRB Chairman and the primary reviewers.	IRB Staff
4	IRB Chairman will notify the primary reviewer to call for a special meeting	IRB Chair
5	IRB Chairman and Primary Reviewers will deliberate on the Reportable Negative Events	IRB Chair and Primary Reviewers
6	IRB Chair communicates with the primary investigator regarding the decision of RNE.	IRB Chair
7	Filing of all related documents	IRB Staff

Detailed Instructions:

3.4.6.1 IRB Staff receives and documents the Reportable Negative Event in the logbook and database.

3.4.6.2 Retrieval of pertinent protocol file to check the information of the research (i.e., name of primary investigator, who are the primary reviewers)

3.4.6.3 Sends the Reportable Negative Event to the IRB Chair and Primary Reviewers to notify them regarding the RNE.

3.4.6.4 IRB Chair notifies the primary reviewers regarding the call for a special meeting to deliberate the RNE.

3.4.6.5 IRB Chair and Primary Reviewers deliberate regarding the Reportable Negative Event.

3.4.6.6 IRB Chair communicates with the primary investigator regarding the decision of the RNE.

3.4.6.7 IRB Staff files all related documents sent by the primary investigator.

3.5 Amendments

3.5.1 Purpose

To describe the IRB review procedures for amendments of the protocol and related documents

3.5.2 Scope

This SOP applies to previously approved study protocols and related documents that are being amended later and submitted for approval by the Makati Medical Center IRB. Any amendment of the study related documents may not be implemented until reviewed and approved by the IRB.

3.5.3 Responsibilities

It is the responsibility of the IRB Secretariat to manage protocol amendment package submitted by the principal investigator.

It is the responsibility of the original primary reviewers to review the amendments and recommend appropriate action.

It is the responsibility of the IRB Chair to determine whether the amendment goes to expedited or full board review. The IRB approves the final decision for amendments submitted by the principal investigator to the IRB.

3.5.4 Process Flow/Steps

NO.	ACTIVITY	RESPONSIBILITY
1	Submit application **(Form 2.1C)** and documents for amendment **(refer to Form 2.4)** ⬇	Investigator
2	Receive amendment package ⬇	Secretariat
3	Determine type of review for the amendment **(Form 2.6)** ⬇	Member-secretary/ Chair
4	Distribute amendment to the original primary reviewers/ IRB members ⬇	Secretariat

5	Review amendment and make a recommendation **(Form 2.9)**	Primary reviewers/ IRB Members
6	Discuss at Full Board/SPARES for decision if necessary	Members
7	Inform investigator about IRB decision **(Form 2.9)**	Chair/ Secretariat
8	Keep a copy of all amendment related in the protocol file	Secretariat
9	Update index **(Form 4.5)** and tracker **(Form 4.4A and 4.4B)**	Secretariat

Detailed Instructions

IRB should properly inform investigators to submit an amendment application (**Form 2.1C and Form 3.2)** whenever there is any change regarding the composition of the study team, the study site and the protocol related documents for approvals previously granted by the IRB.

IRB Secretariat checks the completeness of the amendment package submitted by the Investigator using Requirement Checklist - Amendment **(Form 2.4)**.

Member-secretary recommends the type of review utilizing **Form 2.6**, based on criteria. Chair approves type of review (e.g. full board or expedited).

3.5.4.1 The amendments on the protocol which have been initially approved under expedited review with minor changes will undergo expedited review by the original primary reviewers.

3.5.4.2 Amendments that may potentially alter the risk/benefit ratio of a study are referred for full board review

A. The protocol amendment which increases risk to study participants may include, but is not limited to the following:
   1) a change in study design
   2) additional treatments or the deletion of treatments
   3) any change in the inclusion/exclusion criteria

4) change in method of drug intake or route of drug intake (e.g. oral changed to intravenous)
5) significant change in the number of subjects (increase or decrease in sample size that alters the fundamental characteristics of the study)
6) significant decrease or increase in dosage amount

3.5.4.3 IRB Secretariat refers the amendment package to the original primary reviewers.

3.5.4.4 Original primary reviewers check the amended documents and compare them with the previously IRB approved documents in the protocol files. Amendments are checked if it would alter the risk/ benefit ratio of the study to make appropriate recommendations using **Form 3.2.**

3.5.4.5 If only minor changes are involved in the amendment, the reviewer's recommendation becomes the basis for the final decision of the IRB and a letter granting approval is prepared by the IRB Secretariat.

3.5.4.6 If major changes are involved in the amendment (alters the risk/ benefit ratio of the study), the amendment is referred to full board after review by the primary reviewers.

3.5.4.7 The members discuss the amendment at full board meeting, to arrive at a decision.

3.5.4.8 Board decides whether or not there is need for investigator to clarify, elaborate or explain further the amendments. The following are the possible decisions made by the Board:

A. Approval
B. Recommend major changes to the protocol/ Informed Consent Form
C. Recommend minor changes to the protocol/ Informed Consent Form
D. Disapproval
E. Pending Decision
*The board may decide to re-consent the participants currently enrolled in the study when needed.

3.5.4.9 IRB secretariat prepares the Notification of IRB Decision **(Form 2.9)** to inform the investigators about the board decision. The Secretariat forwards

the Notification of IRB Decision **(Form 2.9)** to the investigators for proper action.

3.5.4.10 The Secretariat keeps a copy of all amendment related documents in the protocol files.

3.5.4.11 Secretariat updates IRB database, index **(Form 4.5)**, and document tracker **(Form 4.4A and 4.4B)** accordingly.

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3.6 Progress Report

3.6.1 Purpose

To describe the IRB review procedures for progress and annual reports. This includes the periodic review of the protocols previously approved by the IRB by providing recommendations regarding the criteria, process, and frequency (not less than annually) of continuing review to assure the protection of the rights and welfare of human subjects enrolled in clinical investigations.

3.6.2 Scope

A. This SOP provides instructions for the review of progress reports that are required by the Makati Medical Center IRB to be submitted by the principal investigator to monitor the safety of participants enrolled in a study.
   1) The annual report becomes the basis for continuing review of protocols whose approval needs to be renewed every year.
   2) This SOP applies to the conduct of 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 studies, and the vulnerability of the study participants and duration of the study, the IRB may choose to review or monitor the protocols more frequently.

3.6.3 Responsibility

It is the responsibility of the investigator to maintain the approval of the study protocol by submitting a continuing report or amendment prior to the expiration of IRB approval. The Principal Investigator is given a grace period until 12 working days post expiration date of approval to submit a progress report for the renewal of IRB approval. Failure to submit a progress report will automatically INACTIVATE the status of the study.

It is the responsibility of the Makati Medical Center IRB Secretariat to remind investigators to submit the progress and final reports **(Form 3.3A, Form 3.3B and Form 3.4)** two (2) months before due date, to forward the reports to the primary reviewers for review and comments, to communicate with the investigators if there is need for further information or action and to submit to full board a list of progress for approval.

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 IRB.

3.6.4 Process Flow/Steps

NO.	ACTIVITY	RESPONSIBILITY
1	Remind the principal investigators to submit progress reports or annual report two months before the due date **(Form 3.3A and Form 3.3B)** ⬇	Secretariat
2	Submit the progress/annual or annual report one month or before the date of expiry of approval **(Form 3.3A and 3.3B)** ⬇	Investigators
3	Check for the completeness of information in the report ⬇	Secretariat
4	Determine if progress/ annual report will undergo SPARES/ full board review **(Form 2.6)** ⬇	Chair/ Member-Secretary
5	Forward the report to the primary reviewers/ members for assessment/ comments ⬇	Secretariat
6	Review the progress or annual report if it is in accordance with the approved protocol and related documents. ⬇	Primary reviewers
7	Collate the comments of the primary reviewers and finalize the agenda ⬇	Secretariat
8	Report approval or other recommendations by the primary reviewers of progress/ annual report to the board meeting. ⬇	Chair
9	Discuss at full board and make a decision ⬇	Members

10	Communicate IRB decision to Principal Investigator **(Form 2.9C)**	Secretariat
11	File the Progress/ Annual Report in Active File and the Final Report folder in Inactive File.	Secretariat
12	Update the database.	Secretariat

Detailed Instructions

Submission and management of Annual Reports

3.6.4.1 Secretariat checks the database and tracks due dates of progress or annual reports of Study Protocols approved by the Makati Medical Center IRB. The Secretariat prepares and sends reminder letter/notice addressed to the principal investigator two months before the due date of the expiration of approval.

3.6.4.2 Principal investigator submits the progress or annual report **(Form 3.3A and Form 3.3B)** within one month or 30 days before the date of expiry of approval.

3.6.4.3 Secretariat reviews the completeness of submitted report based on the items in Progress Report **(Form 3.3A and Form 3.11)**

The secretariat checks the following:

A. The GCP training of the Principal Investigator and all key persons are current (within the last three years).
B. Sufficient copies for IRB members for full board review together with other documents that may be required for submission.
C. ALL REQUIRED DOCUMENTS MUST BE submitted ONE (1) MONTH prior to the expiration date.
    1. Five (5) clear copies of the informed consent/ assent/ information sheet currently in use (if applicable).
    2. Five (5) copies of the complete Progress/ Annual Report signed by original Investigator.
    3. Five (5) copies of the revised consent/ assent form (clean copy).

4. Five (5) copies of the revised consent/ assent form, if applicable, with tracked changes. To highlight the changes, the revisions should be in **bold** and underlined.
5. One copy of all approved amendments/ revisions since the last renewal and a copy of each previously submitted Progress Report, if applicable.
6. The letter of intent addressed to the IRB Chair specifies the reason for renewal of approval.

3.6.4.4 The member-secretary recommends the type of review and the Chair approves if the progress/ annual report will undergo Expedited or Full board review **(Form 2.6)**.

(NB. The full board for continuing review for a study previously approved under full board review and SPARES for continuing review for research that qualified for expedited review.)

3.6.4.5 The secretariat forwards the report within 7 calendar days upon receipt of the report(s) to the primary reviewers who conducted the initial review of the involved study protocol.

Progress/ Annual Report received within the cut-off period of fourteen (14) working days before the regular MMC IRB meeting are sent to the primary reviewers at least fourteen (14) calendar days before the meeting.

3.6.4.6 Primary reviewers conduct continuing review of progress/ annual report if they are in accordance with the protocol and related documents approved by the IRB using F**orm no. 3.3A and 3.3B**.

A. Primary reviewers refer to the protocol file to check compliance with approval given by the IRB during initial review and upon submission of amendments.
B. In the review of the Progress/ Annual Report, the following are the key evaluation points **(Form 3.3B)**:
    1) Risk Assessment
        a. The risks to the subjects are minimized
        b. The risks to the subjects are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may be expected to result.

2) Adequacy of Informed Consent
   a. Informed consent/ Assent forms current (most recent)
   b. Appropriate, new significant findings since the last continuing review that may be related to the subjects' willingness to continue participation provided to enrolled subjects (e.g., important toxicity or adverse event information)
3) Local Issues
   a. Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, medical license; involvement in numerous clinical trials)
   b. Evaluation, investigation and resolution of complaints related to the research
   c. Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and regulations, applicable state and local law, or standards of professional conduct of practice.
   d. Report from third party observation of the research (including the informed consent process) carried out
   e. Investigator concerns about trial conduct at the local site (e.g., study coordinator ineffectiveness, inability of subjects to understand sections of the informed consent document required by institutional policies).
4) Trial Progress
   a. Study start data and expected duration
   b. Total subject enrollment (onsite and other sites)
      1. Expected enrollment rate
      2. Actual enrollment rate
      3. Reason for the difference between the expected and actual enrolment rate
      4. Enrollment issues
   c. Subject withdrawal
      1. Number of subjects who withdrew
      2. Summary of reasons for withdrawal at local site

C. The IRB may also request the Principal Investigator to provide additional information.
D. The reviewers may request verification from sources other than the Principal Investigator when:

1) The IRB has concerns about information provided by the principal investigator.
2) There is conflicting information between investigator provided materials and knowledge obtained by the IRB.
3) Non-compliance with Continuing Review requirements.
4) Concerns expressed by research participants, employees, sponsor, regulatory agencies, and/or a member or the general public.
5) Complex projects involving unusual levels or types of risk to subjects.
6) Concerns about possible material changes without IRB approval.

E. The primary reviewer must complete the review within 7 days prior to the IRB meeting using reviewer form 3.3B.

F. Primary reviewers recommend approval of the progress/ annual report if there is no deviation or violation of IRB approval.
   - If there is any deviation or violation of approvals given by the IRB, the primary reviewers recommend that appropriate action to be taken by the principal investigator (e.g. amendment of the protocol or consent form, etc. for progress reports; explanation of deviation or violation for final reports, etc.)

3.6.4.7 The secretariat collates the comments of the primary reviewers and finalizes the agenda.

A. The renewal application is finalized on the agenda and becomes available to all board members.

B. The IRB file, including relevant IRB meeting minutes, should be made available to IRB members prior to the meeting at which continuing review will be conducted to allow members to resolve any questions that may arise.

3.6.4.8 Approval or other recommendations by the primary reviewers of progress/ final report is reported to the board meeting by the Chair.
- In the meeting, the primary reviewers will present a synopsis of the progress of the research, any significant issues and his/her recommendation to the convened IRB. They summarize changes or critical issues for the other members, and lead the discussion at a convened meeting.

3.6.4.9 Board Decision

The board determines the need for the investigator to elaborate, explain or clarify any aspect of the progress or annual report as deemed necessary. The following are the possible IRB decisions for progress/ annual reports **(Form 2.9C)**:

A. Uphold approval with no further action
B. Approval pending:
    1) Request additional information
    2) Recommend modification
C. Recommend suspension of:
    1) enrollment of new subjects
    2) research procedures in currently enrolled subjects
    3) the entire study
D. Termination of approval
E. Others

For studies that are approved to continue, the notification states the date when approval is effective, the period of time for which the study is approved, the next continuing review date and any conditions of re-approval.

For the studies that do not receive renewal of approval until after the current expiration date, the new expiration date is from the date of the convened meeting at which IRB approval of the renewal application is granted.

Lapses of IRB Approval

A. If the IRB has not reviewed and approved a research project by the end of the approval period specific by the IRB, the study will be considered in non-compliance. The IRB approval automatically expires and the protocol is considered inactive.
B. The investigator will be notified of expiration of approval in writing within a week of the expiration date.
C. Continuation of research interventions or interactions in previously enrolled subjects should only continue if the safety of the patient is at stake.
D. A request to continue research interventions or interactions with previously accrued subjects after the expiration date must be submitted in writing to the IRB **(Form 3.9)**.

E. The IRB will document **(Form 3.3A)** why the lapse in approval occurred and identify any steps that need to be taken to prevent future lapses in approval.
F. If there is a pattern of non-compliance with the requirements for continuing review, the IRB will determine the appropriate corrective actions and may be grounds for suspension or termination **(Form 3.10)**.
G. The IRB duly notifies the sponsor of any instance of serious or continuing non-compliance with IRB requirements.

3.6.4.10 Secretariat takes note of the decision and/or discussion during the board meeting in the meeting minutes **(Form 4.2)** and communicates **(Form 2.9C)** the board decision to the principal investigator.

- MMC IRB Secretariat notifies the investigator of IRB decision **(Form 2.9C)**. The IRB accepts the annual/ progress report and notifies the investigator about the renewal of approval of the protocol and related documents to enable the principal investigator to continue the conduct of the research.

3.6.4.11 Secretariat keeps a copy in the protocol files of the progress/ annual report signed by the Primary Reviewers and the Chair or Member-Secretary.

- The progress report is filed in the Active file.

3.6.4.12 Database and document tracker **(Form 4.4A and Form 4.4B)** are updated.

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3.7 Final Report

3.7.1 Purpose

To describe the IRB review procedures for final reports.

3.7.2 Scope

This SOP also aims to provide instructions for the review of final reports that are submitted by the Principal Investigator after completion of subject enrollment and all follow up procedures.

3.7.3 Responsibility

It is the responsibility of the Principal Investigator to submit a Final report after completion of the approved study protocol.

Process Flow

NO.	ACTIVITY	RESPONSIBILITY
1	Submit the final report after completion of subject enrollment and all follow up procedures **(Form 3.4)** ↓	Investigators
2	Check for the completeness of information in the report ↓	Secretariat
3	Forward the report to the primary reviewers ↓	Secretariat
4	Collate the responses of the primary reviewers. ↓	Secretariat
5	Discuss and acknowledge the final report during the IRB meeting. ↓	Primary reviewers/ Chair
6	Communicate IRB decision to Principal Investigator **(Form 2.9B)** ↓	Secretariat
7	File the Final Report folder in Inactive File. ↓	Secretariat
8	Update the database.	Secretariat

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Detailed Instructions

3.7.3.1 The Investigator submits the Final Report **(Form 3.4)** once the study has been completed.

3.7.3.2 The secretariat checks for the completeness of the final report including five copies of the following:

a. Letter of Intent addressed to the IRB Chair specifying the date the study was initiated and the date it was completed.
b. Final Report Form **(Form 3.4)**
c. Final paper, for investigator-initiated protocols only.

3.7.3.3 The secretariat forwards the final report to the primary reviewers.

3.7.3.4 The secretariat collates the response of the primary reviewers.

3.7.3.5 The primary reviewers and IRB Chair acknowledges the final report

The following are the possible IRB decisions for final reports **(Form 2.9B)**:

A. Acknowledged
B. Request further information
C. Recommend further action
D. Others

3.7.3.6 Secretariat takes note of the decision and/or discussion during the board meeting in the meeting minutes and communicates the board decision to the principal investigator.

- The IRB acknowldges the Final Report and considers the study completed **(Form 2.9B)**.

3.7.3.7 Secretariat keeps a copy in the protocol files of the final report signed by the Primary Reviewers and the Chair or Member-Secretary.

A. Secretariat marks the folder of the completed protocol and archives the entire study protocol accordingly. Completeness of protocol is through the index prior to archiving to inactive files.
B. Completed protocol is archived in the inactive file for three (3) years.

3.7.3.8 Database and document tracker **(Form 4.4A and Form 4.4B)** are updated.

3.8 Patient's Requests/Queries

3.8.1 Purpose

To describe the IRB procedures related to participant requests and queries.

3.8.2 Scope

This SOP applies to all queries and requests related to the rights and well-being of the research participants in studies approved by the Makati Medical Center IRB.

3.8.3 Responsibility

A designated member of the secretariat is responsible for receiving participant queries and requests related to their participation, refers relevant issues to the IRB Chair or members for the IRB to take appropriate action. The Secretariat keeps records of all action taken by the IRB.

3.8.4 Process Flow/Steps

NO.	ACTIVITY	RESPONSIBILITY
1	Receive and document the request or query **(Form 3.6)** ⬇	Secretariat
2	Assess the nature of the request and refer to the appropriate person ⬇	Secretariat and Chair
3	Take action and refer to full board if necessary	Chair, Members
4	⬇ Communicate the decision to the person who made the query **(Form 2.9G)**	Secretariat
5	⬇ File the documents in protocol folder ⬇	Secretariat
6	Update database	Secretariat

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Detailed Instructions

3.8.4.1 Receive the request or query.

A. The Makati Medical Center IRB secretariat receives the inquiry or requests from research participants/patients or the community through various forms of communication (email, telephone call, letter, walk-in etc.)
B. For telephone requests, requestor is asked to formalize request through email, letter or through website.

3.8.4.2 Secretariat and Chair assess the nature of the request and refer to the appropriate person

3.8.4.3 Take action

A. Reply to the request or query, if it is within the authority of the Secretariat or refer to the Chair or IRB member for appropriate action.
B. A designated IRB member takes appropriate action.
   1) Investigate the fact.
   2) Record information and any action or follow-up taken in the
   3) **Form 3.6**
   4) Sign and date the form and forward to the Secretariat for filing.
   5) Report to the Makati Medical Center IRB about the action taken and the outcomes.

3.8.4.4 The secretariat communicates the decision to the person who made the query **(Form 2.9G)**.

3.8.4.5 Record the request and information in the request record form **(Form 3.6)** and keep a copy in the files.

A. Keep the record form in the "response" file.
B. Keep a copy in the protocol folder
C. Store the file in the appropriately labeled shelf

3.8.4.6 Update database and tracker.

3.9 Early Protocol Termination or Withdrawal

3.9.1 Purpose

To describe the IRB procedures related to early termination or withdrawal of protocol implementation.

3.9.2 Scope

This procedure describes how the IRB proceeds and manages the premature or early termination or withdrawal 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, principal investigator, by the IRB itself or other authorized bodies.

3.9.3 Responsibility

It is the responsibility of the IRB to act on any early protocol termination application. It is also the responsibility of the IRB 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 Secretariat is responsible for the receipt and management of the termination documentation. The primary reviewers review the reasons for early termination and make a recommendation to full board.

3.9.4 Process Flow/Steps

NO.	ACTIVITY	RESPONSIBILITY
1	Receive the application or recommendation for early termination utilizing the Study Termination Form **(Form 3.8)**. ↓	Members and Secretariat
2	Check approval given by the IRB from the protocol files and collect relevant information. ↓	Primary reviewers/ Designated IRB Member
3	Review the termination package or termination issues and make recommendations. ↓	Primary reviewers/ Designated IRB Member

4	Discuss at full board for the appropriate decision.	Members
5	Communicate the board decision to the principal investigator utilizing the Notification of IRB Decision Form **(Form 2.9)**.	Secretariat
6	File copies of the documents and update database.	Secretariat

Detailed Instructions

3.9.4.1 Receive application or recommendation for early study termination/ withdrawal.

A. Receive recommendation and comments from the Sponsor, DSMB, IRB members, Scientific Director, or other authorized bodies for study protocol termination.
B. Inform the principal investigator to prepare and submit a protocol termination package.
C. Receive the study protocol termination package prepared and submitted by the principal investigator.
D. Check the completeness of the contents of the package to include the Study Termination **(Form 3.8)**
E. The request for termination memorandum should contain a brief written summary of the protocol, its results, accrual data and the actions of the investigator on the management of participants still enrolled in the study after termination.

3.9.4.2 Check approval given by the IRB from the protocol files and collect relevant information.

3.9.4.3 The Primary Reviewers review the termination package safety data or termination issues and make recommendation. It is important for the termination package to contain a plan to follow up the participants who are still active in the study.

3.9.4.4 Discuss at full board for appropriate decision:

A. Acknowledged
B. Request Additional Information

C. Request Meeting with the Principal Investigator
D. Others

3.9.4.5 Communicate the IRB decision utilizing the Notification of IRB Decision Form **(Form 2.9)**.

3.9.4.6 Keep the files in protocol folder and archive in inactive files. Inactive files are archived three (3) years.

- Update IRB database, protocol index **(Form 4.5)** and tracker **(Form 4.4A and 4.4B)** accordingly.

MMC IRB SOP Version 5
Document History (Chapter 3)

Author	Chapter	Version	Date	Summary of Changes
Darwin A. Dasig, M.D.	3	6	November 17, 2020	• Added Section 3.4 Review of RNE Reports