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GUIDELINES ON MEDICAL DEVICES

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

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-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 interest 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.

**MEDICAL DEVICES DIRECTIVES
CLINICAL INVESTIGATION**

**GUIDELINES FOR ADVERSE EVENT REPORTING
UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC**

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1. INTRODUCTION

This guidance defines Serious Adverse Event (SAE) reporting modalities and includes a summary tabulation reporting format. Individual reporting should be performed in accordance with national requirements. The objective of this guidance is to contribute to the notification of SAEs to all concerned National Competent Authorities (NCAs) ¹ 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. 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 ² clinical investigations ³⁻⁴ conducted with:

- 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.

¹ For the purpose of this guidance, " NCAs" encompasses the National Competent Authorities of the EU, the EEA and of Switzerland and Turkey.

² A specific guidance on Post Market Clinical Follow-Up Studies is available as MEDDEV 2.12/2 rev. 2: http://ec.europa.eu/health/medical-devices/files/meddev/2_12_2_ol_en.pdf .

³ 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.

⁴ 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.

3. DEFINITIONS (in line with EN ISO 14155)

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.

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 definition includes events related to the investigational device or the comparator.

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

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

Serious Adverse Event (SAE)

Adverse event that:

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

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

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 abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of 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 SADE (ASADE): 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 Directives⁵ :

- any SAE,
- any Device Deficiency that might have led to a SAE if:
 - a) suitable action had not been taken or

⁵ The definition of the term SAE has changed over time. A distinction between SAE and device deficiencies was introduced with the adoption of standard ISO 14155 in 2011. While this MEDDEV document uses terminology according to the international standard, please be aware that the European medical device directives pre-date the split in the terminology. In order to fulfil reporting requirements under the European medical device directives, device deficiencies as well as SAE need to be documented during the course of the clinical investigation and reported to competent authorities as described in this chapter.

- 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 Countries⁶ in which a clinical investigation is performed under the same clinical investigation plan have to be reported to the NCA(s) in accordance with this guidance. This includes events occurring in third Countries after European sites have closed.

5. REPORT BY WHOM.

Reportable events have to be reported by the sponsor of the clinical investigation, which could be the manufacturer, the authorized representative or another person or entity⁷⁻⁸.

6. REPORT TO WHOM.

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced⁹⁻¹⁰ using the summary tabulation featured in the Appendix.

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.

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.

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

- for all reportable events as described in section 4 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons ¹¹ or a new finding to it: immediately, 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.
- 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 as defined under chapter 4 will be provided by the investigator to the sponsor immediately, but not later than 3 calendar days after investigational site study personnel's awareness of the event.

In some cases, a different periodicity or different modalities ¹² 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.

8. CAUSALITY ASSESSMENT

The relationship between the use of the medical device ¹³ (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and

¹¹ This includes:

A) 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 manufacturer.

B) the possibility of multiple deaths occurring at short intervals.

¹² In line with Annex 7.2.3.5 of Directive 90/385/EEC and Annex X.2.3.5 of Directive 93/42/EEC

¹³ Intended as both medical device investigated in the investigation and comparator.

categorized.¹⁴ During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

For the purpose of harmonising reports, each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational¹⁵ medical device or procedures.

- 1) Not related: relationship to the device or procedures can be excluded when:
 - the event is not a known¹⁶ side effect of the product category the device belongs to or of similar devices and procedures;
 - the event has no temporal relationship with the use of the investigational device or the procedures;
 - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
 - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
 - the event involves a body-site or an organ not expected to be affected by the device or procedure;

¹⁴ Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events.

¹⁵ Investigational device: any device object of the clinical investigation, including the comparators.

¹⁶ When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.

- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
 - the event does not depend on a false result given by the investigational device used for diagnosis ¹⁷, when applicable;
 - harms to the subject are not clearly due to use error;
 - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- 2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- 3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- 4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
- 5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
 - the event has a temporal relationship with investigational device use/application or procedures;
 - the event involves a body-site or organ that
 - o the investigational device or procedures are applied to;

¹⁷ If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis ¹⁷, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of

the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

9. 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, if so requested by using the individual reporting form. 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 colour 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 in Excel to the participating NCAs, or an equivalent format which allows using the inserted filters.

Appendix – Summary Reporting Form

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.
2. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, last amended by Directive 2007/47/EC.
3. EN ISO 14155:2011 Clinical investigation of medical devices for human subjects – Good clinical practice