Independent
Ethics Committee
(Clinical Research) India

Standard Operating Procedures

(SOP -14/01)

For

For Review of Serious Adverse Event SAE Reports

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1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to provide instructions on the review of initial and follow-up reports of serious adverse experience and unexpected events occurring at trial sites for any active study approved by the Independent Ethics Committee (IEC). The Serious Adverse Event (SAE) must be reported to the IEC by the investigators within 7 working days after the SAE occurred. All the unexpected events, adverse event should be included in the Annual Study Progress Report submitted to IEC.

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 IEC 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 event reports, adverse event reports occurring at trial sites submitted by investigators.

3. Responsibility

The primary responsibility of the IEC is to review and address SAE and unexpected events occurring at the trial site approved by the IEC or occurring at other sites for the given project/related project involving risks to subjects or others as well as ethics complaints. In addition, the Committee is authorized to offer mediation under appropriate circumstances.

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

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4. Flow chart

No.	Activity	Responsibility
1	SAE related activities before an IEC meeting	IEC Secretariat, members
2	During the IEC meeting	IEC members and Chairperson
3	After the meeting inform Investigator	IEC Secretariat and Chairperson

5. Detailed instructions

5.1 SAE related activities before an IEC meeting

5.1.1 Review and determine the review channel

- The IEC Secretariat will receive the SAE report or the unexpected event report occurring at the trial sites approved by the IEC for a given project. The Administrative Officer will verify that the reports are complete, signed and dated by the Principal Investigator (PI) and is received at the IEC office within 7 working days of occurrence of the SAE. The Administrative Officer will sign and date the report and will fill the SAE Assessment Form (AF/01/01-SOP14/01) based on the SAE Report received from the PI. The Administrative Officer will forward the SAE Assessment form along with the SAE report/unexpected event report to the Member Secretary. The Member Secretary will review the SAE Report, write comments and forward it to the Chairperson.

5.1.2 Action to be taken

- The Chairperson on basis of the information and comments received will determine whether the report requires emergency review by full Board (electronic) or by other qualified IEC member(s) or will be reviewed in the forthcoming scheduled Full Board meeting. The Chairperson will sign and date the SAE Assessment report and send it to the Secretariat. Irrespective of these actions, all SAEs will be informed to full board.
- As per the actions documented on the SAE Assessment form by the IEC Chairperson, the IEC Secretariat will follow instructions as per SOP 17/01 (Procedures for Conduct of Emergency Meeting) or SOP 16/01 (Full Board Meeting Procedures) or make copies of SAE report and along with SAE Assessment report form forward it to the IEC members delegated to review the SAE report by the Chairperson.

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5.2 During the IEC meeting

- The IEC Secretary informs all the members about the SAE, comments of other IEC members (if any), SAE updates that have occurred earlier at that site.
- After reading and reviewing the report, the Chairperson entertains discussion on the study and similar adverse experiences.
- If appropriate to the discussions, the Chairperson may call for a consensus on whether to:
  - *Request an amendment to the protocol or the consent form.*
  - *Request further information.*
  - *Terminate the study.*

  This decision is recorded by the Secretary in the SAE Assessment form.

5.3 After the meeting inform Investigator

- The IEC secretariat member drafts a formal letter to the Investigators to notify them of the action they should take according to the IEC decision.
  1. The IEC members may request for a Protocol amendment and clarify the change required in the Protocol. The IEC may also request in writing that the PI add additional risks to the consent/assent forms. Changes to the consent/assent must take into consideration both prospective subjects and subjects already enrolled in the study. If the change might affect the subject's decision to remain in the study, the subject/parents must be re-consented using the revised consent/assent forms. The revised consent/assent forms, protocol amendment must be forwarded to the IEC for approval promptly.
  2. The IEC may terminate research if the information gained during its review of the SAEs indicates that Clinical subjects in a research project are exposed to unexpected serious harm. When such action occurs, the IEC will provide a Project termination letter to the investigator and will forward a copy to the Regulatory authorities, Sponsor, CRO and the trial site MS/Dean/Director.
  3. The IEC decision can be to request further information regarding the SAE. During this period the trial can continue with additional measures to be taken by the PI to ensure patient safety or the trial be suspended by the IEC till this additional information is reviewed.
  4. In addition the PI will be requested to forward follow-up reports of the SAE to the IEC.
- The Chairperson will sign and date the letter.
- The Administrative Officer will send the letter and record the delivery date and record the SAE in the Independent Ethics Committee SAE database.

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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 Clinical in order to verify their potential effects and safety for Clinical 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** - Report if the patient's death is suspected as being a direct outcome of the adverse event. **Life-Threatening** - 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) - 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 - 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 - Report if there are suspicions that exposure to a medical product prior to conception or 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 – 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).

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7. References

1. World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, (Geneva 2000)- *www.who.int/tdr/publications/publications/* (lastaccessed 24 March 2008).
2. International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996 - *http://www.ich.org/LOB/media/MEDIA482.pdf* (last accessed 24 March 2008)
3. Nationwide Children's Hospital, Standard Operating Procedure: SAE Reporting and Review – http://etrac.ccri.net/CRI/Doc/0/2137HUSRMVKKFBHAT542EHDME8/011%20Adverse%20Event.pdf (last accessed 16 July 2008)

8. Annex

ANNEX 1	AF/01/01-SOP14/01	Serious Adverse Event Report Assessment Form

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Annex 1
AF/01/01-SOP14/01

Serious Adverse Event Report Assessment Form

Principal Investigator:……..

Study Title:……. Protocol No.:

Name of the study medicine/device……..……

Sponsor:……

Report Date :……
F initial F follow-up
Onset date:……
Date of first use:
……..

Subject's initial/number:	Age:	F Male F Female
Subject's history:	Laboratory findings:	
SAE:	Treatment: Outcome: F resolved F on-going	
Seriousness: F Death F Life threatening F Hospitalization – { initial { prolong F Disability / Incapacity F Congenital Anomaly F Other……	Relation to { Drug { Device { study F Not related F Possibly F Probably F Definitely related F Unknown	

Comments of the Secretary:

_____
_____
_____

Secretary sign & date: _____

Action taken by the Chairperson:

- To be discussed in Emergency meeting

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- To be discussed in scheduled Full Board meeting
- Reviewed by additional IEC members
  Name of members: _____

Comments of Chairperson:

_____
_____
_____

Chairperson sign & date: _____

Response of IEC at meeting held on: …….

- Changes to the protocol recommended? F No F Yes
  Recommendations:
  _____
  _____
- Changes to the informed consent form recommended? F No F Yes
  Recommendations:
  _____
  _____
- Terminate the project
- Request for additional information
  Recommendations:
  _____
  _____
- Till additional information is received trial will be
  F continued F suspended

_____
IEC, Chairperson sign & date