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1. Purpose

The purpose of this SOP is to provide instructions on the review and follow-up reports of serious adverse experience and unexpected events for any active study approved by the MRIN EC. The SAE must be reported by the investigators or sponsors within 5 working days after the incident occurred and unexpected events should be included in the continuing review report submitted to EC.

Unanticipated risks are sometimes discovered during the course of studies. Information that may impact on the risk/benefit ratio should be promptly reported to and reviewed by the MRIN EC to ensure adequate protection of the welfare of the study participants.

The unanticipated risks may as well include any event that in the investigator's opinion, may adversely affect the rights, welfare or safety of subjects in the study.

2. Scope

This SOP applies to the review of SAE and unexpected events reports submitted by investigators, Data Safety Monitoring Board (DSMB), sponsor, local safety monitor, EC members or other concerned parties.

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3. Responsibility

The primary responsibility of the MRIN EC is to review and address SAE and unexpected events involving risks to subjects or others as well as ethics complaints.

MRIN EC should also make sure that researchers are made aware of the policies and procedures concerning reporting and continuing review requirements.

The EC Secretary is responsible for first screening the assessment of the reports and seeing whether they need a review of full Board, Chairperson, other qualified EC members or experts.

4. Flow chart

No.	Activity	Responsibility
1	SAE related activities before an MRIN EC/KEPK MRIN meeting	MRIN EC Secretariat, Members
	↓	
2.	Review and determine the review channel	MRIN EC Secretary, Members
	↓	
3	Criteria for the review	MRIN EC Secretary, Members
	↓	
4.	During MRIN EC meeting	MRIN ECMembers, Vice Chairperson/chairperson
	↓	
5.	Review and discuss	MRIN EC Members, Vice Chairperson /Chairperson
	↓	
6.	Decide what action should be taken.	MRIN EC Members and Chairperson
	↓	
7.	Inform investigator or clinical trial office	MRIN EC Chairperson/ Secretary

5. Detailed instructions

5.1 Before each MRIN EC meeting

5.1.1 Review and determine the review channel

- ☐ MRIN EC Secretary or initial reviewers re-evaluate the reporter's assessment to determine whether the report requires review by full Board or by the Chairperson or other qualified IEC/IRB member(s).

5.1.2 Criteria for the review

- ☐ The **review criteria** are as follows:
  - ☐ Assessment of SAE or SUSAR is unknown or unlikely
    - ☐ Report is forwarded to the Chairperson/ Secretary for review and determination if report should be reviewed at the convened meeting by full Board.
  - ☐ Assessment of SAE or SUSAR is possibly caused by, or probably caused by the investigational product.
    - ☐ The report is added to the agenda for review at a convened meeting by full Board.

- ☐ An adverse experience/IND Safety Report has been previously seen by full Board but being resubmitted by another investigator participating in the multi-study site (as part of a multi-center/site study).
  - ☐ This notification does not require full Board review.
  - ☐ Reviewed by the Chairperson or other qualified MRIN EC members

5.2 During the MRIN EC meeting

5.2.1 Review and discuss

- ☐ After reading and reviewing the report, the Chairperson or designee entertains discussion on the study and similar adverse experiences or advisories.
- ☐ If necessary, MRIN EC may invite Principal Investigator to the meeting for explanation of the research result.
- ☐ If appropriate to the discussions, the Chairperson or another Board member may call for a consensus on whether to:
  - Request an amendment to the protocol or the consent form.
  - Request further information.
  - Suspend or terminate the study.

5.2.2 Decide what action should be taken.

- ☐ If any of the above *actions are taken*, the MRIN EC Secretary or designee notifies the investigator of the action taken.
- ☐ If the MRIN EC *takes no action*, a notation is made in the minutes and the study is allowed to continue.

5.2.3 Inform investigator or clinical trial office

- ☐ The MRIN EC Secretary drafts a formal letter to the investigators or the clinical trial office to notify them of the action they should take according to the MRIN EC decision.
- ☐ Get the Chairperson to approve, sign and date the letter.
- ☐ Send the letter and record the delivery date.

6. Glossary

Adverse Event	Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. The adverse event can therefore be any unfavorable or unintended sign or experience associated with

	the use of the investigational product, whether or not related to the product.
Adverse Drug Reaction	In the pre-clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not established all noxious or unintended responses to the product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between the product and the adverse event is at least a reasonable possibility, i.e., the relationship can not be ruled out. Regarding marketed products, a response to a product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.
IND	Investigational New Drugs means substances with potential therapeutic actions during the process of scientific studies in human in order to verify their potential effects and safety for human use and to get approval for marketing.
SAE (Serious Adverse Event)	The adverse event is SERIOUS and should be reported when the patient outcome is: **Death** – Principal Investigator should report if the patient's death is suspected as being a direct outcome of the adverse event. **Life-Threatening** – PI should report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. *Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing.* **Hospitalization** (initial or prolonged) – PI should report if admission to the hospital or prolongation of a hospital stay results because of the adverse event. *Examples: Anaphylaxis; pseudomembranous colitis; or*

bleeding causing or prolonging hospitalization.

Disability – PI should report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.

Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy.

Congenital Anomaly – PI should report if there are suspicions that exposure to a medical product during pregnancy resulted in an adverse outcome in the child.

Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.

Requires Intervention to Prevent Permanent Impairment or Damage – PI should report if suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

Examples: Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

Unexpected ADR — Unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the informed consent / information sheets or the applicable product information (e.g., investigator's brochure for the unapproved investigational product or package insert / summary of product characteristics for an approved product.

SUSAR — Suspected Unexpected Serious Adverse Reaction (SUSAR) : Serious adverse reactions in subjects given a drug, that may or may not be dose related, but are unexpecxted, as they are not consistent with current information. A SUSAR may occur

during clinical trials or clinical care. Reporting is mandatory for clinical investigators.

7. Annex

Annex 1 AF/01-019/2017/01.2 Serious Adverse Event Report
Annex 2 AF/02-019/2017/01.2 Unexpected Adverse Drug Reaction Report
Annex 3 AF/03-019/2017/01.2 Document History

8. References

- Peraturan Pemerintah Republik Indonesia Nomor 39 Tahun 1995 tentang Penelitian dan Pengembangan Kesehatan, http://www.litbang.depkes.go.id /unduh_pp
- Operational Guidelines for Ethics Committees that Review Biomedical Research, World Health Organization, 2000, Geneva. DELETE
- Surveying and Evaluating Ethical Review Practices, World Health Organization, 2002, Geneva.
- International Conference on Harmonisation (ICH) Harmonised Tripartite : Guideline for Good Clinical Practice E6(R1), Current Step 4 version dated 10 June 1996, November 2005.
- Undang-undang Kesehatan No. 36 Tahun 2009 pasal 44. Delete
- Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, 2011, World Health Organization,
- FERCAP Standard Operating Procedures (SOPs) for Ethics Committees (ECs)/Institutional Review Boards (IRBs), http://www.fercap-sidcer.org/ selftool.php, accessed January 2013.
- ICH -GCP: Guideline For Good Clinical Practicee6(R2) , 2016

Annex 1
Form AF/01-019/2017/01.2

Principal Investigator:…….. Application No:

Study Title:……. Protocol No.:

Name of the study medicine/device……..…… Report Date :……
☐ initial ☐ follow-up
Onset date:……
Date of first use:
……..

Sponsor:……

Subject's initial/number:	Age:	☐ Male ☐ Female

Subject's history:	Laboratory findings:

SAE / SUSAR :	Treatment: Outcome: ☐ resolved ☐ on-going

Seriousness:	Relation to ○ Drug ○ Device ○ study
☐ Death ☐ Life Threatening ☐ Hospitalization –○ initial ○ prolong ☐ Disability / Incapacity ☐ Congenital Anomaly ☐ Other……	☐ Not related ☐ Possibly ☐ Probably ☐ Definitely related ☐ Unknown

Changes to the protocol recommended?	☐ No ☐ Yes , attach proposal
Changes to the informed consent form recommended?	☐ No ☐ Yes , attach proposal

Reviewed by:…… Date:……
Comment:…… Action:……
…… ……

Annex 2
Form AF/02-019/2017/01.2

Unexpected Adverse Event Summary Report

Principal Investigator:……. **Application No:**

Study Title:……... **Protocol No.:**

Name of the studied medicine/device……..…….. **This report covers the period :**

Sponsor:……... **From……To…….**

#	Description of Unexpected Adverse Events	Date of Event (D/M/Y)	Date start and end of Tx (D/M/Y)	For M	Ini-tial	Age (Y)	Serious Yes No	Related to Study Yes No	Concomitant medication	Intervention
							☐ ☐	☐ ☐		
							☐ ☐	☐ ☐		
							☐ ☐	☐ ☐		
							☐ ☐	☐ ☐		

Annex 3
Form AF/03-019/2017/01.2

Document History

Author	Version	Date	Description
EC Members	01.0	2 January 2013	**Final version**
Ivet, Lia, Mona	01.1	11 October 2014	1. Synchronize the topic number and SOP number 2. Format Document History : Author, Version, Date and Description of the main change 3. SOP Title : Review of Serious Adverse Event (SAE) / Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports 4. Section 5.1.2. : Criteria for review of SAE and SUSAR 5. Glosarry of SUSAR 6. Annex 1 : Addtion of SUSAR

Debbie S. Retnoningrum, Yan Nuryanto	01.2	1 April 2017	1. Delete Komite Etik Penelitian Kesehatan (KEPK) on the header