Standard Operating Procedure
Protocol Deviation

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REVISION HISTORY

Rev #	Section	Revision Date	Reason for Revision	Signature of MREC Secretary
0	All	04/07/2016	Version 2.0, new format with additional information	
1	All	14/05/2018	Version 2.1, New flow chart for PD review using the new platform with added abbreviations	
2	All	14/12/2018	Version 3.0, clarification on flowchart, detailed instruction and appendix	

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1. PURPOSE

This SOP adheres to the ICH principle 4.5.1, that the investigator(s) / institution conduct the study in compliance with the protocol approved by the sponsor and, if applicable, regulatory authorities and to which the MREC has given its approval

2. SCOPE

This standard operating procedure describes the management, documentation and submission of protocol deviation and incidents of non-compliance and scientific misconduct.

3. ABBREVIATIONS

MREC	Medical Research and Ethics Committee
NMRR	National Medical Research Register
PD	Protocol Deviation
PDRP	Protocol Deviation Reporting Platform
PDSC	Protocol Deviation Sub-Committee

4. GLOSSARY

Term	Definition
Protocol Deviation (Minor)	A protocol deviation occurs when, without significant consequences, the activities on a study diverge from the Institutional Review Board-approved protocol.
Protocol Violation (Major)	A divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare.
Scientific misconduct	Falsification of generated or documented research data and the international omission of data during a clinical study

5. REQUIRED AND RELATED DOCUMENTS

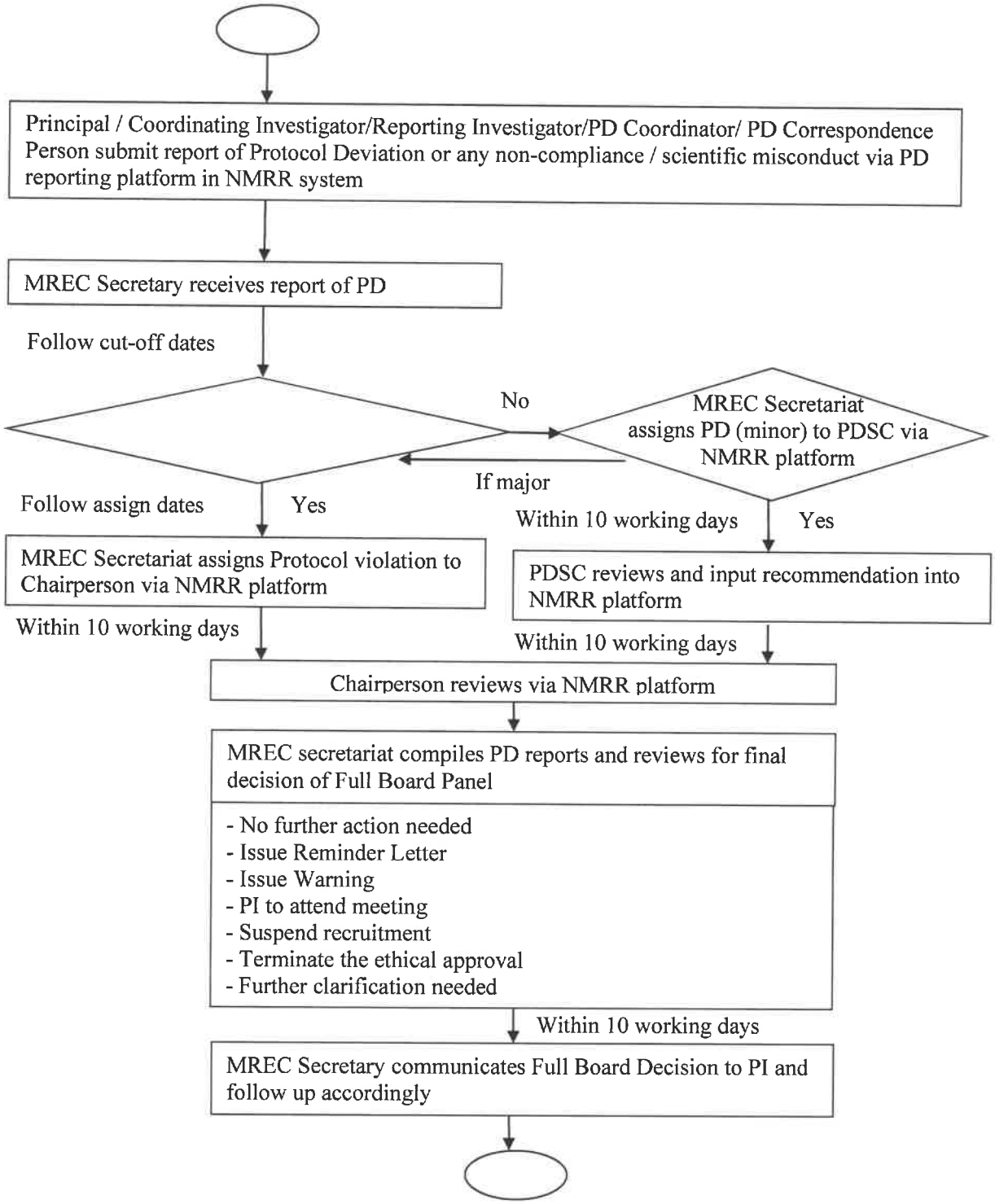
#	Document Title
1.	SOP 5-1: Maintenance, Archival and Disposal of Study and Non-Study Files
2.	TP5-1-1: Template for reminder letter
3.	TP 5-1-2: Template for warning letter

PROCEDURE

Step #	Process	Responsibility
1	Principal / Coordinating Investigator/Reporting Investigator/PD Coordinator/ PD Correspondence Person submit report of Protocol Deviation or any non-compliance / scientific misconduct via PD reporting platform in NMRR system	Principal / Coordinating Investigator/Reporting Investigator/PD Coordinator/ PD Correspondence Person
2.	MREC Secretary receives report of Protocol Deviation or any non-compliance / scientific misconduct via PD reporting platform in NMRR system	Secretary
3.	MREC secretariat screens through PD report according to the criteria (refer to flow chart) - Protocol Deviation (Minor) - Protocol Violation (Major)	Secretariat
4.	MREC secretariat assigns Protocol Violation (Major) report to MREC Chairperson and Protocol Deviation (Minor) report to PDSC to be reviewed within 10 working days	Secretariat/Chairperson/PDSC
5.	PDSC reviews and provide recommendation/Chairperson reviews and provides decisions: - Further clarification needed -Protocol Violation (Major) -Table at Full Board Meeting - PI to be present (where applicable) - Issue Reminder Letter (where applicable) - Issue Warning (where applicable) - Suspend recruitment (where applicable) - Protocol Deviation (Minor) - Table at Full Board Meeting for endorsement	Secretariat/Chairperson/PDSC
6.	Enter decision from MREC panel into the PD-Reporting Platform on NMRR and feedback/follow up is sent to (when required). a. Principal / Coordinating Investigator b. Reporting Investigator c. PD Coordinator, PD Correspondence Person d. Person who created or submitted the PD Report (when required). Follow-up on action to be taken by investigator (where applicable).	Secretariat

7.	If follow up report on a PD is received, it is discussed with the Chairperson if further action is needed, which may include: -Table at Full Board Meeting - PI to be present (where applicable) - Issue Reminder Letter (where applicable) - Issue Warning (where applicable) - Suspend recruitment (where applicable)	Secretary
8.	End	

6. FLOWCHART


Principal / Coordinating Investigator/Reporting Investigator/PD Coordinator/ PD Correspondence Person submit report of Protocol Deviation or any non-compliance / scientific misconduct via PD reporting platform in NMRR system
MREC Secretary receives report of PD
Follow cut-off dates
No
MREC Secretariat assigns PD (minor) to PDSC via NMRR platform
If major
Follow assign dates
Yes
Within 10 working days
Yes
MREC Secretariat assigns Protocol violation to Chairperson via NMRR platform
PDSC reviews and input recommendation into NMRR platform
Within 10 working days
Within 10 working days
Chairperson reviews via NMRR platform
MREC secretariat compiles PD reports and reviews for final decision of Full Board Panel
- No further action needed
- Issue Reminder Letter
- Issue Warning
- PI to attend meeting
- Suspend recruitment
- Terminate the ethical approval
- Further clarification needed
Within 10 working days
MREC Secretary communicates Full Board Decision to PI and follow up accordingly

8. DETAILED INSTRUCTIONS

8.1 The investigator should document, explain, and report to the MREC any noncompliance from the approved protocol, whether minor or major, at the soonest possible time **within 30 calendar days from the date of awareness.**

8.2 The Investigator(s) informs the MREC of protocol deviations / non-compliance / scientific misconduct. If the deviation results in protocol modification, approval by the MREC is required before it can be applied, UNLESS the modification has to be implemented immediately to eliminate an immediate hazard to the subjects via NMRR platform.

8.3 Reporting of study protocol noncompliance is facilitated through the submission via PD Reporting Platform, in NMRR.

8.4 Establishment of Protocol Deviation Sub Committee (PDSC)

8.4.1 The PDSC is established to assist the MREC in the post approval monitoring of Protocol Deviations/ Violations reports received from the investigators.

8.4.2 Members of the PDSC are appointed by the MREC Chairperson, as and when the need arises. The membership of this committee may comprise of medical members of the secretariat.

8.5 Review of Protocol Deviation/ Violation

8.5.1 MREC Secretary receives the PD reports via NMRR platform.

8.5.2 MREC secretariat receives PD reports and checks completeness of the PD Report. If incomplete, Secretary contacts Investigator to resubmit the necessary information via NMRR platform. Investigator to response to the request and resubmit **within 5 working days.**

8.5.3 MREC Secretary checks PD reports on cut-off date for Panel Meeting and assigns Protocol Deviation to PDSC and Protocol Violation to Chairperson.

8.5.4 The classification of the type of protocol deviation/ violation reported is based and not limited to the following:

- Protocol deviations (Minor) that do not affect the scientific soundness of the study protocol or compromise the rights, safety, or welfare of human participants in the study.
- Protocol violations (Major) that consist of persistent protocol noncompliance with potentially serious consequences that could critically affect data analysis or put patients' safety at risk
    - Inadequate or delinquent informed consent
    - Inclusion/exclusion criteria not met
    - Unreported serious adverse events
    - Improper breaking of the blind
    - Use of prohibited medication
    - Incorrect or missing tests
    - Mishandled samples
    - Multiple visits missed or outside permissible windows

- Materially inadequate record keeping
- Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
- Subject repeated non-compliance with study requirements

8.5.5 For Protocol Deviation, PDSC conducts a preliminary assessment of the report and provide recommendation for Chairperson to review within 10 working days.

8.5.6 For Protocol Violation, Chairperson reviews and provides feedbacks within 10 working days.

8.5.7 MREC Secretariat compiles all PD reports and reviews and sends listing to Panel of the nearest full board meeting to makes a final decision. PDSC representative presents the PD report and review to the Panel.

8.5.8 Protocol Deviations deemed as minor/ administrative deviations are endorsed in the panel meeting if no further communication with the PI is required.

8.5.9 Protocol violations deemed as major may be followed by and not limited to the following actions:

- Issuance of Warning letter to investigator.
- Issuance of reminder letter to investigator.
- Meeting with the investigator.
- Full Board Review - Discussion of the reported deviation/ violation in a panel meeting. Following the discussion, the panel decides on the next course of action which may be any of the above/
  i. suspending recruitment of new subjects in the study
  ii. termination of ethical approval
  iii. any others (whichever applicable)

8.5.10 In the case of when the recruitment has been suspended, the suspension may be revoked once all noncompliance issues are addressed.

8.5.11 For the major protocol deviations, the PI will be communicated with where relevant and the PI may be requested to provide additional information, submit additional documents, or implement corrective action(s).

8.5.12 If PD is submitted more than 30 calendar days from the date of awareness, email reminders will be sent to Principal Investigator to ensure timely submission of PD report to MREC.

8.5.13 If follow up report on a PD is received, it is discussed with the Chairperson if further action is needed, which may include:

- Retable at Full Board Meeting
- PI to be present
- Issue Reminder Letter
- Issue Warning
- Suspend recruitment
- no further communication with the PI is required

8.6 Tracking of PD

8.6.1 Tracking of PD reports can be done via PD Platform in the NMRR website

9. REFERENCES

9.1 International Council on Harmonization, Guideline on Good Clinical Practice (ICH GCP) 1996.

9.2 World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects, 2008.

10. APPENDIX

Terms of Reference for PD Subcommittee Members

Appendix

Terms of Reference for Protocol Deviation Subcommittee Members

1. Membership:
   - Appointed by MREC Chairperson for a term of two (2) years or for the remaining duration of term of office of the sitting MREC, whichever is less.
   - Headed by the MREC secretariat representative.
   - A minimum of 4 members per term consisting of medical/ pharmaceutical/ allied health personnel whom are experienced/ familiar in protocol deviation in human researches.
   - Resignation in writing should be tendered to the MREC Chairperson one month in advance.

2. The roles of members:
   - Evaluate the PD reports/ follow up of PD reports
   - Present the evaluated PD reports in MREC full board meetings

3. The responsibilities of members:
   - Evaluate the assigned reports within the required timeline. Recommendation shall be given upon evaluation, in which final decision shall be determined by the MREC full board/ Chairperson
   - Present the PD reports summary in the MREC full board meetings
   - Participate in PD Subcommittee related meetings for discussions on PD related issues
   - Revise the PD Standard Operating Procedures (SOP) when necessary

4. The frequency of meetings shall be at least once a year at the call of the subcommittee chair

5. Provide suggestions to MREC full board on training programmes to improve the competency of members

Standard Operating Procedure
Monitoring Serious Adverse Events

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0	All	01/03/2011	Version 1.0, first issue	
1	All	14/11/2014	Version 2.0, new format with additional information	
2	All	4/7/2016	Version 2.1, New flow chart for SAE review using the new platform with added abbreviations	
3	All	14/12/2018	Version 3.0, Major clarification on flowchart and detailed instruction	

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1. PURPOSE

The rights, safety, and well-being of human subjects are the most important considerations in clinical research studies, and should prevail over interests of science. Monitoring Adverse Event (AE) and Serious Adverse Event (SAE) enforces this commitment of Medical Research and Ethics Committee (MREC) to subject safety. MREC has to ensure that SAEs are reported as per protocol and their significance assessed. The sponsor and clinical research staff at the site must ensure that all safety information is appropriately reported and documented.

The purpose of this Standard Operating Procedure (SOP) is to provide instructions on monitoring of Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions by the Medical Research and Ethics Committee (MREC).

2. SCOPE

This SOP applies to all research approved by the MREC.

3. ABBREVIATIONS

AE	Adverse Event
SAESC	Serious Adverse Event Sub-Committee
CIOMS	Council for International Organizations of Medical Sciences
IB	Investigator's Brochure
ICH GCP	International Conference on Harmonization, Guideline on Good Clinical Practice
MGCP	Malaysian Guideline on Good Clinical Practice
MREC	Medical Research and Ethics Committee
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
NMRR	National Medical Research Register
SAE-RP	SAE Reporting Platform

4. GLOSSARY

Term	Definition
Adverse Events	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product
Life threatening	The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event
Serious Adverse Event/ Reaction	Any untoward medical occurrence that at any dose: - results in death, - is life-threatening, - requires inpatient hospitalization or prolongation of existing hospitalization, - results in persistent or significant disability/incapacity, or - is a congenital anomaly/birth defect
Suspected Unexpected Serious Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Sponsor-investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.
SADE	Serious Adverse Device Defect
Global SUSAR	Definition non mrec site

5. REQUIRED AND RELATED DOCUMENT

#	Document Title
1.	SOP 4-1: Preparation of Agenda, Meeting Procedures and Minutes
2.	SOP 5-1: Maintenance, Archival and Disposal of Study and Non-Study Files
3.	WS 3-2-1: Minimal requirement for Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions reporting to Medical Research and Ethics Committee.

6. PROCEDURE

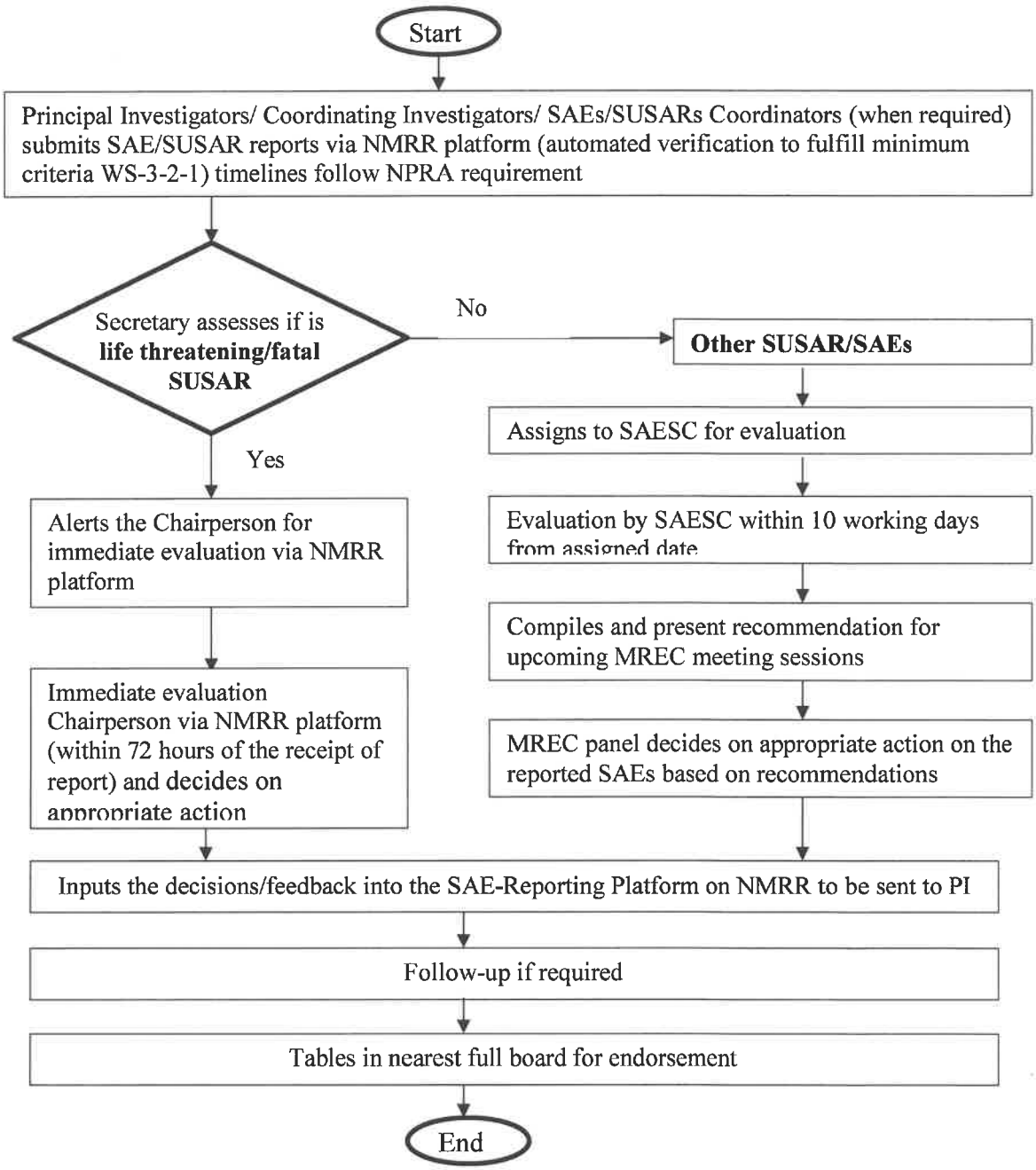
6.1. Fatal/ life threatening SUSAR

Step #	Process	Responsibility
1.	Principal Investigators/ Coordinating Investigators/ SAEs/- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required) submits SAE/SUSAR reports (** NMRR system verified the completeness of report submission)	Principal Investigators/ Coordinating Investigators/ SAEs/- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required)
2.	Receives SAE/SUSAR report	Secretary
3.	Alerts the Chairperson for immediate evaluation via NMRR platform	Secretary
4.	Immediate evaluation is done by the Chairperson (within 72 hours of receiving a SUSAR report).	Chairperson
5.	Decides on appropriate action on the reported SUSAR within 72 hours	Chairperson
6.	Inputs the SUSAR into the SAE-Reporting Platform on NMRR and feedback is sent to Principal Investigators/ Coordinating Investigators/ SAEs/- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required). Follow-up on action to be taken by investigator (where applicable).	Chairperson
7.	If follow up report on a SUSAR is received, it is discussed with the Chairperson if further action is needed.	Secretary
8.	Tables decision on SUSAR at the nearest MREC meeting for endorsement.	Secretariat

6.2 Other SUSAR and SAEs

Step #	Process	Responsibility
1.	Principal Investigators/ Coordinating Investigators/ SAEs/- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required) submits SAE/SUSAR reports (** NMRR system verified the completeness of report submission)	Principal Investigators/ Coordinating Investigators/ SAEs/- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required)
2.	Receives report and assigns to SAESC for evaluation	Secretary
3.	Assigns to SAESC for evaluation via NMRR platform.	Secretary
4.	Evaluation is done within 10 days after being assigned	SAESC
5.	Generate SAE summary report from the SAE Reporting Platform for all current reports reviewed	Secretary
6.	Compiles all current local report decisions and schedule for upcoming MREC meeting sessions	Secretary
7.	Presents review recommendations (**WS 3-2-2**) during each MREC Panel board meeting	SAESC representative
8.	Decide on appropriate action on the reported SAEs (see below item **8.8**)	MREC panel members
9.	Feedback of decision is updated to Principal Investigators/ Coordinating Investigators/ SAEs- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required). Follow-up on action to be taken by investigator (where applicable).	Secretary
10.	If follow-up action required, it is directly received and reviewed by the SAESC who reviewed the initial report within 10 days for further evaluation.	Secretary
11.	Tables decision on SUSAR/SAE at the nearest MREC meeting for endorsement.	Secretariat

7. Flowcharts


Start
Principal Investigators/ Coordinating Investigators/ SAEs/SUSARs Coordinators (when required) submits SAE/SUSAR reports via NMRR platform (automated verification to fulfill minimum criteria WS-3-2-1) timelines follow NPRA requirement
Secretary assesses if is life threatening/fatal SUSAR
No
Other SUSAR/SAEs
Assigns to SAESC for evaluation
Evaluation by SAESC within 10 working days from assigned date
Compiles and present recommendation for upcoming MREC meeting sessions
MREC panel decides on appropriate action on the reported SAEs based on recommendations
Yes
Alerts the Chairperson for immediate evaluation via NMRR platform
Immediate evaluation Chairperson via NMRR platform (within 72 hours of the receipt of report) and decides on appropriate action
Inputs the decisions/feedback into the SAE-Reporting Platform on NMRR to be sent to PI
Follow-up if required
Tables in nearest full board for endorsement
End

8. DETAILED INSTRUCTIONS

8.1. Investigator (s) and/or sponsor must adhere to Section 4.11 on SAFETY REPORTING in ICH-GCP and MGCP.

8.2. SUSARS and SAEs must be reported to MREC within the following timeline (following NPRA requirement):

8.2.1. **Fatal/Life threatening SUSAR:** Initial report as soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.

8.2.2. **All other SUSAR/all local SAEs:** Initial report as soon as possible but no later than 15 calendar days from awareness of event by investigator. Follow up information should be actively sought and submitted as it becomes available.

8.3. All SUSARs and SAEs must be reported via SAE Reporting Platform on National Medical Research Register (NMRR) website. A SUSAR/ SAE report should consist of the minimal required details as stipulated in **WS 3-2-1**.

8.4. MREC Secretary will assign the SUSARs and SAEs accordingly:

8.4.1. **Fatal/Life threatening SUSAR:** Review by Chairperson

8.4.2. **All other SUSAR/all local SAEs:** Review by SAESC

8.5. NMRR system (via system data verification) will ensure all SAE/SUSAR report fulfilling the minimum criteria (refer WS 3-2-1).

8.6. Establishment of Serious Adverse Event Sub Committee (SAESC)

8.6.1. An SAESC is established to assist the MREC in the post approval monitoring of SAE and SUSAR reports received from the sponsors and/or the investigators.

8.6.2 Members of the SAESC are appointed by the MREC Chairperson for a term of two years or for the remaining duration of term of office of the sitting MREC, whichever is less. The membership of this subcommittee shall comprise a minimum of 6 members per term consisting of medical/ pharmaceutical/ allied health personnel whom are experienced/ familiar in adverse events in human researches.

8.7 Review of local death or life threatening SUSAR

8.7.1 MREC Secretary receives SUSAR report and alerts the Chairperson for immediate evaluation via NMRR platform

8.7.2 Immediate evaluation is done by the Chairperson (within 72 hours of receiving a SUSAR report).

8.7.3 Chairperson decides on appropriate action on the reported SUSAR within 72 hours upon evaluation.

8.7.4 Chairperson inputs the decision on the SUSAR into the SAE-Reporting Platform on NMRR and Secretary sends feedback to Principal Investigators/ Coordinating Investigators/ SAEs/- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required).

8.7.5 Follow-up on action to be taken by investigator (where applicable).
8.7.6 If follow up report on a SUSAR is received, MREC Secretary or Secretariat discussed with the Chairperson if further action is needed.
8.7.7 MREC Secretariat tables decision on SUSAR at the nearest MREC meeting for endorsement.

8.8 Review of other SUSAR and SAE

8.8.1 MREC Secretary receives report and assigns to SAESC for evaluation via NMRR platform.
8.8.2 Evaluation is done by SAESC within 10 days after being assigned.
8.8.3 Secretariat generates SAE summary report from the SAE Reporting Platform for all current reports reviewed.
8.8.4 Secretariat compiles all current local report decisions and schedule for upcoming MREC meeting sessions.
8.8.5 MREC panel members decide on appropriate action on the reported SAEs.
8.8.6 Secretariat updates feedback of decision to Principal Investigators/ Coordinating Investigators/ SAEs- SUSARs Coordinators/ Reporting Investigators/ Corresponding Persons (when required). Follow-up on action to be taken by investigator (where applicable).
8.8.7 If follow-up action required, it is directly received and reviewed by the SAESC who reviewed the initial report within 10 days for further evaluation.
8.8.8 Secretariat tables decision on SUSAR at the nearest MREC meeting for endorsement.

8.9 Global SUSAR/SAE

8.9.1 MREC Secretary receives report via NMRR platform.
8.9.2 MREC Secretary reviews and sends email via NMRR platform to acknowledge the receipts of the Global SUSAR/SAE.

8.10 Decision of the MREC

8.10.1 The MREC is responsible to ensure that any changes in the risk/benefit balance of a clinical trial are compatible with continued ethical approval.
8.10.2 The MREC may decide on the followings based on the reported SUSAR/SAE and the Chairperson/SAESC recommendations.
8.10.2.1.1 Uphold original approval with no further action.
8.10.2.1.2 Uphold original approval with recommendations for corrective or preventive actions.
8.10.2.1.3 Suspend the study until satisfactory corrective and preventive actions are implemented.
8.10.2.1.4 Terminate the study.
8.10.2.1.5 Defer decision and request for more information.
8.10.3 To protect and preserve the safety of all trial participants, the MREC may suspend or terminate the ethical approval of any studies.

8.11 Tracking of SUSAR/SAE

8.11.1 Tracking of SUSAR/SAE reports can be done via SAE Platform in the NMRR website.

9 REFERENCES

9.1 International Conference on Harmonization, Guideline on Good Clinical Practice (ICH GCP) 1996.
9.2 ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitiond and Standards for Expedited Reporting E2A, Step 4 version, 1994.
9.3 Malaysian Guideline for Good Clinical Practice, 3rd Edition, 2011.
9.4 National Pharmaceutical Control Bureau (MOH). Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption in Malaysia, 5th Edition, 2009.
9.5 NPCB Malaysian Guideline for safety reporting of investigational products (1st edition 2014)

10 APPENDIX

Terms of Reference for SAE Subcommittee Members

APPENDIX 1

Terms of Reference for SAE Subcommittee Members

1. Membership:
   - Appointed by MREC Chairperson for a term of two (2) years or for the remaining duration of term of office of the sitting MREC, whichever is less
   - Headed by the MREC secretariat representative
   - A minimum of 6 members per term consisting of medical/ pharmaceutical/ allied health personnel whom are experienced/ familiar in adverse events in human researches
   - Resignation in writing should be tendered to the MREC Chairperson one month in advance

2. The roles of members:
   - Evaluate the SAE reports/ follow up of SAE reports and local SUSARs
   - Present the evaluated SAE reports in MREC full board meetings

3. The responsibilities of members:
   - Evaluate the assigned reports within the required timeline. Recommendation shall be given upon evaluation, in which final decision shall be determined by the MREC full board/ Chairperson
   - Present the SAE reports summary in the MREC full board meetings
   - Participate in SAE Subcommittee related meetings for discussions on SAE related issues
   - Revise the SAE Standard Operating Procedures (SOP) when necessary

4. The frequency of meetings shall be at least once a year at the call of the subcommittee chair

5. Provide suggestions to MREC full board on training programmes to improve the competency of members

Standard Operating Procedure
Conduct of Compliance Review for Clinical Research

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0	All	14/11/2014	Version 1.0, first issue	G.K.
1	7	04/07/2016	Updated Flowchart	G.K.

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1. PURPOSE

To describe the procedure associated with conduct of a routine compliance review at Investigator Site for all research reviewed and approved by the Medical Research Ethics Committee (MREC). Compliance Review is conducted as part of section 3.1.4 of the ICH-GCP and Malaysian GCP.

The purpose of the Compliance Review is to:

a. Confirm if the Principal investigator (PI) is complying with protocol and regulatory requirements. Assist the PI in complying with Regulations and Protocol.

b. Confirm if the PI is taking appropriate and timely action to ensure protection of the rights, safety and well-being of research subjects at all times.

c. Provide assurance to the public as well as to the Ministry of Health Malaysia that MREC is providing the continued oversight of studies and ensuring that rights, safety and well-being of research subjects are safeguarded.

2. SCOPE

This procedure applies to all research approved by the MREC.

3. ABBREVIATIONS

CAPA	Corrective Action and Preventive Action
CR	Compliance Review
FS	Full scope
FCR	For Cause Review
ICF	Informed Consent Form
IP	Investigation Product
LS	Limited scope
MOH	Ministry of Health Malaysia
MREC	Medical Research & Ethics Committee
PI	Principal Investigator
SAE	Serious Adverse Event

4. GLOSSARY

Term	Definition
Compliance Review	A review conducted by MREC or on behalf of MREC to assess compliance of an approved study to Regulatory and MREC requirements for safeguarding the rights, safety and well being of research subjects.
Compliance Team	The team identified by MREC, which conducts the review. It can be an external third party that conducts the review on behalf of the MREC
For Cause Review	A review conducted in response to a. Complaints of a study, received from sponsor, study monitor or any other source. b. Concerns noted in the monitoring of a study, e.g. too many deaths /SAEs. c. Investigator not complying with the requests from MREC.

5. REQUIRED AND RELATED DOCUMENT

#	Document Title
1.	**SOP 5-1:** Maintenance, Archival and Disposal of Study and Non-Study Files
2.	**WS 3-3-1**: Checklist for Compliance Review
3.	**WS 3-3-2**: Compliance Review Notes
4.	**WS 3-3-3**: Issue Tracking Log
5.	**TP 3-3-1**: Notification Letter for Compliance Review
6.	**TP 3-3-2**: Compliance Review Report
7.	**TP 3-3-3**: Confirmation of Conduct of Compliance Review

6. PROCEDURE

6.1. Compliance Review (Full /Limited Scope)

Step #	Process	Responsibility
1.	Identify study and site for conduct of Compliance Review. Determine whether Full or Limited Scope Review.	MREC chairperson and selected members
2.	Identifies and appoints the team for Review. Appoints Lead Reviewer.	MREC chairperson
3.	Fix date for Review	Lead Reviewer and PI
4.	Sends official notification of Review to PI (**TP 3-3-1**)	Secretary
5.	Prepares for Review	Review Team
6.	Conducts Compliance Review at the site using **WS 3-3-1**	Review Team
7.	Prepares a draft CR Report (**TP 3-3-2**)	Review Team
8.	Finalise the report and sends CR Report (**TP 3-3-2**) to the investigator	Review team, Secretary
9.	Responds to the findings and prepares CAPA in the CR Report	PI
10.	Reviews CAPA and reports to MREC members	Review team
11.	Monitors the CAPA (**WS 3-3-3**)	Secretary

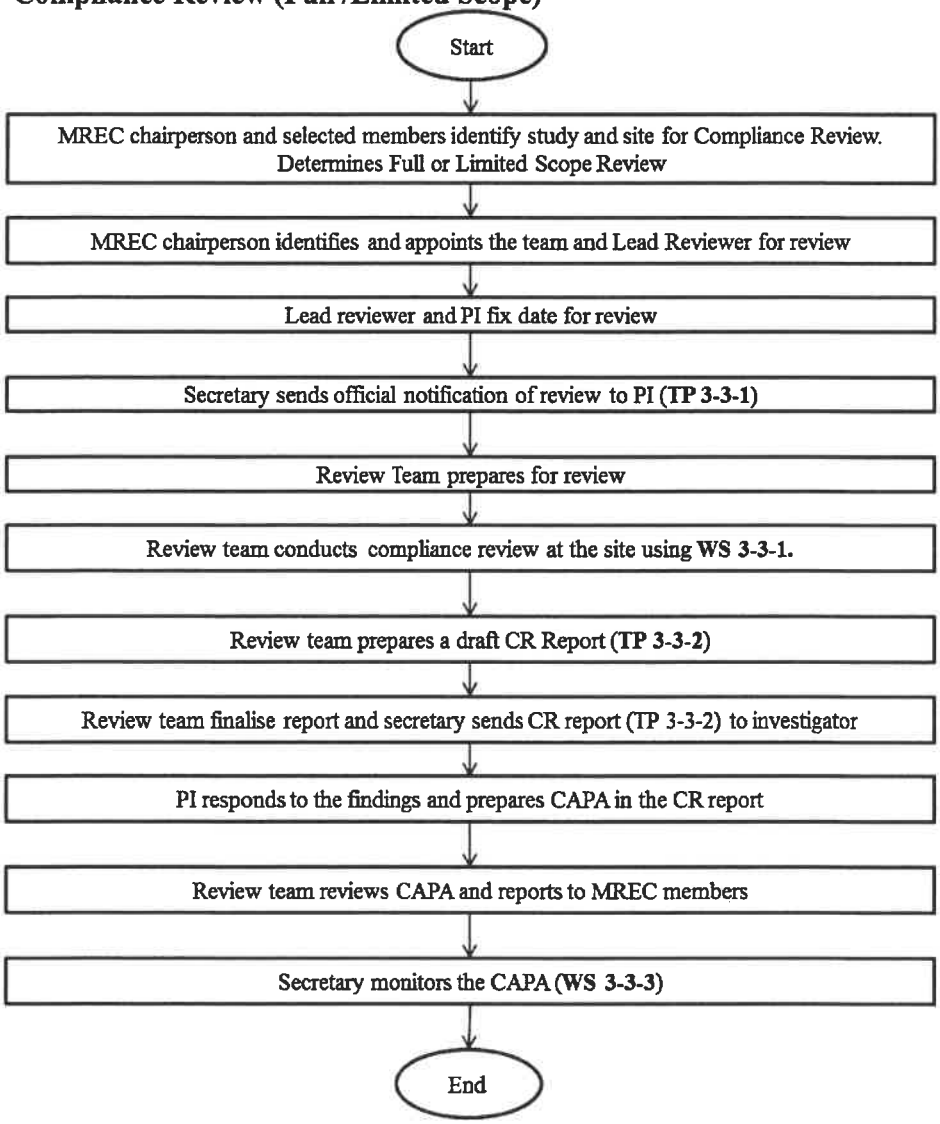
6.2. For Cause Review

Step #	Process	Responsibility
1.	Identifies need for a For Cause Review	MREC chairperson
2.	Identifies and appoints the team for Review. Appoints Lead Reviewer.	MREC chairperson
3.	Fix date for FCR	Lead Reviewer and PI
4.	Sends official notification of Review to PI (**TP 3-3-1**)	Secretary
5.	Prepares for Review	Review Team
6.	Conducts Review at the site using **WS 3-3-1**	Review Team
7.	Prepares a draft CR Report (**TP 3-3-2**)	Review Team
8.	Finalise the report	Review team, Secretary
9.	Presents and discusses report with relevant stakeholders. Decides on CAPA	Chairperson

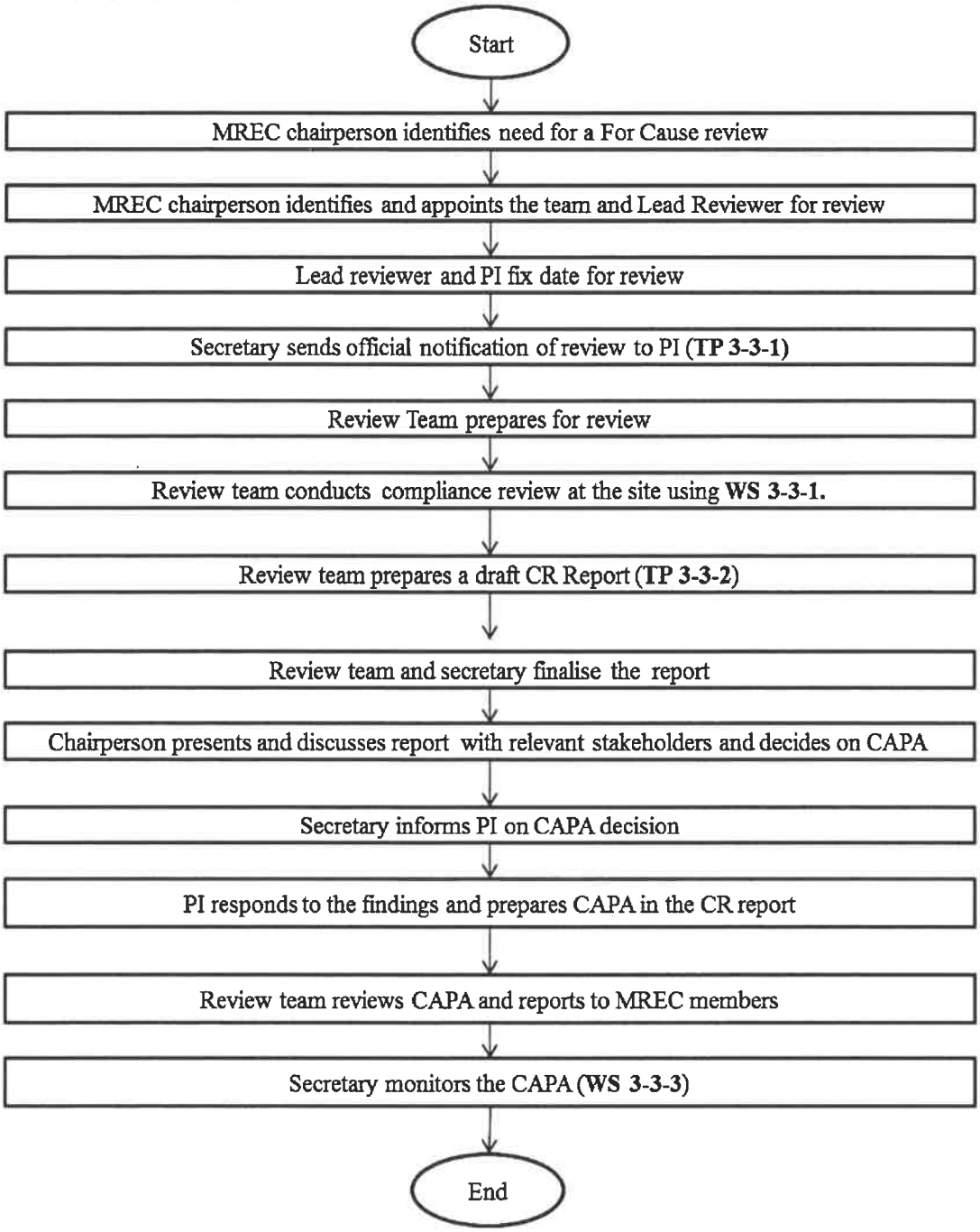
Step #	Process	Responsibility
10.	Informs PI on CAPA decision	Secretary
11.	Responds to the findings and prepares CAPA report	PI
12.	Reviews CAPA report and reports to MREC	Review team
13.	Monitors the CAPA (**WS 3-3-3**)	Secretary

7. FLOWCHART

7.1. Compliance Review (Full /Limited Scope)



7.2. **For Cause Review**



8. DETAILED INSTRUCTIONS

8.1. Type of Compliance Reviews

8.1.1. **Full scope Compliance Review**
All elements in Review Checklist (**WS 3-3-1**) are audited.

8.1.2. **Limited scope Compliance Review**
Only selected elements in Review Checklist (**WS 3-3-1**) are audited.

8.1.3. **For Cause Review**
This is triggered by receipt of serious complaint or when concerns related to study conduct and/or Investigators are noted that can potentially impact subject safety and or data integrity.

8.2. Quantum and frequency of Compliance Reviews

8.2.1. Each year the MREC strives to conduct FS or LS Compliance Reviews on not less than 5% of the total number of MREC full-board approved studies conducted in the preceding year. Compliance Reviews are only done for studies that have been conducted for at least 1 year.

8.2.2. FCRs are conducted when a need arises as per section **8.1.3**.

8.3. Identification of study and site for FS or LS Compliance Review conduct

8.3.1. Chairperson identifies and endorsed by MREC members, studies for compliance review based on, but not limited to, any or a combination of the following criteria:

8.3.1.1. The risk profile of the study
8.3.1.2. The number of subjects recruited in the study
8.3.1.3. Therapeutic indication as well as complexity of study
8.3.1.4. Any possible/known conflict of interest
8.3.1.5. Vulnerable subjects
8.3.1.6. Number of non compliances noted
8.3.1.7. Number of SAEs noted
8.3.1.8. Results of previous CR
8.3.1.9. Experience of the Investigator in the conduct of Clinical Trials
8.3.1.10. Number of studies managed by the PI.
8.3.1.11. Any complaint/concerns about the study

8.3.2. Compliance team prepares for CR on each MREC approved site for the selected study.

8.4. Identify the type of Compliance Review

8.4.1. Chairperson determines and endorsed by MREC members, whether CR to be conducted is FS or LS, and the time when the review will be conducted.

8.4.2. FCR is initiated under the instruction of the Chairperson.

8.4.3. FS or LS Compliance Review is conducted anytime during the conduct of a study as well as after the study is closed.

8.4.4. Subjects participating in the study are interviewed if required/desired. In such instances, the PI is responsible for contacting the subjects and arranging for the interview.

8.5. **Identify Team for Compliance Review**

8.5.1. The Chairperson identifies and appoints the Review Team for the conduct of the Compliance Review. One member of the Review Team will be appointed the Lead Reviewer.

8.5.2. The Compliance Review team consists of at least 2 members (may include Member Secretary and Member Secretariat) depending on the scope and the volume of the review to be performed.

8.5.3. The team shall have sufficient expertise to evaluate compliance with medical procedures, inventory and dispensing of investigational product, informed consent, and SAE reporting or issues identified for a FCR.

8.5.4. If required, the MREC designates an external third party resource to perform this review.

8.6. **Compliance Review Notification**

8.6.1. Secretary notifies the Investigator **at least 14 working days** (for FS/LS CR) or **at least 3 working days** (for FCR) before the conduct of the review. **(TP 3-3-1)**.

8.6.2. The notification contains at a minimum the following information:

8.6.2.1. Start date and time of review

8.6.2.2. The protocol number and title of the protocol identified for review

8.6.2.3. The scope of the review

8.6.2.4. The duration of review

8.6.2.4.1. FS compliance review: At least 2 working days

8.6.2.4.2. LS compliance review: At least 1 working day

8.6.2.5. Standards against which the review would be performed

8.6.2.6. Any other specific requirements – e.g. availability of documents, study staff, logistic request (work room, photocopier, etc.)

8.7. **Preparation for Compliance Review**

8.7.1. In preparation for the FS or LS Compliance Review the team reviews documents and gathers information pertaining to the study. These include:

8.7.1.1. A copy of the latest protocol

8.7.1.2. A copy of the Investigator Brochure

8.7.1.3. A copy of the latest Informed Consent Form and advertisement (if applicable)

8.7.1.4. Minutes of all MREC meetings where the study is discussed

8.7.1.5. All the study information shared by the Investigator with the MREC including protocol deviations, SAEs etc.

8.7.1.6. Any other information available

8.7.2. In preparation for a FCR the team reviews relevant documents and gathers pertinent information for which the FCR is required.

8.7.3. The Compliance Team has the authority to request additional documents not submitted earlier for the registration of the study.

8.8. **Compliance Review Conduct**

8.8.1. On the day of the review, the Compliance Team arrives at the scheduled time at the site to perform the review.

8.8.2. Study team conducts an opening meeting to :

8.8.2.1. introduce the study team

8.8.2.2. provide brief overview and progress of the study

8.8.3. Lead reviewer briefs opening meeting to:

8.8.3.1. introduces Compliance team

8.8.3.2. provide briefing on objective, scope and conduct of CR

8.8.4. Based on the audit scope, Compliance Team conducts review on the study documents, Informed Consents, subject records (electronic and/or paper), Case Reports forms, procedures, computer systems, interviews staff and subjects, etc. **(WS 3-3-1)**

8.8.5. FS Compliance Review includes auditing the following:

8.8.5.1. **Essential Documents:**

8.8.5.1.1. Approval letters from MREC

8.8.5.1.2. Signed Protocol and Investigator Brochure

8.8.5.1.3. Insurance Certificate or Letter of Indemnity

8.8.5.1.4. Instructions for handling Investigational Product

8.8.5.1.5. Contract/ Clinical Trial Agreement

8.8.5.1.6. Informed Consent Form

8.8.5.1.7. Recruitment procedures and its Approval (e.g. any advertisement)

8.8.5.1.8. Updates/Progress Reports submitted to MREC

8.8.5.1.9. Financial Disclosures

8.8.5.2. **Staffing and Infrastructure**

8.8.5.2.1. Curriculum Vitae and training records for study team

8.8.5.2.2. Availability of infrastructure and equipment based on the study requirements and its maintenance records

8.8.5.2.3. Oversight or monitoring performed by sponsor/CRO

8.8.5.3. **Informed Consent Forms** (review samples of ICF if subject number is greater than 10)

8.8.5.3.1. Different versions (if applicable) of ICF used and its approval by MREC

8.8.5.3.2. Compliance of ICF document with Malaysia GCP requirements.

8.8.5.3.3. Select patients consent records and review the process followed

8.8.5.3.4. Availability of consent forms for all screened subjects

8.8.5.3.5. Timely re-consent from subjects in case of update of documents.

8.8.5.4. **Review of Patient Records**
Compliance Team reviews 2 to 3 subject records during routine review to confirm:
8.8.5.4.1. Subject eligibility per protocol
8.8.5.4.2. Compliance to Protocol processes and timelines
8.8.5.4.3. Correct use and dose of Investigational Product
8.8.5.4.4. Review of AE/SAE reporting and its management
8.8.5.4.5. Investigator follow up and medical care

8.8.5.5. **Review of SAE reports**
Compliance team reviews all SAEs reported from site to:
8.8.5.5.1. Confirm the accuracy details after verification with patient records.
8.8.5.5.2. Verify if the SAEs have been reported in timely manner to MREC

8.8.5.6. **Review the Investigational Product (IP)**
8.8.5.6.1. Storage and security of IP
8.8.5.6.2. Accountability of IP and disposal records
8.8.5.6.3. Environment monitoring of IP

8.8.5.7. If necessary, the Compliance team visits other facilities involved in the study including Laboratory or Radiology department.

8.8.6. The Compliance team records any findings, objective evidence and evaluates the severity using **WS 3-3-2.** The findings severity is defined as follows:
8.8.6.1. **Critical**: Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data
8.8.6.2. **Major:** Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data.
8.8.6.3. **Minor:** Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

8.8.7. For FCR, an in-depth investigation is performed by Compliance team for the concern/issue identified to confirm the facts and validity of the significant concern.

8.8.8. A closing meeting will be held at the end of the day the Compliance review is completed.
8.8.8.1. On completion of a FS or LS CR, the Compliance team presents a verbal summary of the details after verification with patient records. When necessary, Compliance team will share findings and seek clarifications from site study team.
8.8.8.2. On completion of a FCR, the Compliance Team will send a detailed report to the Chairperson after completion of the FCR. On confirmation of the issue, MREC Chairperson will inform relevant stakeholders (e.g. Regulators, Sponsors and Head of Institute) as soon as possible and consult them on next course of action.

8.8.9. In case serious critical issue(s) are identified, Compliance team inform the MREC chairman **within 24 hours of its identification.** Depending upon the nature of the issue, MREC may decide to involve other stakeholders – sponsor, CRO and the Institute head, to discuss and agree on further course of action. Investigator may be asked to appear before the MREC board for further clarifications before a decision is taken on the next steps

8.9. **Report preparation, distribution and tracking**

8.9.1. The compliance team prepares draft CR report (**TP 3-3-2**) within **10 working days** of completion of the review.

8.9.1.1. Review team completes the following sections in the CR report:

8.9.1.1.1. **Part 1 , Section A** on the general information

8.9.1.1.2. **Part 1, Section C** on Executive summary

8.9.1.1.3. **Part 1, Section D** on Introduction

8.9.1.1.4. **Part 1, Section E** on Scope

8.9.1.1.5. **Part 1, Section F** on Recommendation using the following:

8.9.1.1.5.1. Continue trial

8.9.1.1.5.2. Withhold new subject recruitment until assessment and verification of CAPA by MREC review team

8.9.1.1.5.3. Suspend the site from trials until assessment and verification of CAPA by MREC review team

8.9.1.1.5.4. Suspend trial

8.9.1.1.6. **Part 1, Section G** on Summary of Findings severity

8.9.1.1.7. **Part 2, Section A** for each finding

8.9.2. The draft findings are forwarded to MREC Chairperson for comments. The Chairperson may select members and invites them to comment on the report.

8.9.3. Chairperson decides on the Recommendation of the CR in **Part 1, Section F.**

8.9.4. Compliance team addresses the changes suggested and finalise the report within **7 working days** of receiving the Chairperson's comments and forwards to the Secretary.

8.9.5. Secretary sends the Compliance Report (in both in hard copy and Word document file) to the investigator for response and forwards a hardcopy to the Head of Institute.

8.9.6. Investigator or representative completes **Part 1, Section B** for Acknowledgement of receipt of the CR report and emails scanned copy of the page back to the MREC Secretariat.

8.9.7. The study investigator provides responses to the findings and completes **Part 2, Section B** for the CAPA within **30 working days** from the receipt of the findings.

8.9.8. If recommendation is to suspend the trial, investigator need not fill in **Part 2, Section B.**

8.9.9. If there is no response from the investigator after the deadline, the Secretary sends a reminder requesting the investigator to submit the respond to the findings **not later than 7 working days** from the date of the reminder letter. If the investigator

fails to respond after the second deadline, the Compliance team will bring to the attention of the MREC panel for subsequent actions to be taken.

8.9.10. The Compliance team reviews the CAPA and provides necessary comments. The CAPA will be finalised within **30 working days** of the release of the Findings to the study team.

8.9.11. The Findings and CAPA will be presented to the earliest Panel meeting for endorsement.

8.9.12. The Review team leader will update and verify the Compliance report (**Part 2, Section C**) and follow up on the CAPA until sufficiently satisfied with the actions taken and the findings closure.

8.9.13. The Secretary will track and the findings on the Issue Tracking Log (**WS 3-3-3**). Secretary updates the Panel that endorsed the findings, on the progress of the CAPA.

8.9.14. If requested or required by the Study investigator, a document confirming the conduct of the Compliance Review may be provided.

8.10. **Management and Storage of CR related documents**

8.10.1. Secretariat files all CR related documents into the File for CR Review as per **SOP 5-1**.

8.10.2. Secretariat files a copy of the CR report into the relevant study files.

9. REFERENCES

9.1. Malaysian Guideline for Good Clinical Practice, 3rd Edition, Ministry of Health, October 2011.

9.2. International Conference on Harmonization, Guideline on Good Clinical Practice (ICH GCP) 1996

10. APPENDIX

None