SOP 7 MANAGEMENT OF POST-APPROVAL SUBMISSIONS

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7. Management of Post Approval Submission

7.1 Review of Protocol Amendment
7.2 Review of Progress/Annual Report
7.3 Review of Final Report
7.4 Review of Serious Adverse Event (SAE) & SUSAR Report
7.5 Review of Protocol Violation/Deviation Report
7.6 Review of Early Termination of Study Report

SOP 7 MANAGEMENT OF POST-APPROVAL SUBMISSIONS

SOP 7.1 REVIEW OF PROTOCOL AMENDMENT

1. Objective of the Activity

To describe the MDMRCI-ARMCI CRERC procedures for the review of application for protocol amendment *to ensure the protection of the safety, rights and welfare of study participants, and the integrity of research data*.

2. Scope

This SOP applies to all study protocol-related submissions after the approval of the study protocol by CRERC. Any changes in the approved protocol package shall be approved by the CRERC before this can be implemented by the Researcher/Principal Investigator (PI) unless the changes are necessary for the safety and welfare of study participants.

This SOP begins with the receipt of the application for protocol amendment package and ends with the filing of the document package in the protocol file folder, and the updating of the protocol file index and the protocol database.

3. Responsibilities

*The CRERC Administrative Secretary is responsible for: **a**) ensuring that the application uses the correct template/form, protocol identification details are correct, documents in the application package are complete, and that application form is completely filled up; **b**) stamping the date of receipt of the submission and recording the submission in the Log of Protocol-Related Submissions (CRERC Form 9.1); **c**) identifying the Primary Reviewers, and forwarding the document package to them; **d**) following up the results of the review; **e**) including the major protocol amendment in the agenda of the forthcoming meeting; **f**) communicating CRERC's review decision to the Researcher/PI within the specified timeline and recording it in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2); and **g**) filing the documents in the protocol file folder and updating the protocol file index and protocol data base.*

*The Primary Reviewer is responsible for **a**) assessing the application for protocol amendment, and **b**) returning the Form 7.1 with the results of the assessment to the CRERC Administrative Secretary within the specified timeline.*

The CRERC Chair is responsible for **a**) determining the type of review for the submission, **b**) designating Primary Reviewers if those who did the initial review are not available, and **c**) *reviewing, signing, and dating the Notification of CRERC decision to the Researcher/PI.*

4. Workflow

No.	Activities	Person/s Responsible
1	Receive the application for protocol amendment package and determine the type of review	Admin Secretary, CRERC Chair or Member-Secretary
2	Identify the Primary Reviewers and send the application for protocol amendment package	Admin Secretary, CRERC Chair

3	Review the application for protocol amendment	Primary Reviewers
4	Include the protocol amendment applications in the agenda of the forthcoming CRERC meeting	Administrative Secretary
5	Communicate the CRERC decision to the Researcher/Principal Investigator (PI)	Admin Secretary, Member-Secretary, Chair
6	File the protocol amendment documents in the protocol file folder, and update the protocol file index and protocol database	Administrative Secretary

5. Detailed Instructions

5.1 Receive the application for protocol amendment package and determine the type of review

5.1.1 The Administrative Secretary verifies that the protocol identification details are correct, *that the initial approval date or the date of last continuing review approval is valid, and the documents in the submission package are complete. If the ethical clearance is about to expire, the Administrative Secretary requests the Researcher/PI to submit a continuing review application also together with the application for protocol amendment. But if the ethical clearance is already expired, the Researcher/PI must include justification letter for the failure to submit the continuing review application 30 days prior to the expiration of the ethical approval. CRERC shall ask for information on the no. of study subjects recruited, enrolled and/or randomized to treatment groups after expiry of ethical approval.*

5.1.2 If the submission is in order, and the ethical approval is current/valid, the Administrative Secretary stamps the document "Received", writes the date of receipt, and gives the duplicate copy of CRERC Form 7.1 Protocol Amendment to the Researcher/PI or his/her representative.

5.1.3 *The Administrative* Secretary records the submission *in CRERC Form 9.1 Log of Protocol–Related Submissions*, and in the Amendment columns of the protocol database.

5.1.4 *The Administrative Secretary informs the CRERC Chair and Member-Secretary of the submission.*

5.1.5 CRERC Chair/Member Secretary reviews the document to determine whether amendment is major or minor.

a) Major protocol amendments: increase the risk to study participants and require Full Committee review. These include but are not limited to the following:
   i) Modification of treatment – addition or reduction of treatment
   ii) Any changes in inclusion/exclusion criteria
   iii) Change in study design
   iv) Change in method of dosage formulation, such as, oral to parenteral
   v) Significant change in the number of subjects
   vi) Significant decrease or increase in dosage amount
   vii) Any other changes that will entail more than minimal risk.

b) Minor protocol amendments are reviewed by expedited procedure. These are: i) changes which are unlikely to compromise the integrity of the research data, or the safety, welfare and rights of the study

participants and present no new ethical issues (*do not involve significant change in the study populations, do not involve the collection of stigmatizing information, do not change the approved use of anonymized or archived samples, do not involve further recruitment of participants); **ii**) changes that involve study protocols previously classified under expedited review;* **iii**) changes that are administrative in nature.

5.2 Identify the Primary Reviewers and send the application for protocol amendment package to them

5.2.1 The Administrative Secretary identifies the Primary Reviewers who did the initial review.

5.2.2 The Administrative Secretary prepares protocol amendment package by photocopying relevant documents of previous review/s of the protocol that will provide the Primary Reviewers with background information that will facilitate the assessment of the proposed amendment/s.

5.2.3 If the Primary Reviewers are available to do the review, the Administrative Secretary sends the protocol amendment package to the Primary Reviewers *within seven (7) calendar days from the date of receipt of the application.*

5.2.4 If Primary Reviewers are not available to do the review, CRERC Chair and Member-Secretary may do the review provided they do not have COI. Otherwise, the Chair designates qualified Members to do the review.

5.2.5 If the expertise of an Independent Consultant is needed to assist in the review, the Chair informs the Medical Director of MDMRCI of the need to call in an Independent Consultant.

5.2.6 The Administrative Secretary prepares CRERC Form 2.9 Invitation to the Independent Consultant, have this signed by the Chair and sends this to the Independent Consultant chosen by the Chair.

5.3 Review the application for protocol amendment

5.3.1 CRERC reviews the application for protocol amendment under consideration.

a) For detailed instructions on expedited review, refer to SOP 4.1 Expedited Review.

b) For detailed instructions on Full Committee review, refer to SOP 4.2 Full Committee Review

5.3.2 The Primary Reviewers review the amended documents and compare them with the previously CRERC-approved documents in the protocol file folder to assess the proposed amendment's effect on: **i**) the feasibility of the changes in the study, **ii**) the safety and well-being of study subjects, and **iii**) the overall risk-benefit ratio.

5.3.3 Using the "For CRERC Use"-box of CRERC Form 7.1 Protocol Amendment, the Primary Reviewers *write the results of their assessment in the space provided.*

5.3.4 *After the assessment is completed the Primary Reviewers and the Independent Consultant (if any) return all the documents including the completed assessment forms to the CRERC within (seven) 7 calendar days from the date of receipt of the protocol amendment package for*

expedited review or at least seven (7) calendar days before the date of the Full Committee meeting.

5.4 Include the protocol amendment applications in the agenda of the forthcoming CRERC meeting

5.4.1 The Administrative Secretary reviews the completed assessment forms of the Primary Reviewers (and Independent Consultant, if any) to determine if there is agreement in the review decision. For submissions reviewed by expedited procedure, copies of the CRERC Form 7.1 Protocol Amendment where the "For CRERC Use" box is filled by the Primary Reviewers are forwarded by e-mail to the Member-Secretary. The Member-Secretary reviews and finalizes the list of recommendations, if any.

5.4.2 The Administrative Secretary includes the deliberation of the application for protocol amendment classified as major in the meeting agenda of the forthcoming meeting. (Refer to SOP 6.1 Preparation for a CRERC Meeting).

Submissions reviewed by expedited procedure where the amendments are approved are also included in the agenda of the forthcoming meeting for reporting to the CRERC.

5.4.3 For major protocol amendments, the medical/scientific Primary Reviewer presents the results of the assessment during the Full Committee meeting.

5.4.4 The CRERC Members deliberate on the technical and ethical merits of the protocol or protocol-related documents during a Full Committee meeting. (Refer to SOP 6.2 - Conduct of Review Meeting).

5.4.5 Possible review decisions are as follows:

i) Approval (when no further modification is required)

ii) Minor revision
Revision is said to be minor when the recommended revisions of the study or related documents do not impact on potential risks to the participants and on the integrity of the research data, e.g. updating of the clinical study protocol and ICF to harmonize with the new edition of the Investigators Brochure, clarificatory changes in the study protocol or the ICF.

iii) Major modification
Revision is said to be major when the recommended revisions of significant aspects of the study involve any of the following: study objectives, recruitment of participants, exclusion/inclusion criteria, collection of data, statistical analysis, mitigation of risks, protection of vulnerability, etc.) that impact on potential risks/harms to participants and on the integrity of the research data.

iv) Disapproval (due to ethical or legal concerns) Reasons for vote of disapproval should be noted in the minutes and communicated to the Researcher/PI.

5.4.6 Letter of appeal for reconsideration of CRERC review decision especially disapproval may be made. (Refer to SOP 5.1 Management of Appeal of CRERC Decision based on CIOMS 2016, Guidelines 23)

5.5 Communicate the CRERC decision to the Researcher/Principal Investigator

5.5.1 The Administrative Secretary prepares Notification of CRERC Decision – Protocol Amendment (CRERC Form 8.3) based on the minutes of the meeting, or on the results of the assessment by Primary Reviewers for review by expedited procedure, for review and signature of CRERC Chair, and sends it to the Researcher/PI after recording the document in the

CRERC Form 9.2 Log of Outgoing Protocol Related Communications. (Refer to SOP 8.2 Communicating CRERC Decision)

5.5.2 Expedited review of application for protocol amendment should be completed (*from date of submission to date of notification of CRERC decision to the Researcher/PI) within nineteen (19) calendar days*. It may take longer for major protocol amendments depending on the schedule of the Full Committee meeting but *should not exceed forty-two (42) calendar days.*

5.6 File the protocol or protocol-related documents in the protocol file folder and update the protocol file index and protocol database

5.6.1 The Administrative Secretary files the protocol amendment package with excerpt of the minutes of the meeting (for major amendment that is reviewed by Full Committee meeting), duplicate copy of CRERC Form 8.3 Notification of CRERC Decision – Protocol Amendment, and CRERC Form 8.2 Certificate of Approval Letter (if review decision is approval) in the protocol file folder; and updates the protocol file index, and the protocol database accordingly. (Refer to the SOP 9.1 Management of Active Study Protocol Files)

6. Related Forms

CRERC Form 3.4	*Document Submission Checklist*
CRERC Form 7.1	Protocol Amendment
CRERC Form 8.2	*Certificate of Approval*
CRERC Form 8.3	*Notification of CRERC Decision – Review of Initial Submission/Resubmission/Protocol Amendment*
CRERC Form 9.1	*Log of Protocol-Related Submissions*
CRERC Form 9.2	*Log of Outgoing Protocol Related Communications*

7. SOP Document History

Version No.	Version Date	Description of Changes
01	23 Jan 2015	Refer to SOP v. 01
02	21 May 2015	Refer to SOP v. 02
03	05 Feb 2016	Refer to SOP v. 03
04.1	17 May 2019	Refer to SOP v. 04.1
05	01 Dec 2021	▪ Changed Purpose to Objective, and Process Flow/Steps to Workflow to harmonize with PHREB's section titles. ▪ Changed the section on Scope, - included the start and end tasks of the SOP ▪ Added the detailed responsibilities of the CRERC Chair/member-Secretary, Primary Reviewers, and those of the Administrative Secretary ▪ Combined Tasks #1 and #2 of version 4.0; and added 5.1.1 – verification of the completeness and correctness of the submission, 5.1.2 – stamping "Received" with date of receipt on CRERC Form 7.1, and 5.1.3 – recording the submission in CRERC Form 9.1 Log of Protocol-Related Submissions ▪ Added timelines: from date of receipt of submission to forwarding this to Primary Reviewers in 5.2.3; from receipt of document package for review by Primary Reviewers to

		return of results of assessment to CRERC in 5.3.4; turn around time of expedited review (from date of receipt of submission to date of notification of CRERC decision to the PI) – within 19 calendar days of Full Committee review – within 42 calendar days in 5.5.2 ▪ Added definition of major revision and minor revision in 5.4.5 ▪ Introduced new forms – CRERC Form 3.4 Document Submission Checklist, CRERC Form 8.3 – Notification of CRERC Decision – Protocol Amendment, CRERC Form 9.1 Log of Protocol-Related Submissions, and CRERC Form 9.2 Log of Outgoing Communications ▪ Cross referenced related SOPs ▪ Used Administrative Secretary instead of CRERC Secretariat or Administrative Staff, Full Committee instead of full board

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SOP 7.2 REVIEW OF PROGRESS/ANNUAL REPORT

1. Objective of the Activity

To describe the procedure for the review of Progress/Annual Report *to determine if there is a significant change in the study risk-benefit ratio to study participants and whether ethical approval for the implementation of the study can be renewed*.

2. Scope

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 the duration of the study, the CRERC may require more frequent submission of progress report.

This SOP starts with the receipt of the Progress Report document package and ends with the filing of the protocol and related documents, and the updating of the protocol file index and data base.

3. Responsibilities

*The CRERC Administrative Secretary is responsible for: **a**) reminding the Researcher/Principal Investigator (PI) of the submission of the Progress Report at least 60 days before the expiry date of the study protocol's approval; **b**) ensuring that the application uses the correct template/form, protocol identification details are correct, the documents in the application package are complete, and that CRERC Form 7.3 Progress/Annual Report is completely filled up; **c**) ensuring that the reporting period covers at least the approval period (in months) minus one (1) month for the first Annual Report; **d**) stamping the date of receipt of the submission and recording the submission in the Log of Protocol-Related Submissions (CRERC Form 9.1); **e**) identifying the Primary Reviewers, and forwarding the document package to them; **f**) following up the results of the review from the Primary Reviewers; **g**) communicating CRERC's review decision to the PI/Researcher within the specified timeline and recording it in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2); and **h**) filing the documents in the protocol file folder and updating the protocol file index, and protocol database.*

The Primary Reviewers are responsible for **a**) assessing the Progress Report to determine if there is significant change in the study risk-benefit ratio to study participants, and **b**) *returning the Progress Report Form 7.3 with the results of the assessment to the CRERC Administrative Secretary within the specified timeline.*

The CRERC Chair is responsible for **a**) designating Primary Reviewers if those who did the initial review are not available, and **b**) *reviewing, signing, and dating the Notification of CRERC decision to the Researcher/PI.*

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4. Workflow

No.	Activities	Person/s Responsible
1	Receive the application for Continuing Review package and determine the type of review	Administrative Secretary
2	Identify the Primary Reviewers and send the application for Continuing Review package	Admin Secretary, CRERC Chair
3	Review the application for Continuing Review	Primary Reviewers
4	Include the Progress Report in the agenda of the forthcoming CRERC meeting	Admin Secretary
5	Communicate the CRERC decision to the Researcher/Principal Investigator (PI)	Admin Secretary, Member-Secretary, Chair
6	File the documents in the protocol file folder, and update the protocol file index and protocol database	Administrative Secretary

5. Detailed Instructions

5.1 Receive the application for Continuing Review package and determine the type of review

5.1.1 Ethical approval is given for a period of one year or less depending on the level of risk of the study. *The frequency of the submission of the Progress Report for continuing review and the end-date of the ethical approval period are indicated in the CRERC Form 8.2 Certificate of Approval*.

5.1.2 *For studies that require renewal of its ethical approval, the Researcher/PI is expected to submit the CRERC Form 7.3 Progress Report within 30 days prior to the expiry date of the ethical approval*.

5.1.3 The Administrative Secretary periodically checks the protocol database to track due dates of progress reports of study protocols approved by the CRERC and prepares and sends the reminder letter addressed to the PI sixty (60) calendar days before the expiry date of the ethical approval using *CRERC Form 7.2 Reminder Letter for Submission of Progress Report or Final Report*.

5.1.4 If Researcher/PI has not submitted the Progress/Annual Report after 30 calendar days from the expiry date of the ethical approval, the Administrative Secretary sends another reminder letter CRERC Form 7.8 Reminder Letter for Long-Overdue Progress/Final Report.

5.1.5 *Upon receipt of the application for Continuing Review package, the Administrative Secretary checks the completeness of the documents submitted as per CRERC Form 3.4 Document Submission Checklist, verifies if the CRERC Protocol No. is correct, the initial approval date and the date of approval of the last continuing review to identify whether the protocol has valid ethical approval and that the coverage of the report is at least 11 months if the frequency of progress report is annual or at least five (5) months if the frequency of progress report is semi-annual.*

The Continuing Review Application package is said to be complete when the following documents are present: a) CRERC Form 7.3 Progress/Annual Report that is properly filled up, b) copy of the Informed Consent/Assent

document/s currently in use, and c) valid Good Clinical Practice (GCP) Training certificate of the members of the Research Team.

5.1.6 *If the ethical clearance is already expired, the Researcher/PI must include justification letter for the failure to submit the continuing review application within 30 days prior to the expiration of the ethical approval. CRERC shall ask for information on the no. of study subjects recruited, enrolled and/or randomized to treatment groups after expiry of ethical approval.*

5.1.7 a) If the submission is in order, and the ethical approval is current/valid, the Administrative Secretary stamps the document "Received", writes the date of receipt and gives the duplicate copy of CRERC Form 7.3 Progress/Annual Report to the Researcher/PI.
b) If the ethical approval is expired, the Researcher/PI has to submit justification for the delay on the submission of the Progress Report.

5.1.8 The Administrative Secretary records the submission *in CRERC Form 9.1 Log of Protocol–Related Submissions*, and in the Continuing Review columns of the protocol database.

5.1.9 *The Administrative Secretary informs the CRERC Chair and the Member Secretary of the submission.*

5.1.10 The Administrative Secretary reviews the protocol database to determine the type of review.

a) If the protocol was initially reviewed by Full Committee, the review of the application for continuing review is also by Full Committee.
b) If the protocol was initially reviewed by expedited procedure by the Primary Reviewers, the review of the application for continuing review is also by expedited procedure unless the implementation of the study is problematic (e.g. many protocol deviations by the Research Team).

5.2 Identify the Primary Reviewers and send the application for Continuing Review package to them

5.2.1 The Administrative Secretary identifies the Primary Reviewers (and the Independent Consultant, if needed) who did the initial review.

5.2.2 The Administrative Secretary scans relevant documents of previous review/s of the protocol such as current version of the protocol summary and informed consent/assent form/s, approved Protocol Amendments (CRERC Form 7.1), Protocol Deviation Reports (CRERC Form 7.6), on-site SAE/SUSAR reports (CRERC Form 7.5), and Study Site Visit Report (if any, CRERC Form 10.3) since the initial approval or last continuing review. These will provide the Primary Reviewers with background information to facilitate the assessment of risk-benefit ratio.

5.2.3 If the Primary Reviewers are available to do the review, the Administrative Secretary sends by e-mail the application for continuing review package to the Primary Reviewers within seven (7) calendar days from the date of receipt of the application.

5.2.4 If Primary Reviewers are not available to do the review, CRERC Chair or Member-Secretary does the review provided s/he does not have COI. Otherwise, the Chair designates qualified Members to do the review.

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5.3 Review the application for continuing review

5.3.1 CRERC reviews the protocol under consideration.

a) For detailed instructions on expedited review, refer to SOP 4.1 Expedited Review.

b) For detailed instructions on Full Committee review, refer to SOP 4.2 Full Committee Review.

5.3.2 The Primary Reviewers assess the Progress/Annual Report based on the following considerations:

a) Conduct of the study

i) Changes in the participant population, recruitment or selection criteria since the last review/approval

ii) Changes in the informed consent process or documentation since the last review/approval

iii) Any new information that might affect the evaluation of the risk/benefit assessment of human participants involved in this study protocol

iv) Additional investigational new drug/device registrations associated with this study, new intervention/s or method/s in the conduct of study that is/are not in the approved protocol

v) Changes in the investigators and study personnel – e.g. suspension of hospital privileges of PI/Co-I, medical license; PI/Co-I's involvement in numerous clinical trials

vi) Changes in collaborating sites/institutions; changes in the acceptability of the research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and regulations, applicable national law, or standards of professional conduct of practice.

b) Protection of subjects' welfare

i) *Updates or measures in the protocol to guarantee protection of privacy and confidentiality of participant information in compliance with local regulations (e.g. Data Privacy Act of 2012)*

ii) *Any unexpected discomforts, complications, or side effects noted or any safety issues* that may affect study subjects' willingness to continue participation

iii) *Participants who have withdrawn from this study since the last review/approval*

iv) *Effects of protocol deviations by the Research Team on risk-benefit ratio*

v) *Changes in the conflict of interest of the investigators*

vi) *Management of biobank, as applicable*

vii) Findings during the site visit conducted for this study (if any)

c) *Assessment of progress status on overall risk-benefit assessment ratio*

The risks to the study participants shall be reasonable in relation to the anticipated benefits, and there is social value in the knowledge that may be expected to be gained from the study.

The Primary Reviewers through CRERC may also request the Principal Investigator to provide additional information, when necessary.

5.3.3 Using the "For CRERC Use"-box of CRERC Form 7.3 Progress/Annual Report, the Primary Reviewers *write the results of their assessment in the space provided.*

5.3.4 After the assessment is completed the Primary Reviewer/s and the Independent Consultant (if any) return all the documents including the completed assessment form/s to the CRERC within (seven) 7 calendar days from the date of receipt of the protocol/protocol related documents for expedited review or at least seven calendar days before the date of the meeting.

5.4 Include the Progress Report in the agenda of the forthcoming CRERC meeting

5.4.1 The Administrative Secretary reviews the completed assessment forms to determine if there is agreement in the review/decision.

a) For submissions reviewed by expedited procedure, copies of the CRERC Form 7.3 Progress/Annual Report where the "For CRERC Use"-box is filled by the Primary (and Independent Consultant, if any) are forwarded by e-mail to the Member-Secretary. The Member-Secretary finalizes the list of recommendations, if any.

Progress report reviewed by expedited procedure where ethical approval is renewed is also included in the agenda of the forthcoming meeting for reporting to the CRERC.

b) For application for continuing review of protocol initially reviewed by Full Committee, the Administrative Secretary includes this in the meeting agenda of the forthcoming meeting. (Refer to SOP 6.1 Preparation for a CRERC Meeting).

5.4.2 During the deliberation of the application for continuing review the medical/scientific Primary Reviewer presents the results of the assessment during the Full Committee meeting.

5.4.3 The CRERC Members deliberate on the technical and ethical merits of the protocol or protocol-related documents. (Refer to SOP 6.2 Conduct of Review Meeting).

5.4.4 The CRERC members vote to arrive at a decision. *Possible review decisions are:*

a) Renew approval
b) Pending, if further information (specify information), or modifications (specify modifications) are required before a decision can be made
c) Suspend:
i) Suspend enrollment of subjects
ii) Suspend research procedures in currently enrolled subjects
iii) Suspend entire study
d) Disapprove renewal/Terminate study

5.4.5 Letter of appeal for reconsideration of CRERC review decision especially disapproval may be made. (Refer to SOP 5 - Management of Appeal of CRERC Decision based on CIOMS 2016, Guidelines 23)

5.5 Communicate the CRERC decision to the Researcher/Principal Investigator

5.5.1 The Administrative Secretary prepares Notification of CRERC Decision – Progress Report (CRERC Form 8.4) based on the minutes of the meeting, and CRERC Form 8.2 Approval Letter (if review decision is renewal of ethical approval) for review and signature of CRERC Chair, and sends it to the Researcher/PI after recording the document in the Log of Outgoing

Protocol Related Communications (CRERC Form 9.2) (Refer to SOP 8.2 Communicating CRERC Decision)

5.5.2 Expedited review of application for continuing review should be completed (*from date of submission to date of notification of CRERC decision to the Researcher/PI) within nineteen (19) calendar days*. It may take longer for submissions for review by Full Committee depending on the schedule of its meeting *but should not exceed forty-two (42) calendar days or six (6) weeks*.

5.6 File the documents in the protocol file folder, and update the protocol file index and protocol database

5.6.1 The Administrative Secretary files CRERC Form 7.3 and related documents with relevant excerpt of the minutes of the meeting, duplicate copy of CRERC Form 8.4 Notification of CRERC Decision – Progress Report, and CRERC Form 8.2 Approval Letter (if review decision is renewal of ethical approval) in the protocol file folder; and updates the protocol file index and the data fields for the Annual Report in the protocol database accordingly. (Refer to the SOP 9.1 Management of Active Study Protocol Files)

6. Related Forms

CRERC Form 7.2 Reminder Letter for Submission of Progress Report
CRERC Form 7.3 Progress Report
CRERC Form 7.8 Reminder Letter for Long-Overdue Progress/Final Report
CRERC Form 8.4 Notification of CRERC Decision – Progress Report
CRERC Form 9.1 Log of Protocol-Related Submissions
CRERC Form 9.2 Log of Outgoing Protocol Related Communications

7. SOP Document History

Version No.	Version Date	Description of Changes
01	23 Jan 2015	Refer to SOP v. 01
02	21 May 2015	Refer to SOP v. 02
03	05 Feb 2016	Refer to SOP v. 03
04.1	17 May 2019	Refer to SOP v. 04.1
05	01 Dec 2021	▪ Changed Purpose to Objective, and Process Flow/Steps to Workflow to harmonize with PHREB's section titles. ▪ Changed the section on Scope - included the start and end tasks of the SOP ▪ Added the detailed responsibilities of the CRERC Chair/Member-Secretary, Primary Reviewers, and those of the Administrative Secretary ▪ Combined Tasks #1 and #2 of version 4.0; and added 5.1.4 – verification of the completeness and correctness of the submission; 5.1.6 – stamping "Received" with date of receipt on CRERC Form 7.1; and 5.1.7 – recording the submission in CRERC Form 9.1 Log of Protocol-Related Submissions ▪ Added timelines: from date of receipt of submission to forwarding this to Primary Reviewers in 5.2.3, from receipt of document package for review by Primary Reviewers to return of results of assessment to CRERC; turnaround time of expedited review (from date of receipt of submission to date of notification of CRERC decision to the PI) ▪ Modified assessment points (5.3.2) and categories of

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		review decisions (5.4.5) ▪ Introduced new forms – Form 7.2 Reminder Letter for Submission of Progress Report, CRERC Form 7.8 Reminder Letter for Long-Overdue Progress/Final Report, CRERC Form 8.2 Certificate of Approval, CRERC Form 8.4 – Notification of CRERC Decision – Progress/Annual Report, CRERC Form 9.1 Log of Protocol-Related Submissions, and CRERC Form 9.2 Log of Outgoing Protocol Related Communications ▪ Cross referenced related SOPs ▪ Used Administrative Secretary instead of CRERC Secretariat and Full Committee instead of full board

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SOP 7.3 REVIEW OF FINAL REPORT

1. Objective of the Activity

To describe the procedure for the review of the Final Report to ensure *that the study was implemented according to the approved protocol, and that the safety and welfare of study participants were protected, and the integrity of the data was upheld all throughout the study.*

2. Scope

This SOP applies to the review of Final/Closure Report submitted by the Researcher/Principal Investigator (PI) at the completion of the study or closure of the study site. *This SOP begins with the receipt of the Final Report and ends with filing of the document in the protocol file folder and the updating of the protocol file index and the protocol database*.

The Final Report when approved/accepted by the CRERC becomes the basis for the initiation of the archiving procedure for the protocol file.

3. Responsibilities

*The CRERC Administrative Secretary is responsible for: **a**) reminding the Researcher/Principal Investigator (PI) of the submission of the Final/Closure Report at least sixty (60) days before the expiry date of the study protocol's ethical approval using CRERC Form 7.2 Reminder letter for Submission of Progress/Annual or Final Report, and sending CRERC Form 7.8 Reminder Letter for Long Overdue Annual/Final Report if Final/Closure Report is not yet submitted 30 days after the expiry date of ethical approval; **b**) verifying that the submission uses the correct form and protocol identification details, and that CRERC Form 7.4 Final/Closure Report is completely filled up; **c**) stamping the date of receipt of the submission and recording the submission in the Log of Protocol-Related Submissions (CRERC Form 9.1); **d**) determining the type of review; **e**) identifying the medical/scientific Primary Reviewer, and forwarding the final report document package to him/her; **f**) following up the results of the review from the Primary Reviewers; **g**) communicating CRERC's review decision to the Researcher/PI within the specified timeline and recording it in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2); **h**) filing the documents in the protocol file folder, and updating the protocol file index and protocol database; and **i**) transferring the protocol file to the storage cabinet for inactive files*.

The Primary Reviewer is responsible for **a**) assessing the Final Report to determine any protocol non-compliances that may have harmed the study participants and compromised the integrity of the study results, and **b**) *returning the CRERC Form 7.4 with the results of the assessment to the CRERC Administrative Secretary within the specified timeline.*

*The CRERC Chair is responsible for **a**) designating Primary Reviewers if those who did the initial review are not available, and **b**) reviewing, signing and dating the Notification of CRERC decision to the Researcher/PI.*

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4. Workflow

No.	Activity	Person Responsible
1	Receive the Final/Closure Report and determine the type of review	Administrative Secretary
2	Identify the medical/scientific Primary Reviewer and send the Final Report and related documents to him/her	Admin Secretary, CRERC Chair
3	Review the Final Report with the use of the assessment form	Primary Reviewer
4	Include the Final Reports in the agenda of the forthcoming CRERC meeting	Administrative Secretary
5	Communicate the CRERC decision to the Researcher/Principal Investigator (PI)	Admin Secretary, CRERC Chair
6	File the documents in the protocol file folder, and update the protocol file index and protocol database	Administrative Secretary

5. Detailed Instructions

5.1 Receive the Final/Closure Report and determine the type of review

5.1.1 One of the reportorial responsibilities of the Researcher/PI is to provide CRERC with a summary of the outcome of the study, especially of the human participants who were involved, in a form of Final/Closure Report.

5.1.2 Ethical approval is given for a period of one year or less depending on the level of risk of the study. One of the responsibilities of the PI is to submit the Final/Closure Report before the expiry date of its ethical approval if the implementation of the study is already completed.

5.1.3 The Administrative Secretary periodically checks the protocol database to track expiry date of ethical approval of study protocols, prepares in duplicate copies and sends the reminder letter addressed to the Researcher/PI sixty (60) calendar days before the expiry date of the ethical approval using *CRERC Form 7.2 Reminder Letter for Submission of Progress Report or Final Report, and keeps the duplicate copy of the communication in the protocol file folder*.

5.1.4 If the Researcher/PI has not submitted the Final Report after 30 calendar days from the expiry date of the ethical approval, the Administrative Secretary sends another reminder letter CRERC Form 7.8 Reminder Letter for Long-Overdue Progress/Final Report.

5.1.4 Upon receipt of CRERC Form 7.4 Final/Closure Report together with documents deemed relevant by the Researcher/PI to clarify information indicated in the final report, the Administrative Secretary checks the completeness of the documents submitted, verifies if the CRERC Protocol No. is correct, and if the initial approval date, or the date of approval of the last continuing review is valid to determine whether the protocol's ethical approval is not expired.

5.1.5 If the ethical approval is already expired, the Researcher/PI has to include justification letter for the failure to submit the Final Report before the expiry date of the ethical approval. *CRERC shall ask for information if study subjects were recruited, enrolled and/or randomized to treatment groups after expiry of ethical approval.*

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5.1.6 If the submission is in order, and the ethical approval is current/valid, the Administrative Secretary stamps the document "Received", writes the date of receipt and gives the duplicate copy of CRERC Form 7.4 Final Report to the Researcher/PI or his/her representative.

5.1.7 The Administrative Secretary records the submission *in CRERC Form 9.1 Log of Protocol–Related Submissions*, and in the Final Report columns of the protocol database.

5.1.8 *The Administrative Secretary informs the CRERC Chair and the Member Secretary of the submission.*

5.1.9 The Administrative Secretary reviews the document to determine the type of review.

a) If the protocol was initially reviewed by Full Committee, the review of the Final Report is also by Full Committee.
b) If the protocol was initially reviewed by expedited procedure, the review of the Final Report is also by expedited procedure unless, the implementation of the study is problematic (e.g., many protocol deviations from the approved protocol by the Researcher/PI or the Research Team).

5.2 Identify the medical/scientific Primary Reviewer and send the Final Report and related documents to him/her

5.2.1 The Administrative Secretary identifies the medical/scientific Primary Reviewer who did the initial review.

5.2.2 The Administrative Secretary photocopies relevant documents of previous review/s of the protocol such as current version of the protocol summary and informed consent/assent form/s, and CRERC Form 10.3 Study Site Visit Report (if any) since the initial approval or last continuing review. These will provide the Primary Reviewer with background information to facilitate the assessment of the Final/Closure Report.

5.2.3 If the Primary Reviewer is available to do the review, the Administrative Secretary sends the CRERC Form 7.4 Final Report and related documents to him/her within seven (7) calendar days from the date of receipt of the Final Report.

5.2.4 If the Primary Reviewer is not available to do the review, CRERC Chair or the Member-Secretary does the review provided s/he does not have COI. Otherwise the Chair designates a qualified Member to do the review.

5.3 Review the Final Report with the use of the assessment form

5.3.1 CRERC reviews the protocol under consideration.

a) For detailed instructions on expedited review, refer to SOP 4.1 Expedited Review.
b) For detailed instructions on Full Committee review, refer to SOP 4.2 Full Committee Review.

5.3.2 *The Primary Reviewer should comment on compliance with the terms of the approved protocol including post-approval review requirements, and overall assessment of risks against benefits in the conduct of the study.*

5.3.3 Using the "For CRERC Use"-box of CRERC Form 7.4 Final Report, the Reviewer *writes the results of his/her assessment in the space provided.*

5.3.4 After the assessment is completed the Primary Reviewer returns all the documents to the CRERC within seven (7) calendar days from the date of receipt of the document package.

5.4 Include the Final Report in the agenda of the forthcoming CRERC meeting

5.4.1 For Final Report initially reviewed by Full Committee, the Administrative Secretary includes this in the meeting agenda of the forthcoming meeting. (Refer to SOP 6.1 Preparation for a CRERC Meeting).

Submissions reviewed by expedited procedure where the review decision is approved/accepted are also included in the agenda of the forthcoming meeting for reporting to the CRERC.

5.4.3 During the review of the Final Report by the CRERC *en banc*, the medical/scientific Primary Reviewer presents the results of the assessment.

5.4.4 The CRERC members vote to arrive at a decision. *Possible review decisions are:*

i) Accepted
ii) Request for further information, specify ____
iii) Require action from the Researcher/PI, specify_____.

5.4.5 Letter of appeal for reconsideration of CRERC review decision may be made. (Refer to SOP 5 - Management of Appeal of CRERC Decision based on CIOMS 2016, Guidelines 23)

5.5 Communicate the CRERC decision to the Researcher/Principal Investigator

5.5.1 The Administrative Secretary prepares Notification of CRERC Decision – Final Report (CRERC Form 8.5) based on the minutes of the meeting if review was by Full Committee or on the review decision of the Primary Reviewer if review was by expedited procedure, for review and signature of CRERC Chair, and sends it to the Researcher/PI after recording the document in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2) (Refer to SOP 8.2 Communicating CRERC Decision)

5.5.2 Expedited review of Final Report should be completed (*from date of submission to date of notification of CRERC decision to the Researcher/PI) within nineteen (19) calendar days*. It may take longer for submissions for review by Full Committee depending on the schedule of the Full Committee meeting *but should not exceed forty-two (42) calendar days*.

5.6 File the documents in the protocol file folder and update the protocol file index and protocol database

5.6.1 The Administrative Secretary files CRERC Form 7.4 Final/Closure Report and related documents with relevant excerpt of the minutes of the meeting, duplicate copy of CRERC Form 8.5 Notification of CRERC Decision – Final Report; and updates the protocol file index and the protocol database accordingly. (Refer to the SOP 9.1 Management of Active Study Protocol Files)

5.6.2 Upon approval of the Final Report, the study protocol is classified as inactive, the Protocol Code No. is updated, and the protocol file folder re-labelled and transferred to the storage cabinet for inactive files.

5.6.3 The Administrative Secretary enters relevant study protocol data into the protocol database to signify the end of the study. (Refer to SOP 9.3 Archiving of Inactive Files)

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6. Related Forms

CRERC Form 7.2 Reminder Letter for Submission of Final Report
CRERC Form 7.4 Final Report
CRERC Form 7.9 Reminder Letter for Long-Overdue Progress/Final Report
CRERC Form 8.5 Notification of CRERC Decision – Final Report
CRERC Form 9.1 Log of Protocol-Related Submissions
CRERC Form 9.2 Log of Outgoing Protocol Related Communications

7. SOP Document History

Version No.	Version Date	Description of Changes
01	23 Jan 2015	Refer to SOP v. 01
02	21 May 2015	Refer to SOP v. 02
03	05 Feb 2016	Refer to SOP v. 03
04.1	17 May 2019	Refer to SOP v. 04.1
05	01 Dec 2021	▪ Changed Purpose to Objective, and Process Flow/Steps to Workflow to harmonize with PHREB's section titles. ▪ Changed the section on Scope - included the start and end tasks of the SOP ▪ Added the detailed responsibilities of the CRERC Chair/Member-Secretary, Primary Reviewers and those of the Administrative Secretary ▪ Combined Tasks #1 and #2 of version 4.0; and added 5.1.5 – stamping "Received" with date of receipt on CRERC Form 7.4, and 5.1.3 – recording the submission in CRERC Form 9.1 Log of Protocol-Related Submissions ▪ Added timelines: from date of receipt of submission to forwarding this to Primary Reviewers = 7 calendar days in 5.2.3, from receipt of document package for review by Primary Reviewers to return of results of assessment to CRERC = 7 calendar days; turn around time if by expedited review (from date of receipt of submission to date of notification of CRERC decision to the PI) = 19 calendar days; turn around time if by Full Committee review = within 42 calendar days ▪ Modified categories of review decisions (5.4.4) ▪ Introduced new forms – CRERC Form 7.2 Reminder Letter for Submission of Progress Report, CRERC Form 7.8 Reminder Letter for Long-Overdue Progress/Final Report, CRERC Form 8.5 – Notification of CRERC Decision – Final Report, CRERC Form 9.1 Log of Protocol-Related Submissions, and CRERC Form 9.2 Log of Outgoing Protocol Related Communications ▪ Cross referenced with related SOPs ▪ Used Administrative Secretary instead of CRERC Secretariat and Full Committee instead of full board

SOP 7 MANAGEMENT OF POST-APPROVAL SUBMISSIONS

SOP 7.4 REVIEW OF SERIOUS ADVERSE EVENT (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) REPORTS

1. Objective of the Activity

To describe the procedures for the review of the initial and follow-up reports of SAE and unexpected events related to the study protocols approved by CRERC *to ensure that the safety and welfare of study participants are protected, and that information on SAEs and SUSARs are properly documented and evaluated.*

2. Scope

This SOP applies to the review of on-site initial and follow-up (for final outcome) SAE or SUSAR reports (CRERC Form 7.5 On-site Serious Adverse Event Report) submitted by Researcher/Principal Investigator (PI) to the CRERC to comply with ICH GCP standards. The CRERC reviews such reports to determine appropriate action to protect the safety and welfare of study participants in an approved study. *This SOP starts with the receipt of the SAE Report and ends with the filing of the document in the protocol file folder and the updating of the protocol file index*.

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

- results in death,
- is life threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- results in a congenital anomaly or birth defect.

A suspected unexpected serious adverse reaction (SUSAR) is a serious event the nature and severity of which is not consistent with the applicable product information. In the case of an unapproved investigational product, the event is not listed in 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.

One of the reportorial responsibilities of the Researcher/Principal Investigator (PI) is to submit SAE/SUSAR Reports on time.

3. Responsibilities

*The CRERC Administrative Secretary is responsible for: **a**) verifying that the submission uses the correct form, and protocol identification details, and that CRERC Form 7.5 Onsite Serious Adverse Event Report is completely filled up; **b**) stamping the date of receipt of the submission, and recording the submission in the Log of Protocol-Related Submissions (CRERC Form 9.1); **c**) identifying the medical/scientific Primary Reviewer, and forwarding CRERC Form 7.5 SAE Report and other relevant documents to him/her; **d**) following up the results of the review from the Primary Reviewer; **e**) communicating CRERC's review decision to the Researcher/PI within the specified timeline and recording it in the Log of Outgoing Protocol Related Communications (CRERC Form*

*9.2); and **f**) filing the document in the protocol file folder, and updating the protocol file index*.

The Primary Reviewer is responsible for **a**) assessing the SAE Report to determine significant change in the study risk-benefit ratio to study participants, and **b**) *returning the CRERC Form 7.5 SAE Report with the results of the assessment to the CRERC Administrative Secretary within the specified timeline.*

The CRERC Chair is responsible for **a**) designating a Reviewer if the one who did the initial review is not available, and **b**) *reviewing, signing, and dating the CRERC Form 8.6 Notification – SAE Report to the Researcher/PI*.

4. Workflow

No.	Activity	Person Responsible
1	Receive the SAE Report	Administrative Secretary
2	Identify the Primary Reviewer and send the SAE Report and related documents to him/her	Admin Secretary, CRERC Chair
3	Review the SAE Report	Primary Reviewer
4	Include on-site SAE Report in the agenda of the forthcoming meeting	Administrative Secretary
5	Communicate the CRERC decision to the Researcher/Principal Investigator (PI)	Admin Secretary, CRERC Chair
6	File the documents in the protocol file folder, and update the protocol file index	Administrative Secretary

5. Detailed Instructions

5.1 Receive the SAE Report

5.1.1 The Researcher/PI must report to the CRERC all SAEs according to the following timelines (as per FDA Circular 2012-007 Guidelines on safety Reporting):

a) Fatal or life threatening unexpected adverse drug reactions that occurred on site must be reported to the CRERC promptly, not later than 7 calendar days after the Researcher/PI's first knowledge of it followed by a complete report as soon as possible within 8 additional calendar days to coincide with the reporting to the FDA.

b) All other serious unexpected adverse drug reactions must be reported to the CRERC promptly not later than 15 calendar days after the Researcher/PI's first knowledge of it to coincide with reporting to the FDA.

c) For onsite serious adverse events that are expected and non-life threatening, a summary listing must be reported to the CRERC attached to the submission of the progress report.

d) The Researcher/PI is required to submit an initial and follow-up (final outcome) reports to the CRERC.

e) Deaths must be reported to the CRERC if it occurs within 30 days of the study intervention. Any death occurring greater than 30 days after the last dose of the investigational product/intervention requires expedited reporting if it is possibly, probably, or definitely related to the

investigational product/intervention, or if cause of death cannot be determined based on WHO Causality Assessment definitions.

5.1.2 Upon receipt of CRERC Form 7.5 SAE Report, the Administrative Secretary checks the completeness of the document submitted, verifies if the CRERC Protocol No. is correct, and if the initial approval date, or the date of approval of the last continuing review is valid to determine whether the protocol's ethical approval is not expired.

5.1.3 *If the ethical approval is already expired, the Researcher/PI is required to submit justification letter for the failure to hand over the Progress Report before the expiry date of the ethical approval, and also submit the application for continuing review. The report should contain information on subjects recruited after the expiration of ethical approval.*

5.1.4 If the submission is in order, and the ethical approval is current/valid, the Administrative Secretary stamps the document "Received", writes the date of receipt and gives the duplicate copy of CRERC Form 7.5 SAE Report to the Researcher/PI or his/her representative.

5.1.5 The Administrative Secretary records the submission *in CRERC Form 9.1 Log of Protocol–Related Submissions*.

5.1.6 *The Administrative Secretary informs the CRERC Chair and the Member Secretary of the submission.*

5.2 Identify the Primary Reviewer and send the SAE Report and related documents to him/her

5.2.1 The Administrative Secretary identifies the medical/scientific Primary Reviewer who did the initial review.

5.2.2 *The Administrative Secretary prepares the following documents for forwarding to the Primary Reviewer: a) CRERC Form 7.5 On-Site SAE Report, b) latest edition of the IB, c) latest version of the (main) ICF, and c) latest Study Site Visit Report (if any, CRERC Form 10.3) These will provide the Primary Reviewer with background information to facilitate the assessment of the On-site SAE/SUSAR Report.*

5.2.3 If the Primary Reviewer is available to do the review, the Administrative Secretary sends the CRERC Form 7.5 On-Site SAE Report and other relevant documents to him/her within seven (7) calendar days from the date of receipt of the report.

5.2.4 If Primary Reviewer is not available to do the review, CRERC Chair or the Member-Secretary does the review provided s/he does not have COI. Otherwise, the Chair designates a qualified Member to do the review.

5.3 Review the SAE Report

5.3.1 All on-site SAE and SUSAR Reports are deliberated by CRERC *en banc.* (Refer to SOP 4.2 Full Committee Review and SOP 7.4 Review of Serious Adverse Event) Off-site SAE and SUSAR Reports are reviewed by expedited procedure by the medical/scientific Primary Reviewer and reported to the CRERC during the Full Committee meeting. (Refer to SOP 4.1 Expedited Review, and SOP 6.2 Conduct of CRERC Review Meeting)

5.3.2 For SAEs that occur onsite, the Primary Reviewer should analyze the investigator/sponsor's assessment (whether related or unrelated, definitely, or probably related to the study drug) and whether expected or unexpected based on the information in the latest edition of the IB.

5.3.3 Using the "For CRERC Use"-box of CRERC Form 7.5 On-Site SAE Report, the Reviewers *write the results of their assessment in the space provided.*

5.3.4 After the assessment is completed the Primary Reviewer returns all the documents including the completed assessment form to the CRERC within (seven) 7 calendar days from the date of receipt of the document package.

5.4 Include the On-site SAE Reports in the agenda of forthcoming CRERC meeting

5.4.1 For On-Site SAE/SUSAR Reports, the Administrative Secretary includes this in the meeting agenda of the forthcoming meeting. (Refer to SOP 6.1 Preparation for a CRERC Meeting) Off-site SAE Reports reviewed by expedited procedure by the medical/scientific Primary Reviewer are also included in the agenda of the forthcoming meeting for reporting to the CRERC. (Refer to SOP 4.1 Expedited Review)

5.4.2 During the review of the SAE/SUSAR Report by the CRERC *en banc*, the medical/scientific Primary Reviewer presents the results of the assessment.

5.4.3 The CRERC members vote to arrive at a decision. Possible review decisions are:

i) Take note and continue monitoring
ii) Request for further information, specify ____
iii) Request an amendment to the protocol and/or the informed consent form
iv) Suspend:
- Enrollment of new research participants until further review of the CRERC
- All trial-related procedures (except those intended for safety and well-being of the participant) until further review by the CRERC

v) Terminate the study
vi) Conduct study site visit

5.4.4 Letter of appeal for reconsideration of CRERC review decision may be made. (Refer to SOP 5 - Management of Appeal of CRERC Decision based on CIOMS 2016, Guidelines 23)

5.5 Communicate the CRERC decision to the Researcher/Principal Investigator

5.5.1 The Administrative Secretary prepares Notification of CRERC Decision – SAE Report (CRERC Form 8.6) based on the minutes of the meeting for review and signature of CRERC Chair, and sends it to the Researcher/PI after recording the document in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2) (Refer to SOP 8.2 – Communicating CRERC Decision)

5.5.2 *Turn around time for review of SAE Report (from date of submission to date of notification of CRERC decision to the Researcher/PI) depends on the schedule of the full committee meeting but should not exceed forty-two (42) calendar days.*

5.6 File the documents in the protocol file folder and update the protocol file index

5.6.1 The Administrative Secretary files CRERC Form 7.5 Onsite SAE Report with related documents, relevant excerpt of the minutes of the meeting, and duplicate copy of CRERC Form 8.6 Notification of CRERC Decision –SAE Report, and updates the protocol file index. (Refer to the SOP 9.1 Management of Active Study Protocol Files)

6. Related Forms

CRERC Form 7.5 On-Site SAE Report
CRERC Form 8.6 Notification of CRERC Decision – SAE Report
CRERC Form 9.1 Log of Protocol-Related Submissions
CRERC Form 9.2 Log of Outgoing Protocol Related Communications
CRERC Form 10.3 Study Site Visit Report

7. SOP Document History

Version No.	Version Date	Description of Changes
01	23 Jan 2015	Refer to SOP v. 01
02	21 May 2015	Refer to SOP v. 02
03	05 Feb 2016	Refer to SOP v. 03
04.1	17 May 2019	Refer to SOP v. 04.1
05	01 Dec 2021	▪ Changed the title of the SOP to harmonize with PHREB's SOP titles. ▪ Changed Purpose to Objective, and Process Flow/Steps to Workflow to harmonize with PHREB's section titles. ▪ Changed the section on Scope - included the start and end tasks of the SOP ▪ Added the detailed responsibilities of the CRERC Chair, Primary Reviewers and those of the Administrative Secretary ▪ Added the checking of validity of ethical approval of the study protocol and actions required from the PI if it is not valid in 5.1.2 ▪ Described the actions of the Admin Secretary after validating the completeness and accuracy of protocol identification details on the submission in 5.1.3-5.1.4 ▪ Specified the Primary Reviewer who will review the SAE Report – the medical/scientific Primary Reviewer who did the initial review in 5.2.1 ▪ Described the related documents that have to be forwarded to the Primary Reviewer together with the SAE Report, in 5.2.2 ▪ Added timeline requirements for reporting SAE or SUSAR by Researcher/PI (5.2.5 – 5.2.7) ▪ Added timelines: from date of receipt of submission to forwarding this to Primary Reviewer = 7 calendar days; from receipt of document package for review by Primary Reviewer to return of results of assessment to CRERC = 7 calendar days; turnaround time (from date of receipt of submission to date of notification of CRERC decision to the PI) = 45 calendar days ▪ Introduced new forms – CRERC Form 8.6 – Notification of CRERC Decision – SAE Report, CRERC Form 9.1 Log of Protocol-Related Submissions, and CRERC Form 9.2 Log of Outgoing Protocol Related Communications ▪ Cross referenced related SOPs ▪ Used Administrative Secretary instead of CRERC Secretariat and full committee instead of full board

SOP 7 MANAGEMENT OF POST-APPROVAL SUBMISSIONS

SOP 7.5 REVIEW OF PROTOCOL VIOLATION/ DEVIATION REPORT

1. Objective of the Activity

To describe the procedure for the review of Protocol Violation/Deviation Reports related to study protocols approved by CRERC *to ensure that the safety and welfare of study participants are protected, and that the credibility and integrity of data are maintained.*

2. Scope

This SOP applies to the review of Protocol Violation/Deviation Report (CRERC Form 7.6) submitted by the Researcher/Principal Investigator (PI) to the CRERC to comply with ICH GCP standards. *This SOP starts with the receipt of the Protocol Violation/Deviation Report and ends with the filing of the documents in the protocol file folder and the updating of the protocol file index.*

A study protocol noncompliance is any deviation from, or changes of the approved protocol without agreement by the sponsor, and prior review and documented approval or favorable opinion from the Ethics Committee, except where necessary to eliminate an immediate hazard(s) to study participants, or when the changes involve only logistical or administrative aspects of the trial (e.g., change in monitor/s, change of telephone number/s) (ICH-GCP).

Protocol violation (major non-compliance) is a persistent protocol noncompliance with potentially serious consequences that could put study participants' safety at risk or critically affect integrity of data.

Protocol deviation (minor non-compliance) is a non-systematic protocol noncompliance with minor consequences, in terms of its effect on the study participant's/subject's rights, safety or welfare, or the integrity of study data; includes deviations that are administrative in nature.

3. Responsibilities

*The CRERC Administrative Secretary is responsible for: **a**) verifying that the submission uses the correct form and protocol identification details, and that CRERC Form 7.6 Protocol Violation/Deviation Report is completely filled up; **b**) stamping on CRERC Form 7.6 the date of receipt of the submission and recording the submission in the Log of Protocol-Related Submissions (CRERC Form 9.1); **c**) identifying the medical/scientific Primary Reviewer, and forwarding CRERC Form 7.6 Protocol Violation/Deviation Report and other relevant documents to him/her; **d**) following up the results of the review from the Primary Reviewer; **e**) communicating CRERC's review decision to the Researcher/PI within the specified timeline and recording it in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2); and **f**) filing the document in the protocol file folder, and updating the protocol file index.*

The Primary Reviewer is responsible for **a**) assessing the Protocol Violation/Deviation Report to determine significant change in the study risk-benefit ratio to study participants, and **b**) *returning the CRERC Form 7.6 Protocol Violation/Deviation Report with the results of the assessment to the CRERC Administrative Secretary within the specified timeline.*

The CRERC Chair is responsible for **a**) designating Primary Reviewer if the one who did the initial review is not available, and **b**) *reviewing, signing and dating the to the communication Researcher/Principal Investigator (PI).*

4. Workflow

No.	Activity	Person Responsible
1	Receive the Protocol Violation/Deviation Report	Administrative Secretary
2	*Identify the Primary Reviewer* and send the Protocol Violation/Deviation Report and related documents to him/her	Administrative Secretary, CRERC Chair
3	*Review the Protocol Violation/Deviation Report*	Primary Reviewer
4	*Include the Protocol Violation and Deviation Reports in the agenda of forthcoming CRERC meeting*	Administrative Secretary
5	Communicate the CRERC decision to the Researcher/Principal Investigator (PI)	Admin Secretary, CRERC Chair
6	File the documents in the protocol file folder, and update the protocol file index	Administrative Secretary

5. Detailed Instructions

5.1 Receive the Protocol Violation/Deviation Report

5.1.1 Reports of Protocol Violation/Deviation may come directly from the Researcher/PI, or as result of study site monitoring by the Clinical Monitor/Sponsor or the CRERC Study Site Visit Team, or from related documents received by the CRERC.

5.1.2 It is the responsibility of the Researcher/PI to determine whether the non-compliance is a protocol violation or protocol deviation to ensure proper reporting to the CRERC. If the PI is unsure whether the variance is a violation or a deviation s/he should seek advice from the sponsor to ensure that appropriate action is taken.

5.1.3 *The investigator should document, and report to the CRERC any non-compliance from the approved protocol, whether minor or major, at the soonest possible time, within a month from the event.*

5.1.4 Upon receipt of CRERC Form 7.6 Protocol Violation/Deviation Report, the Administrative Secretary checks the completeness of the document submitted, verifies if the CRERC Protocol No. is correct, and if the initial approval date, or the date of approval of the last continuing review is valid to determine whether the protocol's ethical approval is not expired.

5.1.5 *If the ethical approval is already expired, the Researcher/PI is required to submit justification letter for the failure to hand over the Progress Report before the expiry date of the ethical approval, and submit the application for continuing review. The report should contain information on subjects recruited after the expiration of ethical approval.*

5.1.6 If the submission is in order, and the ethical approval is current/valid, the Administrative Secretary stamps the document "Received", writes the date of receipt, and gives the duplicate copy of CRERC Form 7.6 Protocol Violation/Deviation Report to the Researcher/PI or his/her representative.

5.1.7 The Administrative Secretary records the submission *in CRERC Form 9.1 Log of Protocol–Related Submissions*.

5.1.8 The Administrative Secretary informs the CRERC Chair and the Member Secretary of the submission.

5.2 Identify the Primary Reviewer and send the send the Protocol Violation/Deviation Report and related documents to him/her

5.2.1 *The Administrative Secretary identifies the medical/scientific Primary Reviewer who did the initial review.*

5.2.2 *The Administrative Secretary prepares the following documents for forwarding to the Primary Reviewer: **a**) CRERC Form 7.6* Protocol Violation/Deviation *Report, **b**) latest version of the protocol summary and the ICFs, **c**) list of previously submitted Protocol Violation/Deviation Reports, and d) latest Study Site Visit Report (if any, CRERC Form 10.3) These will provide the Primary Reviewer with background information to facilitate the assessment of the Protocol Violation/Deviation Report.*

5.2.3 If the Primary Reviewer is available to do the review, the Administrative Secretary sends the CRERC Form 7.6 Protocol Violation/Deviation Report and *relevant documents to him/her within seven (7) calendar days from the date of receipt of the Protocol Violation/Deviation Report.*

5.2.4 If Primary Reviewer is not available to do the review, CRERC Chair or the Member-Secretary does the review provided s/he does not have COI. Otherwise, the Chair designates a qualified Member to do the review.

5.3 Review the Protocol Violation/Deviation Report

5.3.1 Protocol Violation – major non-compliance with the approved protocol that increases risk or decreases benefit to participants or significantly affects their rights, safety or welfare or the integrity of the data; also includes persistent protocol noncompliance with potentially serious consequences that could put patients' safety at risk or critically affect integrity of data, eg. incorrect treatment, non-compliance with inclusion/exclusion criteria.

5.3.2 Protocol Deviation – minor non-compliance with the approved protocol that does not increase risk or decrease benefit to participants or does not significantly affect their rights, safety or welfare or the integrity of data, eg. missed visit, non-submission of a food diary on time.

5.3.3 Primary Reviewer assesses if the protocol violation/deviation impacts on the study participants' safety and welfare, or the integrity of the research data, and the completeness and appropriateness of the Researcher/PI's correction and corrective actions.

5.3.4 Using the "For CRERC Use"-box of CRERC Form 7.6 Protocol Violation/Deviation Report, the Primary Reviewer *writes the results of his/her assessment in the space provided.*

5.3.5 *After the assessment is completed the Primary Reviewer returns all the documents to the CRERC within (seven) 7 calendar days from the date of receipt of the document package.*

5.4 Include Protocol Violation and Deviation Reports in the agenda of forthcoming CRERC meeting

5.4.1 All Protocol Violation and Deviation (by the Research Team as differentiated from those by study participants) Reports are deliberated by CRERC *en banc. (*Refer to SOP 4.2 Full Committee Review and SOP 7.5 Review of Protocol Violation/Deviation Report).

5.4.2 The Administrative Secretary includes the Protocol Violation/Deviation Reports in the agenda of the forthcoming meeting. (Refer to SOP 6.1 Preparation for a CRERC Meeting).

5.4.3 During the review of the Protocol Violation/Deviation Report by the CRERC *en banc*, the medical/scientific Primary Reviewer presents the results of the assessment.

5.4.4 The CRERC members vote to arrive at a decision. Possible review decisions are:

i) Take note and continue monitoring
ii) Request for further information, specify ____
iii) Require correction and/or corrective actions from the Researcher/PI
iv) Suspend:
- Enrollment of new research participants until further review of the CRERC
- All trial-related procedures (except those intended for the safety and well-being of the participant) until further review by the CRERC

v) Terminate the study
vi) Conduct study site visit

5.4.5 Letter of appeal for reconsideration of CRERC review decision may be made. (Refer to SOP 5 - Management of Appeal of CRERC Decision based on CIOMS 2016, Guidelines 23)

5.5 Communicate the CRERC decision to the Researcher/Principal Investigator

5.5.1 The Administrative Secretary prepares Notification of CRERC Decision – Protocol Violation/Deviation Report (CRERC Form 8.7) based on the minutes of the meeting for review and signature of CRERC Chair, and sends it to the PI after recording the document in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2) (Refer to SOP 8.2 – Communicating CRERC Decision)

5.5.2 *Turnaround time for review of the Protocol/Deviation Report (from date of submission to date of notification of CRERC decision to the Researcher/PI) depends on the schedule of the full committee meeting but should not exceed forty-two (42) calendar days.*

5.6 File the documents in the protocol file folder and update the protocol file index

5.6.1 The Administrative Secretary files CRERC Form 7.6 Protocol Violation/Deviation Report with relevant excerpt of the minutes of the meeting, duplicate copy of CRERC Form 8.7 Notification of CRERC Decision – Protocol Violation/Deviation Report and updates the protocol file index. (Refer to the SOP 9.1 Management of Active Study Protocol Files)

6. Related Forms

CRERC Form 7.6 Protocol Violation/Deviation Report
CRERC Form 8.7 Notification of CRERC Decision – Protocol Violation/Deviation Report

CRERC Form 9.1 Log of Protocol-Related Submissions
CRERC Form 9.2 Log of Outgoing Protocol Related Communications

7. SOP Document History

Version No.	Version Date	Description of Changes
01	23 Jan 2015	Refer to SOP v. 01
02	21 May 2015	Refer to SOP v. 02
03	05 Feb 2016	Refer to SOP v. 03
04.1	17 May 2019	Refer to SOP v. 04.1
05	01 Dec 2021	▪ Changed the title of the SOP to harmonize with PHREB's SOP titles. ▪ Changed Purpose to Objective, and Process Flow/Steps to Workflow to harmonize with PHREB's section titles. ▪ Changed the section on Scope - included the start and end tasks of the SOP ▪ Added the detailed responsibilities of the CRERC Chair, Primary Reviewers and those of the Administrative Secretary ▪ Added timeline for the required reporting of non-compliance from the approved protocol in 5.1.3 ▪ Added the checking of validity of ethical approval of the study protocol and actions required from the PI if it is not valid in 5.1.5 ▪ Described the actions of the Admin Secretary after validating the completeness and accuracy of protocol identification details on the submission in 5.1.6-5.1.7 ▪ Specified the Primary Reviewer who will review the Protocol Violation/Deviation Report – the medical/scientific Primary Reviewer who did the initial review in 5.2.1 ▪ Described the related documents that have to be forwarded to the Primary Reviewer together with the Protocol Violation/Deviation Report, in 5.2.2 ▪ Added timelines: from date of receipt of submission to forwarding this to Primary Reviewers = 7 calendar days in 5.2.3; from receipt of document package for review by Primary Reviewer to return of results of assessment to CRERC = 7 calendar days; turnaround time = 42 days ▪ Introduced new forms – CRERC Form 4.1 Request for Review, CRERC Form 8.7 – Notification of CRERC Decision – Protocol Violation/Deviation Report, CRERC Form 9.1 Log of Protocol-Related Submissions, and CRERC Form 9.2 Log of Outgoing Protocol Related Communications ▪ Cross referenced related SOPs ▪ Used Administrative Secretary instead of CRERC Secretariat and full committee instead of full board

SOP 7 MANAGEMENT OF POST-APPROVAL SUBMISSIONS

SOP 7.6 EARLY TERMINATION OF THE STUDY REPORT

1. Objective of the Activity

To describe the procedure for the review of Early Termination of the Study Report of study protocols approved by CRERC *to ensure that the safety and welfare of enrolled study participants are taken into consideration*.

2. Scope

This procedure describes how the CRERC proceeds to manage the premature or early termination of a protocol when subject enrollment is discontinued before the scheduled end of the study. The CRERC reviews such reports to determine appropriate action to protect the safety and welfare of study participants in an approved study. This SOP starts with the receipt of the Early Termination of Study Report and ends with the filing of the document in the protocol file folder and the updating of the protocol file index.

A report for early study termination is submitted when a study approved by the CRERC is being recommended for termination before its scheduled completion. This is done when the safety of the study participant is doubtful or at risk and also upon the request of the PI or the sponsor, the Data Safety Monitoring Board (DSMB), the CRERC itself or other authorized bodies owing to the existence of unresolvable valid issues/concerns.

This application when approved by the CRERC becomes the basis for the initiation of the archiving procedure of the protocol file.

3. Responsibilities

*The CRERC Administrative Secretary is responsible for: **a**) verifying that the submission uses the correct form and protocol identification details, and that CRERC Form 7.7 Early Termination of Study Report is completely filled up; **b**) stamping the date of receipt of the submission, and recording the submission in the Log of Protocol-Related Submissions (CRERC Form 9.1); **c**) identifying the medical/scientific Primary Reviewer, and forwarding CRERC Form 7.7 Early Termination of Study Report, and other relevant documents to him/her; **d**) following up the results of the review from the Primary Reviewer, **e**) communicating CRERC's review decision to the Researcher/PI within the specified timeline and recording it in the Log of Outgoing Protocol Related Communications (CRERC Form 9.2); and **f**) filing the document in the protocol file folder, and updating the protocol file index.*

The Primary Reviewer is responsible for **a**) assessing the Early Termination of Study Report to determine significant change in the study risk-benefit ratio to study participants, and **b**) *returning the CRERC Form 7.7 Early Termination of Study Report with the results of the assessment to the CRERC Administrative Secretary within the specified timeline.*

The CRERC Chair is responsible for **a**) designating Primary Reviewer if the one who did the initial review is not available, and **b**) *reviewing, signing, and dating the communication to the Researcher/Principal Investigator (PI).*

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4. Workflow

No.	Activity	Person Responsible
1	Receive the Early Termination of Study Report	Administrative Secretary
2	*Identify the Primary Reviewer* and send the Early Termination of Study Report and related documents to him/her	Administrative Secretary
3	Review the Early Termination of Study Report	Primary Reviewer
4	*Include the Early Termination of Study Report in the agenda of forthcoming meeting*	Administrative Secretary
5	Communicate the CRERC decision to the Researcher/Principal Investigator (PI)	Admin Secretary, Member-Secretary, Chair
6	File the documents in the protocol file folder, and update the protocol file index	Administrative Secretary

5. Detailed Instructions

5.1 Receive the Early Termination of Study Report

5.1.1 Upon receipt of CRERC Form 7.7 Early Termination of Study Report, the Administrative Secretary checks the completeness of the document submitted, verifies if the CRERC Protocol No. is correct, *and if the initial approval date, or the date of approval of the last continuing review is valid to determine whether the protocol's ethical approval is not expired*.

5.1.2 *If the ethical approval is already expired, the Researcher/PI is required to submit justification letter for the failure to timely hand in the Progress Report and submit the application for continuing review. The report should contain information on subjects recruited after the expiration of ethical approval.*

5.1.3 If the submission is in order, and the ethical approval is current/valid, the Administrative Secretary stamps the document "Received", writes the date of receipt, and gives the duplicate copy of CRERC Form 7.7 Early Termination of Study Report to the Researcher/PI or his/her representative.

5.1.4 The Administrative Secretary records the submission *in CRERC Form 9.1 Log of Protocol–Related Submissions*.

5.1.5 *The Administrative Secretary informs the CRERC Chair and the Member Secretary of the submission.*

5.2 Identify the Primary Reviewer and send Early Termination of Study Report and related documents to him/her

5.2.1 *The Administrative Secretary identifies the medical/scientific Primary Reviewer who did the initial review.*

5.2.2 *The Administrative Secretary prepares the following documents for forwarding to the Primary Reviewer: a) CRERC Form 7.7 Early Termination of Study Report, b) latest version of the protocol summary and the ICFs, and other documents deemed relevant by the PI to support or clarify information indicated in the application. These will provide the Primary Reviewer with background information to facilitate the assessment of the Early Termination of Study Report, and the plan of care of study participants still enrolled.*

5.2.3 If the Primary Reviewer is available to do the review, the Administrative

Secretary sends the CRERC Form 7.7 Early Termination of Study Report and *relevant documents to him/her within seven (7) calendar days from the date of receipt of the Early Termination of Study Report.*

5.2.4 If Primary Reviewer is not available to do the review, CRERC Chair or the Member-Secretary does the review provided s/he does not have COI. Otherwise the Chair designates a qualified Member to do the review.

5.3 Review the Early Termination of Study Report

5.3.1 Primary Reviewer assesses how the premature termination of the study impacts on the study participants' safety and welfare, and the plan to follow up the participants who are still enrolled in the study.

5.3.2 The application for early termination of the study should contain a plan to follow up and care for the participants who are still enrolled in the study. The Researcher/PI may be requested to provide additional information or documents, or implement actions to ensure the safety and welfare of study participants.

5.3.3 Using the "For CRERC Use"-box of CRERC Form 7.7 Early Termination of Study Report, the Reviewer *writes the results of their assessment in the space provided.*

5.3.4 *After the assessment is completed the Primary Reviewer returns all the documents including the completed assessment form/s to the CRERC within (seven) 7 calendar days from the date of receipt of the document package.*

5.4 Include Early Termination of Study Report in the agenda of forthcoming meeting

5.4.1 All Early Termination of Study Reports are deliberated by CRERC *en banc.* (Refer to SOP 4.2 Full Committee Review).

5.4.2 The Administrative Secretary includes the Early Termination of Study Reports in the meeting agenda of the forthcoming meeting. (Refer to SOP 6.1 Preparation for a CRERC Meeting).

5.4.3 During the review of the Early Termination of Study Report by the CRERC *en banc*, the medical/scientific Primary Reviewer presents the results of the assessment.

5.4.4 *The CRERC verifies on the status of the current participants being enrolled and might be affected, reason for termination, and deliberates on the implications of the report 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*

5.4.5 The CRERC members vote to arrive at a decision. Possible review decisions are:

i) Approval
ii) Request for further information, specify ____
iii) Require action from the Researcher/PI, specify ____

5.5 Communicate the CRERC decision to the Researcher/Principal Investigator

5.5.1 The Administrative Secretary prepares Notification of CRERC Decision – Early Termination of Study Report (CRERC Form 8.9) based on the minutes of the meeting for review and signature of CRERC Chair, and sends it to the Researcher/PI after recording the document in the Log of

Outgoing Protocol Related Communications (CRERC Form 9.2) (Refer to SOP 8.2 – Communicating CRERC Decision)

5.5.2 *Turnaround time for review of the Early Termination of Study Report (from date of submission to date of notification of CRERC decision to the Researcher/PI) depends on the schedule of the full committee meeting but should not exceed forty-two (42) calendar days.*

5.6 File the documents in the protocol file folder and update the protocol file index

5.6.1 The Administrative Secretary files CRERC Form 7.7 Early Termination of Study Report with relevant excerpt of the minutes of the meeting, duplicate copy of CRERC Form 8.9 Notification of CRERC Decision – Early Termination of Study Report and updates the protocol file index. (Refer to the SOP 9.1 Management of Active Study Protocol Files)

5.6.2 Upon approval of the application for early termination of the study, the study protocol is classified as inactive, the Protocol Code No. is updated, and the protocol file folder re-labelled and transferred to storage cabinet for inactive files.

5.6.3 The Administrative Secretary enters relevant study protocol data into the protocol database to signify the end of study. (Refer to SOP 9.2 Archiving of Inactive Files)

6. Related Forms

CRERC Form 7.7 Early Termination of Study Report
CRERC Form 8.9 Notification of CRERC Decision – Early Termination of Study Report
CRERC Form 9.1 Log of Protocol-Related Submissions
CRERC Form 9.2 Log of Outgoing Protocol Related Communications

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05	01 Dec 2021	▪ Changed the title of the SOP from Review of Early Termination Report ▪ Changed Purpose to Objective, and Process Flow/Steps to Workflow to harmonize with PHREB's section titles. ▪ Changed the section on Scope - included the start and end tasks of the SOP ▪ Added the detailed responsibilities of the CRERC Chair, Primary Reviewers, and those of the Administrative Secretary ▪ Added the checking of validity of ethical approval of the study protocol and actions required from the PI if it is not valid in 5.1.2 ▪ Described the actions of the Admin Secretary after validating the completeness and accuracy of protocol identification details on the submission in 5.1.3-5.1.4 ▪ Specified the Primary Reviewer who will review the Early

SOP 7 MANAGEMENT OF POST-APPROVAL SUBMISSIONS

		Termination of Study Report – the medical/scientific Primary Reviewer who did the initial review in 5.2.1 ▪ Described the related documents that have to be forwarded to the Primary Reviewer together with the Early Termination of Study Report, in 5.2.2 ▪ Added timelines: from date of receipt of submission to forwarding this to Primary Reviewers = 7 calendar days in 5.2.3, from receipt of document package for review by Primary Reviewer to return of results of assessment to CRERC = 7 calendar days in 5.3.4; Turnaround time for review of the Early Termination of Study Report (from date of submission to date of notification of CRERC decision to the Researcher/PI) in 5.5.2 ▪ Introduced new forms – CRERC Form 8.9 – Notification of CRERC Decision – Early Termination of Study Report, CRERC Form 9.1 Log of Protocol-Related Submissions, and CRERC Form 9.2 Log of Outgoing Protocol Related Communications ▪ Cross referenced related SOPs ▪ Used Administrative Secretary instead of CRERC Secretariat and full committee instead of full board