UPM UNIVERSITI PUTRA MALAYSIA	**JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN MELIBATKAN MANUSIA (JKEUPM) UNIVERSITI PUTRA MALAYSIA**
	III. POST APPROVAL

1.0 OBJECTIVES

This SOP describes how JKEUPM processes post approval submissions by the Principal Investigators (PI). The post approval subcommittee (PASC) will review all submissions and make recommendation to JKEUPM. This chapter describes submission procedures, required forms, documentation of board action, communication of board 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, continuing review applications, final 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 required reports listed in JKEUPM approval letter.

The secretariat staff is responsible for receiving and processing all submissions, including inquiries or complaints from research participants and other stakeholders.

When a site visit becomes necessary, it is the responsibility of the Chair to form a site visit team. The responsibilities of the assigned members are to conduct the site visit and issue a report for presentation in JKEUPM meeting. It is the responsibility of the secretariat staff to organize the site visit.

4.0 STUDY PROTOCOL AMENDMENTS, CONTINUING REVIEW APPLICATIONS, FINAL REPORTS, NONCOMPLIANCE REPORTS, EARLY STUDY TERMINATION APPLICATION, AND QUERIES, NOTIFICATIONS AND COMPLAINTS WORKFLOW

Activity	Responsibility
Receive and manage submission of documents ↓	Secretariat Staff
Submit documents to the PASC Chair ↓	Secretariat Staff
PASC reviews submissions in PASC meeting ↓	PASC
Present to full board study protocols in JKEUPM meeting ↓	PASC Chair
Communicate with PI ↓	Secretariat Staff
Manage study protocol files	Secretariat Staff

4.1 Continuing Review Application

4.1.1 Ethical clearance or approval is 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 **JKEUPM FORM 3.1: PROGRESS REPORT.**

4.1.2 For ethical clearance or approval approaching the one-year expiry date and requiring a renewal or extension, it is advisable to submit **JKEUPM FORM 3.1: PROGRESS REPORT ninety (90) calendar days** prior to expiry date.

4.1.3 The secretariat staff informs the respective PIs at least **one hundred twenty (120) calendar days** in advance of the due date of review.

4.2.4 All continuing review application packages will be sent to the PASC together with the originally approved protocol for approval.

4.2.5 All submissions will be reviewed and finalized by PASC at the following meeting.

4.2.6 The secretariat staff places the study protocol continuing review application in the PASC report presentation at the next full board meeting.

4.2.7 PASC Chair to present continuing review application to JKEUPM members for deliberation.

4.2.8 The PI is notified of the JKEUPM decision noting which continuing review application are approved for use. The PI may be required to provide additional

information, or submit additional documents. The PI is requested to submit study protocol or protocol-related document with a new version number and date.

4.2.9 The secretariat staff receives the continuing review application with a new version number and date. The newly approved documents will supersede previous versions of the study protocol or protocol-related document. The secretariat staff stores the signed continuing review application documents in the study protocol folder.

4.3 Study Protocol Amendment

4.3.1 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 JKEUPM that issued the ethical clearance or approval prior to the implementation of an amendment.

4.3.2 A study protocol amendment is facilitated through the submission of a letter to the PASC Chair with the amended study protocol or protocol-related documents.

4.3.3 PASC Chair to assess the urgency of the amendment approval. If PASC Chair assesses it to be needing immediate action, he/she forwards his/her recommendations to the JKEUPM Chair for immediate action and results will be communicated to the PI immediately.

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

a. Additional treatment or the deletion of treatments.
b. Any changes in inclusions/exclusion criteria.
c. Changes in method of dosage formulation, (e.g. oral changed to intravenous).
d. Significant change in the number of subjects.
e. Significant decrease or increase in dosage amounts.

4.3.5 If the proposed study protocol amendment is with minimal risk, it can be recommended for approval by PASC.

4.3.6 PASC Chair to present amendments to JKEUPM members for deliberation.

4.3.7 The PI is notified of the JKEUPM decision noting which amended documents are approved for use. The PI may be required to modify the protocol, provide additional information, or submit additional documents. The PI is requested to submit an amended study protocol or protocol-related document with a new version number and date.

4.3.8 The secretariat staff receives the amended study protocol or protocol-related document with a new version number and date. The newly approved documents will supersede previous versions of the study protocol or protocol-related

document. The secretariat staff stores the signed and approved documents in the study protocol folder.

4.4 Final Report

4.4.1 Upon completion of the study, the PI should provide the JKEUPM with a summary of the outcome of the study in a form of an end of study report through **JKEUPM FORM 3.2: STUDY FINAL REPORT**.

4.4.2 All the final report will be sent to the PASC together with the originally approved protocol for approval. All submissions will be reviewed and finalized by PASC at the following meeting.

4.4.3 Chair of PASC to present the reports to JKEUPM members for deliberation.

4.4.4 The PI is notified of the JKEUPM decision **fourteen (14) calendar days** after the Full Board meeting. The PI may be required to provide additional information or submit additional documents, in which case the final report may be accepted, but action regarding archiving may be deferred pending submission of results of the study. If the final report is approved, the PI is informed of the following:

a. The study protocol is classified as inactive.
b. Ethical clearance is expired effective on the day of the Full Board meeting.
c. Study protocol records will be made available for **three (3) years** for non-clinical trial and **seven (7) years** for clinical trial in the archives after the expiry date.

4.5 Study Protocol Noncompliance (Deviation/Violation) Report

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

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

4.5.3 Reporting of study protocol noncompliance is facilitated through the submission of **JKEUPM FORM 3.3: STUDY PROTOCOL NONCOMPLIANCE (DEVIATION OR VIOLATION) REPORT**, together with documents deemed relevant by the PI to clarify information indicated in the report.

4.5.4 All noncompliance reports will be sent to the PASC together with the originally approved protocol for approval**.** All submissions will be reviewed by PASC at the following meeting.

4.5.5 Chair of PASC to present study protocol noncompliance reports to JKEUPM members for deliberation. JKEUPM may suspend ethical clearance or subject recruitment until noncompliance issues are addressed. JKEUPM may opt to withdraw ethical approval under the following circumstances:

a. Fraud (e.g. data manipulation, major protocol violation, etc)
b. Unresolved serious safety issues

4.5.6 The PI is notified of the JKEUPM decision **fourteen (14) calendar days** after the Full Board meeting. The PI may be requested to provide additional information, submit additional documents, or implement corrective action.

4.5.7 The Secretariat Staff stores the signed study protocol noncompliance report documents in the study protocol file folder.

4.6 Early Study Termination Application

4.6.1 An application for early study termination is submitted when a study approved by JKEUPM is being recommended for termination before its scheduled completion. This is done when the safety of the study participant is in doubt or at risk and also upon the request of the PI or the sponsor owing to the existence of unresolved situations.

4.6.2 Early study termination is facilitated through the submission of **JKEUPM FORM 3.4: 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.

4.6.3 The Secretariat Staff places the early study termination application in the PASC report presentation at the next full board meeting.

4.6.4 The PI is notified of the panel decision **fourteen (14) calendar days** after the Full Board meeting, The PI may be requested to provide additional information or submit additional documents. If the application is approved, the PI is requested to complete and submit **JKEUPM FORM 3.2: STUDY FINAL REPORT**.

4.6.5 The Secretariat Staff stores the early study termination application documents in the study protocol file folder.

4.6.6 JKEUPM may opt for early study termination in the event of non-compliances that affect subjects' safety. PI will be notified through letter from Chair of JKEUPM.

5.0 SERIOUS ADVERSE EVENT REPORTS WORKFLOW

Activity	Responsibility
Ensure completeness and receive serious adverse event (SAE) report/s	Secretariat Staff

<table>
<tr><td colspan="2">↓</td><td></td></tr>
<tr><td colspan="2">Log report/s on Log of Submissions and SAE Database
↓</td><td>Secretariat Staff</td></tr>
<tr><td colspan="2">Forward reports to PASC Chair to assess urgent/non urgent SAE/SUSARs

** PI has to report to site HOD ↓</td><td>Secretariat Staff</td></tr>
<tr><td>URGENT
↓</td><td>NON-URGENT
(Assign to original primary reviewer*)
↓</td><td>PASC Chair</td></tr>
<tr><td>If the report needs immediate action, PASC Chair to assess/ recommend
↓ ←</td><td>Forward to Primary Reviewer within 48 hours after receipt of reports
↓</td><td>Secretariat Staff</td></tr>
<tr><td rowspan="4">Forward PASC recommendation/s to the JKEUPM Chair for immediate action
↓</td><td rowspan="2">Submit review to the secretariat staff seven (7) calendar days after receipt of SAE report
↓
Conduct PASC Meeting
↓</td><td>Onsite: PASC Primary Reviewer, Secretariat Staff,
Offsite: PASC Chair, PASC Members</td></tr>
<tr><td>Secretariat Staff</td></tr>
<tr><td>Present review in the JKEUPM meeting
↓</td><td>Primary Reviewer/ PASC Chair</td></tr>
<tr><td>Deliberation on board action on the report/s
↓</td><td>JKEUPM Chair, JKEUPM Secretary, JKEUPM Members, Primary Reviewer</td></tr>
<tr><td colspan="2">Communicate results to principal investigator
↓</td><td>Secretariat Staff</td></tr>
<tr><td colspan="2">If no further action: send notification of decision to PI</td><td>Secretariat Staff</td></tr>
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If recommend further action: send notification with recommendations to PI;	
Manage study protocol files	Secretariat Staff

* in the absence of the Primary reviewer, PASC to meet and deliberate

5.1 Management of the SAE report upon submission

5.1.1 Serious adverse events are events temporally associated with the subject's participation in research that meets any of the following criteria:

a. Results in death.
b. Is life-threatening (places the subject at immediate risk of death from the event as it occurred).
c. Requires inpatient hospitalization or prolongation of existing hospitalization.
d. Results in a persistent or significant disability/ incapacity
e. Results in a congenital anomaly/ birth defect.
f. Any other adverse event that 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 the definition.

5.1.2 The PI must report serious adverse advents to the JKEUPM panel.

5.1.3 The PI must report suspected, unexpected, serious adverse reactions (SUSAR), and other documents deemed relevant by the investigator to clarify information indicated in the report.

5.1.4 The Secretariat Staff collates all the serious adverse event(s) reports and encodes data in the **JKEUPM FORM 3.5: SAE/ SUSARs REPORT**.

5.2 Processing of Serious Adverse Events Reports

5.2.1 For all Serious Adverse Event(s) and Suspected, Unexpected, Serious Adverse Reactions (SUSARs) Reports, the secretariat staff forwards the report comprised the following documents to the PASC Chair immediately:

a. **JKEUPM FORM 3.5: SERIOUS ADVERSE EVENTS REPORTS/CIOMS Form**.
b. Latest Investigator's Brochure.
c. Protocol Summary.
d. Other supporting documents, if any.

5.2.2 PASC Chair to assess whether the reports are urgent or non-urgent. If PASC Chair assesses the reports which require immediate action, he forwards his recommendation/s to the JKEUPM Chair for immediate action and results will

be communicated to the PI immediately.

5.2.3 In non-urgent reports from both on and off sites, PASC will assign the original primary reviewer to assess the reports. The reports will be forwarded to the primary reviewer within 48 hours after receipt of reports.

5.2.4 For all non-urgent reports, the review should be submitted to the secretariat staff **seven (7) calendar days** after receipt of SAE report package and the review will be discussed in the PASC meeting. During the meeting, the PASC may recommend any of the following actions:

a. No further action
b. Recommend further action.
Further actions may include, but not limited to the following:

i. 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;
ii. Recommend implementation of additional procedures for protecting/safeguarding participants;
iii. Suspension of enrolment of new participants or research procedures among participants who are currently enrolled (check consistency);
iv. Recommend suspension of the entire study.

5.2.5 The review will be presented at the JKEUPM meeting and the JKEUPM Chair calls for a decision on the SAE report with respect to the recommendations of the PASC. The full board may require any of the following actions:

a. No further action
b. Requires further action

5.3 Communication of results

5.3.1 The PI is notified of the panel decision 14 calendar days after the Full Board meeting, noting panel action on the Serious Adverse Event/s Report through an action letter.

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

5.4 Files management

5.4.1 The Secretariat Staff stores the signed serious adverse event/s report in the study protocol file folder.
5.4.2 Files are managed in accordance with SOP 4: Active Files.

6.0 SITE VISIT WORKFLOW

Activity	Responsible Person
Select study sites to visit ↓	JKEUPM
Notify PI of date of "site visit" ↓	JKEUPM Chair
Create Site Visit Team ↓	JKEUPM
Conduct Site Visit ↓	Site Visit Team
Present findings during full board meeting ↓	Visit Team Chair
Communicate results of Site Visit and subsequent panel action to PI ↓	Secretariat Staff
Manage Site Visit documents	Secretariat Staff

6.1 Selection of Study Sites

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

a. The nature of the study being conducted (i.e. high risk studies).
b. Frequent non-submission or failure to submit continuing review requirements.
c. Reports of major protocol noncompliance.
d. Significant number of serious adverse events.
e. Reports of complaints from study participants.
f. Site visits may be conducted upon recommendation of the JKEUPM.

6.1.2 Study sites may also be selected for Site Visit upon recommendation of the PASC.

6.1.3 A decision for Site Visit is deliberated on during a full board meeting.

6.2 Notification of PI of date of site visit

6.2.1 The JKEUPM Chair, through the Secretariat, informs the PI at least **fourteen (14) calendar days** before the scheduled visit through a letter.

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

6.3 Appointment of a Site Visit Team

6.3.1 A Site Visit Team is organized for each site visit.

6.3.2 The members of this team are assigned by the JKEUPM Chair.

6.3.3 The Site Visit Team should consist of at least three (3) people: one (1) JKEUPM member, one (1) PASC Member and one (1) other member preferably the primary reviewer of the protocol or of the SAE.

6.4 Conduct of Site Visit

6.4.1 Upon arrival at the study site, the Site Visit Team uses **JKEUPM FORM 3.6: SITE VISIT REPORT FORM** to do the following:

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

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

a. Discuss the findings with the research team
b. Solicit feedback

6.5 Presentation of findings at PASC Meeting

6.5.1 The Site Visit Team completes **JKEUPM FORM 3.6: SITE VISIT REPORT FORM** which should reflect the consensus opinion of the Site Visit Team members, and submits it to the Secretariat not later than **seven (7) calendar days** after the Site Visit.

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

6.5.3 During the meeting, the Secretariat Staff distributes the completed **JKEUPM FORM 3.6: SITE VISIT REPORT FORM** to Panel Members along with the meeting agenda.

6.5.4 The Site Visit Team Chair presents the findings to the PASC.

6.5.5 PASC will review the outcomes of the site visit team findings and present to the Full Board meeting.

6.5.6 The JKEUPM Panel deliberates on the implications of results 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.

6.6 Communication of results

6.6.1 The PI is notified of the panel decision **fourteen (14) calendar days** after the Full Board meeting.

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

6.7 Site Visit files management

6.7.1 The Secretariat Staff stores the Site Visit documents in the study protocol file folder.