



Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC AND 93/42/EEC



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GUIDELINES ON MEDICAL DEVICES

**CLINICAL INVESTIGATIONS:
SERIOUS ADVERSE EVENT REPORTING
UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC.**

The present guidelines are part of a set of guidelines relating to questions of application of EU-Directives on MEDICAL DEVICES. They are legally not binding. The guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interested parties in the medical devices sector.

These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC.

1. OBJECTIVE

This guidance defines Serious Adverse Event (SAE) reporting modalities and includes a summary tabulation reporting format. Its objective is to contribute to the notification of SAEs to all concerned National Competent Authorities (NCAs) in the context of clinical investigations in line with the requirements of Annex 7 of Directive 90/385/EEC and Annex X of Directive 93/42/EEC, as amended by Directive 2007/47/EC.^{1 2}

According to annex 7 of Directive 90/385/EEC and to annex X of Directive 93/42/EEC: ***"All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed."***

2. SCOPE

The reporting modalities and format set out in this guidance apply to pre-market clinical investigations conducted with:^{3 4 5}

- a. Non-CE marked devices,
- b. CE marked devices used outside the intended use(s) covered by the CE marking.

The tabular format featured in the Appendix needs to be updated for each reportable event or for new findings/updates to already reported events. It shall be transmitted to all NCAs where the clinical investigation is being performed.

3. DEFINITIONS (from ISO/FDIS 14155)

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional misuse.

¹ A template for individual reporting of SAEs is under preparation to harmonize individual SAE forms in case NCAs require individual reporting for the SAEs occurring within their jurisdictions. Further revisions of these template documents may become necessary in line with the forthcoming corresponding GHTEF-Guidance.

² For the purpose of this guidance, "NCAs" encompasses the National Competent Authorities of the EU, the EEA and of Switzerland and Turkey.

³ A specific guidance on Post Market Clinical Follow-Up Studies is in preparation.

⁴ This includes pre-market clinical investigations: which started prior to 21 March 2010 and are continued after that date. [Note: reporting of SAE as covered in this guidance only started on 21 March 2010 with the implementation of Directive 2007/47/EC and is not retrospective to SAEs that occurred prior to 21 March 2010].

For pre-market clinical investigations involving CE marked comparator devices, SAEs occurring in or to subjects that are in the comparator arm of an investigation shall also be reported in accordance with these guidelines.

⁵ Where the right to bear the CE marking has been obtained before the end of the clinical investigation, the SAE reporting continues until completion of the investigation, according to the clinical investigation plan.

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any 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 includes events related to the investigational device or the comparator.

NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).

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

Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Investigational medical device

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

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

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)

Adverse event that:

- a) led to a death,
- b) led to a serious deterioration in health 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 fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if: a) suitable action had not been taken, or b) intervention had not been made, or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

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: Anticipated—an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

4. REPORTABLE EVENTS UNDER ANNEX 7 AND ANNEX X OF DIRECTIVES 90/385/EEC AND 93/42/EEC RESPECTIVELY.

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of the above mentioned Directives:

- any SAE,
- any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate,
- new findings/updates in relation to already reported events.

Reportable events occurring in third countries, in which a clinical investigation is performed under the same clinical investigation plan, have to be reported in accordance with this guidance.⁶

5. REPORT BY WHOM

Reportable events have to be reported by the sponsor of the clinical investigation, which could be the manufacturer (MFR), the authorized representative (AR) or another person or entity.^{7 8}

6. REPORT TO WHOM

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the Appendix.^{9 10}

A list of clinical investigation contact points within the NCAs is published at the Commission's homepage.

7. REPORTING TIMELINES

7.1 Report by sponsor to NCAs.

The sponsor must report to the NCAs where the clinical investigation has commenced:

- a SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately,

⁶ Countries other than Switzerland, Turkey and those belonging to the EU and the EEA.

⁷ Note: Member States may also require separate reporting by clinical investigators/medical professionals.

⁸ Note: SAEs concerning CE marked devices (e.g. comparators) which meet the vigilance reporting criteria may also need to be handled under the post-market surveillance/vigilance system.

⁹ For the purpose of this guidance, an investigation is considered to have commenced in an individual Member State when the sponsor is authorized to start the investigation in accordance with the notification procedures in that Member State.

¹⁰ Note: Member States may also require separate reporting to the Ethics Committee(s) and/or separate reporting to the other clinical investigators/study centers involved in the clinical investigation.

but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.¹¹

- any other reportable events as described in section 4 or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

7.2 Report by the investigator to the sponsor

The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events will be provided by the investigator to the sponsor in acceptable timely conditions, but not later than within 3 calendar days after the occurrence of the event.

In some cases, a different periodicity or different modalities may be agreed by the participating NCAs according to the investigational design and to the pathology under clinical investigation. This would allow adequate provision for clinical investigations (e.g. palliative oncology...) in which SAE frequency is expected to be high due to progression of the disease. This needs to be agreed between the sponsor and relevant NCAs.¹²

8. REPORTING FORM

The reporting form template for the summary SAE tabulation is given in the Appendix of this document.

The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA.

The sponsor shall identify the new/updated information in the status column of the tabular form featured in the Appendix as:

- a = added = new reportable event;
- m = modified = new finding/update to an already reported event;
- u = unchanged.

Changes in a line should be highlighted in bold and/or color in the respective column.

The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan. English is the recommended language for the reporting form. The report should be sent by email preferably in Excel or equivalent format to the participating NCAs.

REFERENCES:

1. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, last amended by Directive 2007/47/EC.

¹¹ This includes:

- events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, e.g. human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD). These concerns may be identified by either the NCA or the MFR.
- the possibility of multiple deaths occurring at short intervals.

2. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, last amended by Directive 2007/47/EC.
3. ISO/FDIS 14155:2010 Clinical investigation of medical devices for human subjects – Good clinical practice.

APPENDIX – REPORTING FORM

MEDDEV 2.7/3 SAE Report Table- Y1										MEDDEV 2.7/3 SAE Report Table- Y1					
EUDAMED - ID:															
Title of Clinical Investigation:															
CIP Number:															
Contact person (Name, Address, E-Mail, Telephone Number)										Device type:					
MS-NCA Reference Numbers for all participating Countries:										Reference Member State:					
No. of Patients enrolled to date (date of report):										No. of Investigational Devices used to date:					
Date of Report:															
Status: a, m, u	Date Sponsor received Report of SAE	Country	Study Center	Patient ID Code	Date of Procedure/ First Use	Date of Event Onset	Event: Organ System	Description of Event	action/ treatment/ patient outcome	Assessment of Relationship to Procedure Yes No Possibly	Assesment of Relationship to Investigational Device: Yes No	Unanticipated SAE Yes/No	Treatment Arm: Investigational Device/ Control Group/ Blinded/ n.a.	Event Status: Resolved/ Resolved with Sequelae/ Ongoing/Des	Date of Event Resolutio n
<p>Note: Submission of this report does not, in itself, represent a conclusion by the sponsor or the competent authority that the content of this report is complete or that the device(s) listed failed in any manner and/or that the device(s) caused or contributed to the alleged death or deterioration in the state of the health of any person.</p>															