UNIVERSITY OF MALAYA MEDICAL CENTRE
MEDICAL RESEARCH ETHICS COMMITTEE
SOP III: POST APPROVAL REVIEW

1.0 OBJECTIVES

This SOP describes how the MREC review post approval submissions by the Principal Investigators. They may undergo either 'expedited' or full board review. This chapter describes submission procedures, required forms, documentation of action, communication of action to the PI, and filing of results.

2.0 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 requests for amendments, progress reports (including annual study reports), study closure reports, non-compliance (deviation or violation) reports, early study termination, queries from stakeholders, serious adverse event reports (SAEs) and suspected unexpected serious drug reactions (SUSARs), and site visit reports.

3.0 RESPONSIBILITIES

It is the responsibility of the PI to comply with post-approval review requirements, including the submission of the following reports:

- Amendments
- Protocol deviation
- Protocol violations
- SAEs and SUSARs
- Annual and closure reports

The Secretariat Staff is responsible for receiving and processing all submissions, including inquiries or complaints from research participants and other stakeholders. The MREC Chair/Deputy Chair are responsible for the review of these post-approval submissions.

4.0 POST-APPROVAL SUBMISSIONS, QUERIES, NOTIFICATIONS AND COMPLAINTS WORKFLOW

ACTIVITY	RESPONSIBILITY
Receive and manage documents submission	Secretariat Staff
Submit documents to the MREC Chair/Deputy Chair to determine classification of review as expedited or full board	Secretariat Staff
MREC Chair reviews submissions classified as expedited or full board review	MREC Chair/Deputy Chair
Review submissions in full board meeting	MREC members
Communicate results to PI/Participant	Secretariat Staff
Manage submission files	Secretariat Staff

Date of acceptance: 19 July 2017
1st revision: 22 October 2018
2nd revision: 28 November 2018

4.1 Study Protocol Amendment

4.1.1 Management of the Study Protocol Amendment Documents

A study protocol amendment is a written description of a change(s) to or formal clarification of a protocol and/or informed consent documents. Approval should be obtained from the MREC prior to the implementation of an amendment.

For ethical clearance or approval approaching the expiry date and requiring an extension, the PI is required to submit a request for protocol amendment via the online system 30 days prior to expiry date.

A study protocol amendment is facilitated through the online submission with the amended study protocol or protocol-related documents by the principal investigator to the MREC. Upon receipt of the study protocol amendment documents, the online system logs the date of submission.

The Secretariat Staff checks the submission for completeness and acknowledges the receipt of the submission to the PI via the online system. The online system logs the date of submission.

4.1.2 Classification of Review by the MREC Chair

The Chair/Deputy Chair reviews the amendment submission online and decide whether it should undergo 'expedited' or full board review.

A full board review is necessary if the proposed study protocol amendment increases risk to study participants, as assessed by the MREC Chair/Deputy Chair, such as a change in study design, which may include but is not limited to:

- Additional treatments or omission of treatments
- Any changes in inclusion/exclusion criteria
- Change in drug formulation, (e.g. oral changed to intravenous)
- Significant change in the number of subjects
- Significant decrease or increase in dosage

4.1.3 Review by MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair reviews all study protocol amendment documents together with the originally approved protocol within 14 working days to determine whether the amendment will change the original risk-benefit assessment.

For submissions under expedited review, action is finalized at the level of the MREC Chair/Deputy Chair within 14 working days.

For study protocol amendment documents requiring full board review, the Secretariat Staff places the study protocol amendment request on the agenda for the next MREC meeting.

4.1.4 Full board review of Study Protocol Amendment Submission Documents

The MREC members review and deliberate the following documents online before the MREC meeting:
amended study protocol or protocol-related document with amended section clearly indicated.
Other documents that have been affected by the revision

For detailed information on the conduct of full board review of study protocol amendments, see SOP II-5.8.1.

4.1.5 Communication of decisions

The PI is notified of the MREC decision noting which amended documents are approved for use through an online action letter.

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

4.1.6 Files management

The amended study protocol or protocol-related document with a new version number and date are archived in the online system with the approval date.

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

4.2 Study Protocol Noncompliance (Deviation/Violation) Report

4.2.1 Management of the study protocol noncompliance reports upon submission

The investigator should document, explain, and report to the MREC any noncompliance from the approved protocol, whether minor or major, at the soonest possible time.

The investigator may implement a deviation from the protocol to eliminate an immediate hazard(s) to study subjects without prior MREC approval, but must submit as soon as possible, a report of deviation or change, the reasons for it, and, if appropriate, a study protocol amendment(s).

Reporting of study protocol noncompliance is facilitated through the online notification of protocol deviation or violation, together with documents deemed relevant by the investigator to clarify information indicated in the notification.

The Secretariat Staff checks the submission for completeness and acknowledges the receipt of the submission to the PI via the online system. The online system logs the date of submission.

4.2.2 Classification of Review by the MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair classifies the submission as either expedited or full board review.

Minor or administrative deviations 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.

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.

4.2.3 Review by MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair reviews all study protocol noncompliance submission documents together with the originally approved protocol within 14 working days to determine whether the noncompliance will change the original risk-benefit assessment.

For submissions under expedited review, action is finalized at the level of the MREC Chair/Deputy Chair within 14 working days.

For study protocol noncompliance documents requiring full board review, the Secretariat Staff places the study protocol noncompliance report on the agenda for the next MREC meeting.

4.2.4 Full board review of study protocol noncompliance report

The MREC members review the following Study Protocol Noncompliance documents:

- Online Protocol Deviation/Violation Notification
- Documents related to the deviation

The MREC members deliberate on the study protocol noncompliance documents, including both the type and degree of noncompliance, and take the appropriate action.

The MREC can suspend ethical approval or subject recruitment until noncompliance issues are addressed.

The MREC may opt to withdraw ethical approval under circumstances including:

- Fraud

- Unresolved serious safety issues

For detailed information on full board review of study protocol noncompliance report, see SOP II-8.15.

4.2.5 Communication of decisions

The PI is notified of the committee's decision through an email.

The PI may be requested to provide additional information, submit additional documents, or implement corrective and preventive action.

4.2.6 Files management

The study protocol noncompliance report documents are stored in the online system.

4.3 Early Study Termination Application

4.3.1 Management of the early study termination application upon submission

An application for early study termination is submitted when a study approved by the MREC is being recommended for termination before its scheduled completion. This is done when 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 unresolvable valid complaints.

Early study termination is facilitated through the online notification of study termination, together with documents deemed relevant by the investigator to support or clarify information indicated in the application.

The Secretariat Staff checks the submission for completeness and acknowledges the receipt of the submission to the PI via the online system. The online system logs the date of submission.

4.3.2 Classification of Review by MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair classifies the submission as either expedited or full board review.

4.3.3 Review by MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair reviews all early study termination application documents together with the originally approved protocol within 14 working days to determine whether the early termination will change the original risk-benefit assessment.

For submissions under expedited review, action is finalized at the level of the MREC Chair/Deputy Chair within 14 working days.

For early study termination application requiring full board review, the Secretariat Staff places the early study termination application on the agenda for the next MREC meeting.

4.3.4 Full board review of early study termination application

The MREC members review the following early study termination application:

- Online early study termination application notification
- Documents related to the early study termination

The MREC 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. The MREC may request information from the PI or invite the PI for clarificatory interview.

For detailed information on full board review of early study termination application, see SOP II-5.8.7.

4.3.5 Communication of decisions

The PI is notified of the committee's decision via email.

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

If the application is approved, the PI is requested to complete the study closure report form (BK-QSU-025-E01).

4.3.6 Files management

The early study termination application documents will be stored in the online system.

4.4 Queries and Complaints

4.4.1 Management of submitted queries or complaints

Communication of queries and complaints, especially from research participants, are major considerations because they provide mechanisms that contribute both to maintaining transparency of MREC decision-making processes, as well as empowerment of study participants.

MREC can also accept communications of queries, notifications, and complaints from other parties provided these communications are relevant to MREC oversight.

Queries and complaints can be made through email, phone or letters to the MREC Secretariat Staff or directly to the Chair/Deputy Chair. The queries or complaints will be investigated and addressed accordingly. If necessary, the queries or complaints will be brought to the attention of the MREC members for information or action.

In case of communication from research subjects, MREC Secretariat Staff can anonymise personal information to protect confidentiality of research subjects, if requested. The communication will be documented and stored in the online system.

4.4.2 Classification of Review by MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair classifies communication for either expedited or full board review depending on the nature of the communication and response needed from MREC.

For non-study-protocol-related queries, review and recommendations can be finalized at the level of the MREC Chair/Deputy Chair.

4.4.3 Review by MREC Chair/Deputy Chair of Study-Protocol-Related Communications

The MREC Chair/Deputy Chair reviews all study-protocol-related communications within 14 working days to determine whether the information will change the original risk-benefit assessment.

For submissions under expedited review, action is finalized at the level of the MREC Chair/Deputy Chair within 14 working days.

For study-protocol-related communications requiring full board review, the Secretariat Staff places the study-protocol-related communications on the agenda for the next MREC meeting.

If necessary, the PI will be contacted to provide clarificatory information.

4.4.4 Full board review of study-protocol-related participant query or complaint

The Secretariat Staff distributes the email to MREC Members along with the meeting agenda.

The MREC deliberates on how best to address the concerns relevant to the query or complaint, and recommends a course of action.

The committee may request information from the PI, invite the PI for clarificatory interview, or require corrective action.

For detailed information on full board review of queries or complaints, see SOP II-5.8.8.

4.4.5 Communication of decisions

The MREC responds to queries and complaints via emails after a course of action of appropriate response is identified whether through expedited or full board review.

4.4.6 Files Management

The documents will be stored in the designated MREC Secretariat computer.

5.0PROGRESS REPORT (INCLUDING ANNUAL STUDY REPORT) AND STUDY CLOSURE REPORT

5.1 Progress Reports (Including Annual Study Reports)

5.1.1 Management of the progress reports (including annual study reports) documents

Ethical approval is typically granted for the duration of the study. After approval, progress reports are required 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 the progress report form (BK-QSU-025-E01) via the online system.

The frequency of progress reports is indicated in MREC approval letter, which is provided to the PI upon approval of the study.

The Secretariat Staff checks the submission for completeness and acknowledges the receipt of the submission to the PI via the online system. The online system logs the dates of submission and acknowledgement.

5.1.2 Action on the Progress Report by the Secretariat Staff

The secretariat staff will screen the progress report for any of the following matters of concern:

- more than 5 SAEs
- more than 5 protocol deviation/violation
- no subject was recruited

If a study reported any of the above, it will be forwarded to the MREC Chair/Deputy Chair for further action. If there is none of the above matter of concern reported, the progress report will be filed.

5.1.3 Review by the MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair reviews the report within 14 working days from notification by the Secretariat Staff. The MREC Chair/Deputy Chair may activate the following decision:

- No further action
- Suspension of the study
- Table for full board review
- Forward to SAE committee for action
- Forward to Site Visit committee for action
- Any other action

For progress reports requiring full board review, the Secretariat Staff places the progress report on the agenda for the next MREC meeting.

If necessary, the PI will be contacted to provide clarificatory information.

5.1.4 Full board review of progress reports (including annual study report)

The MREC members review and deliberate the progress report (including annual study report) prior to the meeting.

For detailed information on the conduct of full board review of progress report, see SOP II-5.8.2.

5.1.5 Communication of decisions

The PI is notified of the decision noting board action on the progress report via email.

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

5.1.6 Files management

The progress reports and related decisions will be stored in the online system.

5.2 Study Closure Report

5.2.1 Management of the study closure report upon submission

Upon completion of the study, the investigator should provide the MREC with a summary of the outcome of the study, especially of the human participants who were involved, in a study closure report.

The end of study reporting is facilitated through the submission of the study closure report form (BK-QSU-025-

E01) together with documents deemed relevant by the investigator to clarify information indicated in the final report.

The Secretariat Staff checks the submission for completeness and acknowledges the receipt of the submission to the PI via the online system. The online system logs the dates of submission and acknowledgement.

5.2.2 Action on the Study Closure Reports by the Secretariat Staff

The secretariat staff will screen the study closure reports for any of the following matters of concern:

- more than 5 SAEs
- more than 5 protocol deviation/violation
- no subject was recruited

If a study reported any of the above, it will be forwarded to the MREC Chair/Deputy Chair for further action. If there is none of the above matter of concern reported, the study closure report will be filed.

5.2.3 Classification of Review by the MREC Chair/Deputy Chair

The MREC Chair/Deputy Chair reviews the report within 14 working days from notification by the Secretariat Staff. The MREC Chair/Deputy Chair may activate the following decision:

- No further action
- Table for full board review
- Forward to SAE committee for action
- Forward to Site Visit committee for action
- Any other action

For study closure reports requiring full board review, the Secretariat Staff places the study closure reports on the agenda for the next MREC meeting.

If necessary, the PI will be contacted to provide clarificatory information.

5.2.4 Full board review of study closure report

The MREC members review and deliberate the study closure report prior to the meeting.

For detailed information on the conduct of full board review of progress report, see SOP II-5.8.2.

5.2.5 Communication of decisions

The PI is notified of the panel decision, noting panel action on the final report through an action letter via email.

The PI may be requested to provide additional information or submit additional documents, in which case the study closure report may be accepted, but action regarding archiving may be deferred pending submission of results of the study.

The PI will be informed of the following:

- The study protocol is classified as inactive.
- Ethical clearance is expired effective on the day of the MREC meeting.

Study protocol records will be made available for three (3) years in the archives after the expiration date.

5.2.6 Files management

The study closure documents will be archived in the online system, upon approval of the final report, when no further action is expected from the PI. It will be labelled as an 'inactive' file.

6.0 SERIOUS ADVERSE EVENT (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) REPORTS WORKFLOW

6.1 Management of the SAE report upon submission

The reporting of the SAE and SUSAR is based on the Malaysian Guideline for Safety Reporting of Investigational Products.

Adverse events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Adverse Drugs Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product).

Serious Adverse Event or Serious Adverse Reaction

A serious adverse event (SAE) or serious adverse drug reaction (Serious ADR) is any untoward medical occurrence that at any dose that:

- results in death
- is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- requires inpatient hospitalization or prolongation of existing hospitalization

- results in a persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Expectedness of the Adverse Drug Reaction
An "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

What Should be Reported
Investigators must report information that might influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation. Examples:

- Single Cases of SUSAR
- For an "expected", serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
- A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).

SAE or SUSAR from the following do not require reporting:

- Clinical Trial not conducted in UMMC
- Suspected drug is known to be other than trial drug (e.g. Other treatments, placebo or comparator drug)

When to Start and End Reporting
The reporting of serious, unexpected adverse drug reactions shall commence from the date of notification of approval from UMMC-MREC and continue till all trial sites in Malaysia are closed.

The reporting timeframe for the investigator to the MREC and type of report to submit are as follows:

- Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSARs) that is fatal/life threatening: As soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.
- All other SUSARs: As soon as possible but no later than 15 calendar days from awareness of event by investigator. Follow up information should be actively sought and submitted as it becomes available.

How to Report
The PI must report Serious Adverse Event (SAE) and Suspected, Unexpected, Serious Adverse Reactions (SUSAR), and submit other documents deemed relevant by the investigator to clarify information indicated in the report. The SAE and SUSAR reporting is facilitated through the submission of the SAE report form (BK-MIS-1118-E01).

Date of acceptance: 19 July 2017
1st revision: 22 October 2018
2nd revision: 28 November 2018

The Secretariat Staff checks the submission for completeness and acknowledges the receipt of the submission to the PI via the online system. The online system logs the dates of submission and acknowledgement.

The Secretariat Staff forward all the serious adverse event/s reports to the SAE Subcommittee Chair.

6.2 Processing of Serious Adverse Event/s and Suspected, Unexpected, Serious Adverse Reactions (SUSARs) Reports

The secretariat staff forwards the SAE Reports Form (BK-MIS-1118-E01) to the SAE Subcommittee Chair within 2 working days from date of receipt.

If the SAE Subcommittee Chair screens the reports to decide whether the reports need expedited review in a special meeting or table for a regular meeting (at least three monthly).

SAE Subcommittee Chair assigns SAE reports to committee members for review. The SAE Subcommittee members will have access to the study protocol and relevant documents via the online system.

The SAE Subcommittee meets to make recommendations which will be presented at the MREC meeting by the SAE Subcommittee Chair.The SAE Subcommittee then inform the secretariat to table the SAE reports for meeting.

During the meeting, the MREC Chair calls for a decision on the SAE report/s with respect to the recommendation/s of the SAE Subcommittee as presented by the SAE Subcommittee Chair. The MREC may take any of the following actions:

- No further action
- Recommend further action
- Request information
- Pending, if major clarifications are required before a decision can be made

6.3 Communication of decisions

The PI is notified of the MREC decision, noting action on the Serious Adverse Event/s Report via email.

The PI may be requested to provide additional information, submit additional documents, or implement corrective action.

6.4 Files management

The SAE reports and related documents are stored in the online system.

7.0 SITE VISIT WORKFLOW

ACTIVITY	RESPONSIBLE PERSON
Select study sites to visit	Site Visit SubcommitteeChair
Notify PI of date of site visit	Secretariat Staff
Create Site Visit Team	Site Visit Subcommittee Chair
Conduct Site Visit	Site Visit Team
Present findings during MREC meeting	Site Visit Subcommittee Chair
Communicate results of Site Visit and subsequent MREC action to PI	Secretariat Staff
Manage Site Visit documents	Secretariat Staff

7.1 Selection of Study Sites

Study sites may be selected for Site Visits based on the following criteria:

- The nature of the study being conducted (i.e. high risk studies)
- Frequent non-submission or failure to submit progress reports
- Reports of major protocol noncompliance
- Significant number of serious adverse events
- Reports of complaints from study participants
- Site visits may be conducted upon recommendation of the MREC
- Study sites may also be selected for Site Visit upon recommendation of the SAE Subcommittee.

A report for Site Visit is deliberated on during an MREC meeting.

7.2 Notification of PI of date of site visit

The Site Visit Subcommittee Chair, through the Secretariat, informs the PI at least 10 working days before the scheduled visit through an email. A copy of the MREC Site Visit Form is attached to the email.

The email provides Site Visit schedule details and instructions on what the PI needs to prepare such as documents and files that will be reviewed during the Site Visit, as well as orderly preparation of the site.

7.3 Creation of a Site Visit Team

A Site Visit Team is organized for each site visit.

The members of this team are assigned by the Site Visit Subcommittee Chair.

The Site Visit Team should be composed of at least three persons, including Site Visit Subcommittee Chair and one Site Visit Subcommittee member. Additional team members could include staff from UMMC Clinical Investigation Centre (CIC) or a UMMC clinician.

The Secretariat Staff prepares a Site Visit Package for each member of the Site Visit Team, inclusive of the MREC Site Visit Report Form, a copy of the approved study protocol and related documents.

The Site Visit Team prepares by reviewing the contents of the Site Visit Package.

7.4 Conduct of Site Visit

Upon arrival in the study site, the Site Visit Team uses MREC Site Visit Report Form to perform the following tasks:

- Review the study protocol
- Review the informed consent documents and verify if the site is using the most recently approved versions
- Ask the PI or staff to explain the informed consent process
- Review the post-approval documents and verify if the site is using the most recently approved versions, or that these have been approved
- Verify security, privacy, and confidentiality of the documents at the study site
- Observe facilities in the study site
- Make an overall determination of the protection of the rights, safety, and welfare of human participants in the study

At the end of the visit, the Site Visit Team will:

- Discuss the findings with the research team
- Solicit feedback

7.5 Presentation of findings at MREC Meeting

The Site Visit Subcommittee Chair completes MREC Site Visit Report which should reflect the consensus opinion of the Site Visit Team members, and submits it to the Secretariat via email not later than 10 working days after the Site Visit.

The Secretariat Staff acknowledges the receipt of the MREC Site Visit Report.

The Secretariat Staff places the Site Visit Report in the agenda of the next MREC meeting.

The Secretariat Staff distributes the MREC Site Visit Report to MREC Members along with the meeting agenda via email.
The MREC deliberates on the implications of the findings of the Site Visit on the rights, safety, and welfare of the study participants; and makes an overall determination of protocol compliance in the study site.

For detailed information on full board review of Site Visit Reports, see SOP II-8.14.

7.6 Communication of decisions

The PI is notified of the MREC action or recommendations via emails.

The PI may be requested to provide additional information, submit additional documents, or implement corrective action.

7.7 Site Visit files management

The Secretariat Staff stores the Site Visit documents in the designated MREC Secretariat computer.