Guidance for Adverse Event Report

from

“Achieving Guidance in Clinical Trial safety information among stakeholder”

Forum for Ethical Review Committee in Thailand (FERCIT)

June, 2011

Preface

Practice in reporting adverse events (AE) varies among institutions, especially timeline and what to report: whether it is external or internal, serious or not serious, unexpected or expected events. In addition the amount of external AE reports is enormous, which is troublesome in terms of required human resources and document storage. Moreover, how to make the reports meaningful to IRB is an important question for effective protection of human subjects. These concerns led FERCIT, in collaboration with PReMA, to harmonize AE reporting requirements across research institutes in Thailand.

Harmonization is based on European Union guidance, OHRP guidance and ICH GCP. A draft guidance was proposed in the meeting organized by FERCIT in collaboration with Pharmaceutical Research and Manufacturers Association (PReMA), National Research Council of Thailand, Thai Food and Drug Administration, Clinical Research Collaboration Network (CRCN), and The Research Affairs, Faculty of Medicine, Chulalongkorn University, at Faculty of Medicine, Chulalongkorn University on March 21, 2011. The consensus was made on the guidance and brought to documentation and distribution among institutes, IRBs, sponsors and stakeholders in Thailand. The following provides guidance on which types of adverse events are required to be reported to the IRB and indicates the timeline for reporting.

Descriptions and Definitions

Adverse Events

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, that occurs during the subject's participation in the research, whether or not it is considered related to the subject's participation in the research. Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasions, they can occur in the context of social and behavioral research.

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug 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

IDMC (Independent Data Monitoring Committee) or DSMB (Data and Safety Monitoring Board) or Monitoring Committee or DMC (Data Monitoring Committee)

An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Unexpected Adverse Drug 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 medicinal product or package insert/summary of product characteristics for an approved product).

Local and Non-Local

In the context of multi-center research projects, adverse events are characterized as either Local or Non-Local adverse events. When investigators are participating in a multi-center studies, Local adverse events are those experienced by subjects enrolled by the investigator(s) under their IRB jurisdiction; whereas Non-Local adverse events are those experienced by subjects enrolled by investigators at another institution(s) engaged in the same research study.

Serious Adverse Event (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.
- is a medically important event or reaction.

SUSARs : Suspected Unexpected Serious Adverse Reactions

Unanticipated Problems

Unanticipated problems, in general, include those events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

Unexpected Adverse Event

An unexpected adverse event is an event not previously known or anticipated to result from:

(a) the interventions and interactions used in the research;
(b) the collection of identifiable private information under the research;
(c) an underlying disease, disorder, or condition of the human subject; and/or
(d) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Guidance

1. For reporting Local SAE
    a. Local serious adverse events which are fatal or life threatening:
        i. Principal investigator must report to IRB immediately, no later than 24 hours after the PI becomes aware of the event.
        ii. The document format is a photocopy of completed SAE report form according to provision of the sponsor.
    b. Local serious adverse events which is non-fatal or non life-threatening
        i. Principal investigator must report to IRB immediately, no later than 7 calendar days after the PI becomes aware of the event.
        ii. Same as a(ii)
2. For reporting Local SUSARs
    a. Local SUSARs which are fatal or life threatening:
        i. Sponsor must report to IRB as soon as possible using CIOMS form, no later than 7 calendar days after the sponsor becomes aware of the event.
        ii. If the initial report is incomplete, the sponsor must report to IRB relevant follow-up information and complete report as soon as possible, within additional 8 calendar days.
        iii. Sponsor must report any significant new information as a follow up report within 15 calendar days
    b. Local SUSARs which are non-fatal or non life-threatening:
        i. Sponsor must report to IRB as soon as possible using CIOMS form, no later than 15 calendar days after the sponsor becomes aware of the event.
        ii. Further relevant follow-up information should be given as soon as possible.

3. For reporting any significant changes on risks to subjects and recommendation of IDMC
    a. Sponsor must report any changes which result in increasing risk to subjects and any new issues that may affect adversely the safety of the subjects or the conduct of the trial to IRB as soon as possible, but no later than 15 calendar days after the change occurs.
    b. Sponsor must report any recommendation from IDMC as soon as possible, but no later than 15 calendar days after receiving the recommendation.
4. For reporting any Non-Local Serious Adverse Reactions
    a. Sponsor must report non-local serious adverse reaction including SUSARs to IRB at least every 6 months as a line listing (see Appendix 4) accompanied by a brief report highlighting the main point of concern.
    b. Other adverse reactions that may increase risks to subjects, the sponsor must report to IRB as soon as possible but no later than 15 calendar days. (see Appendix 4).
    c. Other type of reports ,the sponsor must report to IRB at least every year or periodically or on request as a summarized form or a line listing (see Appendix 4).

References

ICH. E6 Good Clinical Practice Guideline, May 1996.

ICH E2A Guideline for Clinical Safety Data Management : Definitions and Standards for Expedited Reporting, October 1994.

European Commission. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006.

OHRP. Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007.

US FDA. Guidance for clinical investigators, sponsors, and IRBs. Adverse event reporting to IRBs- improving human subject protection. January 2009.

Appendix 1

Table 1. Guidance for reporting LOCAL Serious adverse events

What must be reported	Reporting time frames	How to report	Who report to whom
Fatal/ Life threatening SAE	Immediately , **no later than 24 hours** after PI acknowledgement	The same form reported to sponsor	1.PI to Sponsor 2.PI to IRB
Non-fatal / Non-life threatening SAE	Immediately , **no later than 7 calendar days** after PI acknowledgement	The same form reported to sponsor	1.PI to Sponsor 2.PI to IRB

Appendix 2

Table 2. Guidance for reporting LOCAL SUSARs

What must be reported	Reporting time frames	How to report	Who report to whom
Fatal/ Life threatening SUSARs	• Report as soon as possible but no later than **7 calendar days** after the sponsor has first knowledge • Relevant follow-up information and a report completed as soon as possible, within an **additional 8 calendar days** (if initial report is incomplete) • Significant new information should be reported as a follow-up report **within 15 calendar days**	CIOMS form	Sponsor to IRB
Non-fatal / Non life threatening SUSARs	• as soon as possible but no later than **15 calendar days** after the sponsor has first knowledge • Further relevant follow-up information should be given **as soon as possible**	CIOMS form	Sponsor to IRB

Appendix 3

Table 3. Guidance for reporting any significant changes on risk to subjects or recommendation of independent data monitoring committee (IDMC)

What must be reported	Reporting time frames	How to report	Who report to whom
Any changes increasing the risk to subjects and any new issues that may affect adversely the safety of the subjects or the conduct of the trial	as soon as possible, but no later than 15 days.	Sponsor Form	Sponsor to IRB
Recommendation of Data Monitoring Committee	as soon as possible, but no later than 15 days.	Sponsor Form	Sponsor to IRB

Appendix 4

Table 4. Guidance for reporting NON-LOCAL adverse events

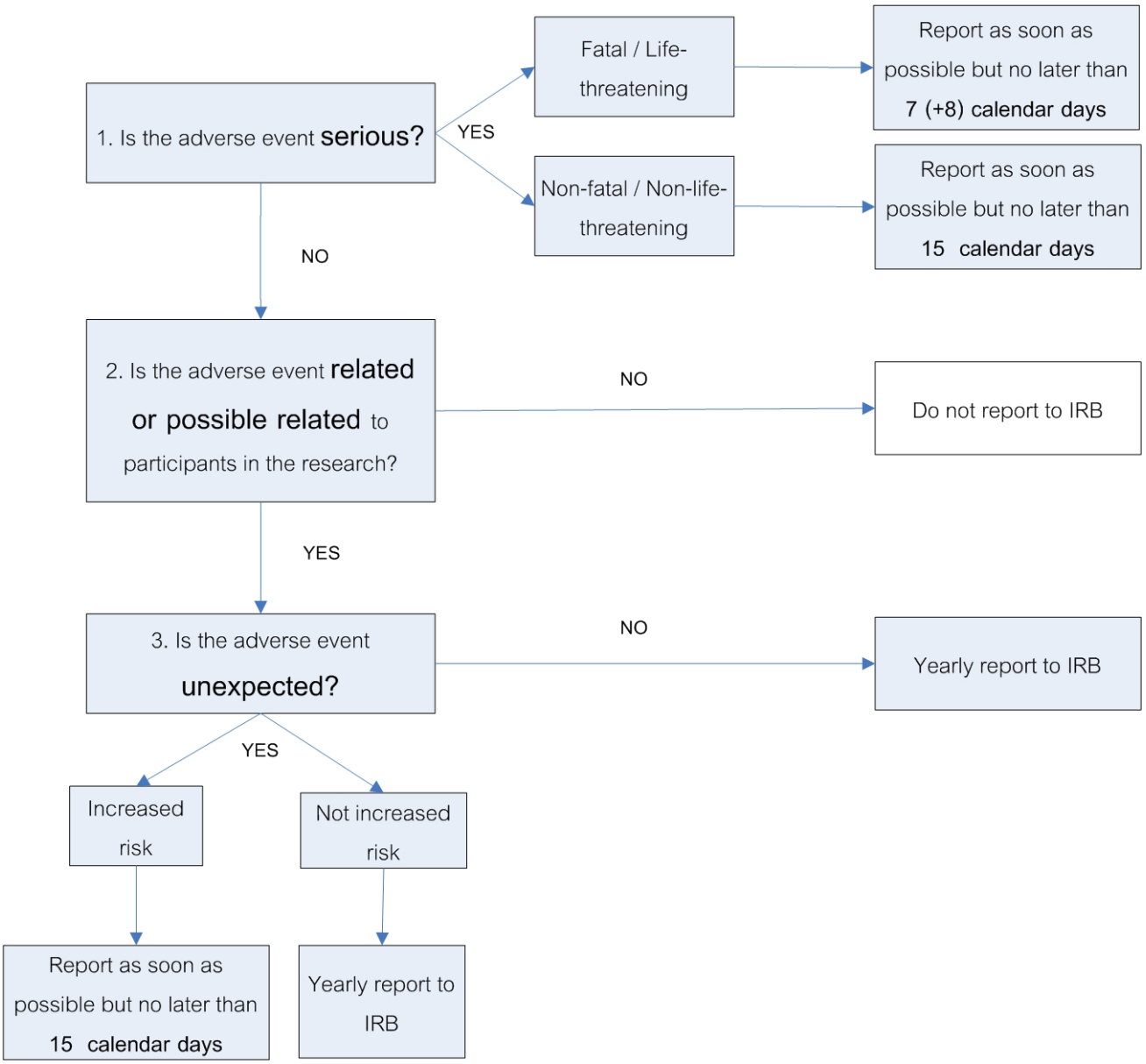
What must be reported	Reporting time frames	How to report	Who report to whom
All SUSARs from other sites in Thailand and from foreign countries (where applicable)	Periodically reported at least **every 6 months**	Line listing form (sponsor form) accompanied by a brief report by the sponsor highlighting the main points of concern	Sponsor to IRB
Other adverse reactions that may increase risks to subjects	As soon as possible but no later than 15 calendar days.	Line listing form (sponsor form)	Sponsor to IRB
Other type of reports	Yearly	Line listing form (sponsor form)	Sponsor to IRB

Appendix 5

Line listing or summarized form from sponsor must have minimal information as followings:

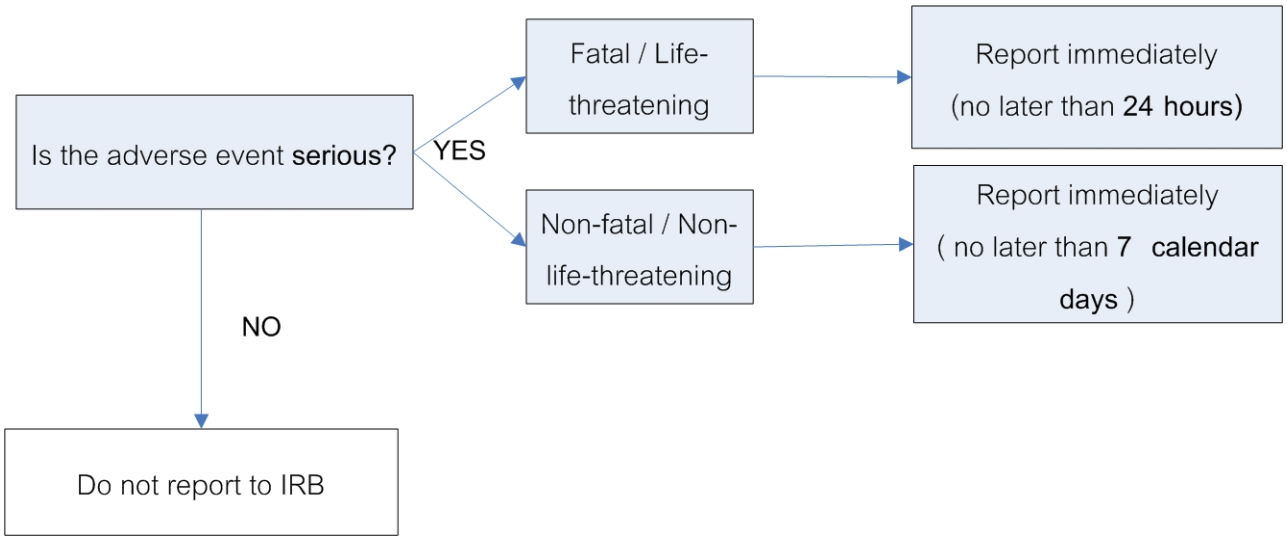
A. clinical trial identification,
B. study subjects identification number in the trial,
C. case reference number (Case-ID-Number)
D. country in which case occurred,
E. age and sex of trial subject,
F. daily dose of investigational medicinal product
G. date of onset of the adverse reaction (if not available, best estimate of time to onset from therapy initiation)
H. dates of treatment. (if not available, best estimate of treatment duration),
I. adverse reaction (description of reaction as reported, and when necessary as interpreted by the sponsor)
J. patient's outcome (e.g. resolved, fatal, improved, sequelae, unknown); using the worst of the different outcomes for multiple reactions,
K. comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge / rechallenge results if available),
L. unblinding results in the case of unblinded SUSARs expectedness

Appendix 6



Work flow for sponsor to report LOCAL adverse event to IRB

Appendix 7



Work flow for investigator to report LOCAL adverse event to IRB

คณะทำงานจัดทำ แนวทางการปฏิบัติการรายงานเหตุการณ์ไม่พึงประสงค์

1.พญ.ขวัญชนก ยิ้มแต้

2.รศ.นพ. วินัย รัตนสุวรรณ

3.นพ.ประวิช ตัญญสิทธิสุนทร

4.ภก.ปรีชา แช่มปรีดา

5.พล.ต.หญิง รศ.พญ. อาภรณ์ภิรมย์ เกตุปัญญา

6.พ.อ. รศ. นพ. สุธี พานิชกุล

7.รศ.พญ.แสงแข ชำนาญวนกิจ

8.พ.อ.สหพล อนันต์นำเจริญ

9.พญ. สุมนมาลย์ มนัสศิริวิทยา

10.รศ.ดร.นิมิตร มรกต

11.พญ.สุเนตรา ชินะผา