



FINAL DOCUMENT

Global Harmonization Task Force

Title: Reportable Events During Pre-Market Clinical Investigations

Authoring Group: Study Group 5 of the Global Harmonization Task Force

Endorsed by: The Global Harmonization Task Force

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A handwritten signature in black ink, which appears to read 'Kazunari Asanuma', is written over a horizontal line.

Dr. Kazunari Asanuma, GHTF Chair

This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

The document is intended to provide non-binding guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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Preface

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1 Introduction

The objective of adverse event reporting during pre-market clinical investigations is to improve protection of the health and safety of patients, users and others by identifying safety issues early in the human use of medical devices so that these can be addressed. These safety issues can therefore be addressed as soon as possible by modification of the device, revision of the instructions for use, modification of the clinical investigation plan or withdrawal of the device from use.

It should be recognized that the requirements for such adverse event reporting should necessarily be more stringent than post-market vigilance requirements because of the fact that such medical devices may not have been previously used in humans and are therefore more likely to be associated with unforeseen physiological or pathological effects.

This document represents a global model, which provides guidance on the types of adverse events associated with clinical investigations of investigational devices that should be reported by sponsors to National Competent Authorities (NCAs). It was drafted as a collaborative effort using the combined expertise of GHTF Study Groups 2 and 5. It incorporates and supplements existing regulatory requirements existing in the participating member countries and international standards specifying the planning, conducting and managing of clinical investigations. However, this guidance may not reflect all current regulatory requirements, because the present reporting criteria of the participating countries, while similarly intentioned are not identical. This document therefore provides a model towards which existing systems should move. The principles laid down in this document should be considered in the development or amendment of regulatory systems in the participating countries or other countries.

2 Scope

This guidance aims to set out a uniform system of Adverse Event Reporting globally and is applicable to pre-market clinical investigations undertaken by, or on behalf of, the manufacturer to obtain regulatory approval for placing the device on the market and/or pre-market investigations that require authorization by the relevant regulatory authority prior to initiation.

This guidance document concerns only adverse events affecting human research subjects enrolled in the pre-market phase. When the investigational medical device used in a clinical study is approved in a particular jurisdiction, the NCA of that country shall apply the post-market reporting requirements. (GHTF/SG2/N54).

This guidance is supported by the requirements provided in ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practices) and definitions have been harmonized to ISO 14155 where possible.

This document does not deal with reporting by users of investigational devices. Users should report in accordance with ISO 14155 and any local requirements.

3 References

GHTF final documents

SG1/N29:2005	<u>Information Document Concerning the Definition of the Term “Medical Device”</u>
SG1/N55:2009	<u>Definition of the Terms Manufacturer, Authorized Representative, Distributor and Importer</u>
SG2/N54:2006	<u>Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices</u>
SG5/N2:2007	<u>Clinical Evaluation</u>
SG5/N3:2010	<u>Clinical Investigations</u>

International standards

ISO 14155:2011	<u>Clinical investigation of medical devices for human subjects – Good clinical practices</u>
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4 Definitions

ADVERSE DEVICE EFFECT: (ISO 14155) (ADE)

An adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

ADVERSE EVENT: (ISO 14155) (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this is restricted to events related to investigational medical devices.

BLINDING/MASKING: (ISO 14155)

Procedure in which one or more parties to the clinical investigation are kept unaware of the treatment assignment(s).

NOTE: Single-blinding usually refers to the subject(s) being unaware of the treatment assignment(s). Double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, centralized assessors being unaware of the treatment assignment(s)

CLINICAL INVESTIGATION PLAN (CIP): (ISO 14155)

Document that states the rationale, objective, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

COMPARATOR: (ISO 14155)

Medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a clinical investigation.

DEVICE DEFICIENCY: (ISO 14155)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunctions, misuse or use errors and inadequate labeling

INVESTIGATIONAL MEDICAL DEVICE: (ISO 14155)

Medical device being assessed for safety or performance in a clinical investigation

NOTE 1: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

NOTE 2: In this standard the terms 'investigational medical device' and 'investigational device' are used interchangeably.

INVESTIGATOR: (ISO 14155)

Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical investigation-related procedures or to make important clinical investigation-related decisions.

NOTE 1: An individual member of the investigation site team can also be called ‘sub-investigator’ or ‘co-investigator’.

PRINCIPAL INVESTIGATOR: (ISO 14155)

Qualified person responsible for the conduct of the clinical investigation at an investigation site

NOTE 1: If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is the person responsible for leading the team.

NOTE 2: Whether this is the responsibility of an individual or an institution responsibility can depend on national regulations.

SERIOUS ADVERSE EVENT: (ISO 14155 and GHTF/SG5/N2)

Adverse event that:

- a) led to a death;
- b) led to a serious deterioration in the health of the subject that either
 - 1) resulted in a life-threatening illness or injury, or
 - 2) resulted in a permanent impairment of a body structure or a body function, or
 - 3) required in-patient hospitalization or prolongation of existing hospitalization, or
 - 4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function;
- c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health is not considered to be a serious adverse event.

SERIOUS HEALTH THREAT: (adapted from GHTF/SG2/N54:2006)

Any event type, which results in imminent risk to the study population of death, serious injury, or serious illness that requires prompt remedial action.

SPONSOR: (ISO 14155)

Individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation.

NOTE: When an investigator initiates, implements and takes full responsibility for the clinical investigation, the investigator also assumes the role of the sponsor and is identified as the sponsor-investigator.

NOTE: *(added for the purpose of this document)* The sponsor may be the manufacturer, may be designated by the manufacturer, or may be designated by the regulatory authority.

SUBJECT: (ISO 14155)

Individual who participates in a clinical investigation

NOTE: A subject can be either a healthy volunteer or a patient.

**UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT: (ISO 14155)
(USADE)**

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

NOTE: *(added for the purpose of this document)* This includes unanticipated procedure-related serious adverse events; that is, serious adverse events occurring during the study procedure that are unrelated to any malfunction or misuse of the investigational medical device.

USE ERROR: (ISO 14155)

An act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1: Use error includes slips, lapses, and mistakes.

NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

5 Reportable Events

Events that must be reported by the sponsor are:

- All **serious** adverse events affecting the patient, user or a third party, including serious health threats, regardless of cause or;
- Device deficiencies that might have lead to (a) serious adverse event(s) if:
 - suitable action had not been taken;
 - intervention had not been made; or
 - if circumstances had been less fortunate.

In cases where the need to report may be in doubt, the sponsor should make reasonable efforts to obtain additional information. However as a general principle, there should be a pre-disposition to report rather than not to report. In the case where opinions on whether an incident represents a serious adverse event, or the causes of an adverse event, differ between the Investigator and the Sponsor, both opinions should be reported.

Note: In assessing whether events represent a serious health threat, discussion should be undertaken with the NCA and consideration should be given to the risk analysis described in the Clinical Investigation Plan.

6 To Whom to Report

All reportable adverse events, as described in Section 5, must be reported to all the NCAs responsible for the jurisdictions where the clinical investigation is conducted, according to applicable requirements in each jurisdiction. NCAs should provide a contact point to sponsors for reporting.

Note: Reporting to Ethics Committees and all Principal Investigators is also necessary (see ISO 14155 Section 8.2.5).

7 Timing for Reporting

Upon becoming aware of events meeting the reportability criteria defined in section 5, above, the following guidelines are to be used to establish the timeline under which events of various levels of severity are to be reported. Note that for the purpose of this document, the date of awareness refers to the first date on which any employee of the Sponsor, authorized representative or Contract Research Organisation for the investigation, becomes aware of a serious adverse event.

- 7.1 Such serious adverse events which have been determined to represent a **serious health threat** to the study population must be reported by the sponsor to the NCAs of all jurisdictions in which centres participating in the investigation are located within **48 hours** following the determination that the serious health threat exists.
- 7.2 To be reported as soon as possible, but not later than **10 elapsed calendar days following the date of awareness of the event:**

- Unanticipated Serious Adverse Device Effects
- Serious adverse events, other than unanticipated serious adverse device effects, resulting in death, or resulting in a serious deterioration in the health of the subject that either:
 - resulted in a life-threatening illness or injury
 - resulted in a permanent impairment of a body structure or a body function
- Serious adverse events, other than unanticipated serious adverse device effects, that have led to fetal distress, fetal death or a congenital abnormality or birth defect

7.3 To be reported as soon as possible, but not later than **30 elapsed calendar days following the date of awareness of the event:**

- Serious adverse events, other than unanticipated serious adverse device effects, resulting in a serious deterioration in the health of the subject that either:
 - required in-patient hospitalization or prolongation of existing hospitalization
 - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- Any device deficiency that might have led to a serious adverse event if either:
 - suitable action had not been taken;
 - intervention had not been made; or
 - circumstances had been less fortunate.

If, after becoming aware of a potentially reportable adverse event, there is uncertainty about whether the event is reportable, the sponsor must submit a report within the timeframe required for that type of event.

8 Content of Reports

Notification of reportable events should include the following information:

(Mandatory information highlighted in yellow, “yes/no” indicates whether that information is mandatory for that type of report, blanks indicate information that should be provided if available but may not be mandatory)

Section	Type of Information	Initial Rep.	Final Rep	Comments / Field content
Administrative Information				

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Section	Type of Information	Initial Rep.	Final Rep	Comments / Field content
	Report type	Yes	Yes	(Initial, Follow-Up, Final, or combined Initial/Final)
	Title of the clinical investigation	Yes	Yes	
	Sponsor's clinical investigation plan identifier	Yes	Yes	
	All NCAs' clinical investigation identifiers	Yes	Yes	
	Report reference number	Yes	Yes	
	List of NCAs this report is being sent to	Yes	Yes	
	NCA event reference number (if applicable)	Yes	Yes	
	Contact details of sponsor	Yes	Yes	Complete address incl. contact point
	Date of report	Yes	Yes	
	Manufacturer Information	Yes	Yes	
	Expected date of next report if this is not a final report	Yes	No	
Device Information				
	Name of the device/ model number	Yes	Yes	
	Serial number/lot number (if applicable)			
	Accessories (if applicable)			
	Number of devices used by the investigator			
	Number of patients enrolled in the site	Yes	Yes	
	Number of patients involved in this incident – if applicable-			
	Number of patients exposed to this device – if reusable device-			
	Number of patients treated in the study			
Event information / serious health threat information				

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Section	Type of Information	Initial Rep.	Final Rep	Comments / Field content
	Center/institution/investigator	Yes	Yes	
	Date the adverse event/events/device deficiency occurred	Yes	Yes	
	Date of awareness by investigator			
	Date of awareness by sponsor/Date of determination of existence of serious health threat by sponsor	Yes	Yes	
	Information on the person affected			Patient, user, other person
	Investigation arm for comparative investigations (if known)	Yes	Yes	
	Description of the event/device deficiency	Yes	Yes	
	Outcome of event	Yes	Yes	Select from picklist according to ISO 14155 SAE definition (e.g. "serious deterioration – perm. impairment")
	Anticipated/Unanticipated	Yes	Yes	Select from picklist of 2
	Relatedness of Event according to sponsor	Yes	Yes	Select from picklist of 3 (device related, procedure related, other; each scaled 1-4 based on relative certainty)*
	Relatedness of Event according to Investigator	Yes	Yes	Select from picklist of 3 (device related, procedure related, other; each scaled 1-4 based on relative certainty)*
	Patient ID code (if applicable)	Yes	Yes	
	Year of birth (if known)	Yes	No	Only if affected person is the patient
	Gender (if known)			
	Weight (if known)			

* Relatedness: 1 = unrelated, 2 = possibly related, 3 = probably related, 4 = definitely related

Section	Type of Information	Initial Rep.	Final Rep	Comments / Field content
	Action taken by investigator (if applicable)			
	Initial action by sponsor (if applicable)			
For final report				
	Final assessment including relatedness and rationale	No	Yes	Includes all investigations done and their results – must include both opinions of sponsor and investigator if these remain different
	Corrective action taken (or planned?) Including timeline			
	Frequency of similar events observed to date in the treatment group.	Yes	Yes	
	Frequency of similar events in comparator groups (in the control arm if applicable, in the historic control as mentioned in the protocol, from other sources used in the risk analysis).	Yes	Yes	
	Opinion of the Sponsor on the acceptability of the SAE and of its current frequency in this clinical trial with rationale.		Yes	
	Patient/Subject Outcome		Yes	
	Actions to be taken to the clinical investigation		Yes	e.g. suspension, early termination, other, none

9 Special Conditions

- i. *Medicinal product/device, biologic product/device combinations*: adverse events/device deficiencies for combination products that involve drugs or biologics acting ancillary to an investigational medical device should be reported in line with the principles set out in this document

- ii. *Controlled clinical investigations*: where an unblinded controlled clinical investigation is being carried out using a marketed medical device as the control, adverse events/device deficiencies of the unmarketed device should be carried out in line with the principles set out in this document. The adverse events involving the marketed device should be reported to the NCA in line with GHTF/SG2/N54 “Global Guidance for Adverse Event Reporting for Medical Devices”.

- iii. *Double blinded controlled clinical investigations*: where a double blinded controlled clinical investigation is being carried out using a marketed medical device as the control, all adverse events/device deficiencies should be reported to the NCA in line with the principles set out in this document. The data should normally not be unblinded, unless requested by the NCA.

- iv. *Implantable medical devices*: Only SAEs that are device deficiencies occurring with devices implanted in a patient in a clinical investigation setting, where the investigation has since closed, should be reported according to the principles outlined above.

FIGURE I

