

Published: March 17, 2011

[Find more content on:](#)

- Regulations and Standards
- Regulations and Standards

## Serious Adverse Event Reporting During European Device Clinical Investigations

In December 2010, two new European guidelines on medical device clinical studies were published. One covers serious adverse event (SAE) reporting while the other provides guidance on when clinical investigations should be conducted, together with general principles to be observed when conducting such investigations. This article discusses the SAE reporting guideline, which is likely to have the greatest impact on European medical device clinical studies.

By: Dr. Maria E. Donawa

### **European clinical guidelines**

All manufacturers marketing or planning to market medical devices in Europe should be very familiar with the European clinical guidelines listed on the European Commission website. This is because an important objective of the recently revised Active Implantable Medical Devices Directive (90/385/EEC; AIMDD) and Medical Devices Directive (93/42/EEC; MDD) was to strengthen the requirements on ensuring that sufficient clinical data exist to support manufacturer claims of safety and performance. The revisions became mandatory on 21 March 2010. The clinical guidelines cover clinical evaluation,<sup>1</sup> how Competent Authorities should assess the clinical investigation during the clinical investigation notification process,<sup>2</sup> SAE reporting,<sup>3</sup> clinical investigations<sup>4</sup> and, for manufacturers of coronary stents, the clinical evaluation of those types of devices.<sup>5</sup> The clinical evaluation guideline, which was discussed in previous articles,<sup>6,7</sup> helps companies understand how to evaluate and document clinical data to meet the strengthened clinical evaluation requirements. Reviewing the guideline on how Competent Authorities should assess a clinical investigation during the notification process will help companies better understand the type of documentation that they are expected to submit during the notification process. Companies will also need to identify any specific national requirements with regard to this process, which are not covered by the directives or guidance document. The clinical investigation guideline discusses general principles when considering the need for a clinical investigation, general principles of clinical investigation design, and ethical considerations for clinical investigations. The guidance on clinical evaluation of coronary stents provides specific guidance for these devices on clinical study design, study population, duration of the study, endpoints and other important aspects of clinical data generation and evaluation. The SAE reporting guideline is discussed below.

### **European guidance on adverse event reporting**

Annex 7 of the AIMDD and Annex X of the MDD require that all SAEs be fully recorded and immediately notified to all Competent Authorities of EU member states in which the clinical investigation is being performed. The new SAE reporting guideline provides important advice on how to meet this new requirement, including the need to report certain types of device deficiencies. The six-page guideline consists of sections on its objective and scope, definitions, reportable events, person responsible for reporting, Competent Authorities to whom reports should be made, reporting

timelines, and a final section providing information on a reporting form template that is included in an Appendix.

Section 3 of the guideline contains definitions for *adverse device effect*, *adverse event*, *device deficiency*, and other terms, which were taken from ISO/FDIS 14155:2010, Clinical investigation of medical devices for human subjects — Good clinical practice. This standard has very recently been published in its final form, ISO 14155:2011. The standard is expected to become a European harmonised standard; however, it is not certain at the time of writing when this will occur.

Nonetheless, it is important to note that some minor differences exist between the definitions in ISO/FDIS 14155:2010, which were included in the SAE reporting guideline, and the published ISO 14155:2011 because of editorial changes made to the definitions before being included in the final standard. For this reason, companies should refer to ISO 14155:2011 for the official definitions.

Section 5 states that reportable events are to be reported by the sponsor of the clinical investigation, which can be the manufacturer, the authorised representative, or another person or entity. Section 6 states that reportable events are to be reported at the same time to all national Competent Authorities where the clinical investigation has commenced, using the summary tabulation provided in the Appendix. Section 7 contains important information on timelines. The guideline specifies that the sponsor is to report the following to the national Competent Authorities where the clinical investigation has commenced:

- an 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 related to the SAE: immediately, but not later than two calendar days after the sponsor becomes aware of a new reportable event or of new information in relation to an event already reported
- any other reportable events or a new finding/update to an already reported event: immediately, but not later than seven calendar days following the date that the sponsor becomes aware of the new reportable event or the new information related to an event already reported.

In addition, Section 7 states that the sponsor is to implement and maintain a system to ensure that the investigator will submit reportable events to the sponsor in “acceptable timely conditions,” but not later than three calendar days after the occurrence of the event. Readers should refer to the SAE reporting guideline for advice that suggests a different periodicity or different modalities as agreed with national Competent Authorities.



### **Important clarification on scope of the guidelines**

The new SAE reporting guideline applies to premarket clinical investigations, which initiated before 21 March 2010 and are continued after that date. In a note in Section 2, the guideline clarifies that reporting of SAEs as covered in the guideline began on 21 March 2010 with the implementation of Directive 2007/47/EC and is not retroactive to SAEs that occurred prior to 21 March 2010.

The same note indicates that for premarket clinical investigations involving CE marked comparator devices,

SAEs involving subjects that are in the comparator arm of an investigation are also to be reported in accordance with SAE reporting guidelines. Another important note clarifies that where the right to bear the CE marking has been obtained before the end of the clinical investigation, the SAE reporting is to continue until completion of the investigation, according to the clinical investigation plan.

### **Device deficiencies**

An important new definition—*device deficiency*—is included in the SAE reporting guideline. Clause 3.15 of ISO 14155:2011 defines a device deficiency as “inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.” An accompanying note states that “device deficiencies include malfunctions, use errors and inadequate labelling.”

This definition is important for two reasons: certain types of device deficiency are now considered reportable events according to the SAE reporting guideline and new responsibilities related to device deficiencies are specified in ISO 14155:2011.

Section 4 of the SAE reporting guideline lists the events that are considered reportable, which are:

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

Section 4 also states that reportable events occurring in third countries, which are considered to be countries other than Switzerland, Turkey and those belonging to the European Union and European Economic Area, must be reported by the sponsor of the clinical investigation. The guideline states that the sponsor could be the manufacturer, authorised representative or another person or entity.

In addition, Clause 9.8, Safety reporting, of ISO 14155:2011 specifies investigator responsibilities related to the documentation and reporting of device deficiencies, which are identified during a clinical investigation. Until the introduction of these responsibilities, no procedures for managing device deficiencies occurring during a clinical investigation, which were not part of adverse events, were included in the standard. Now, to conform with the standard, the principal investigator must take the following actions:

- record every adverse event and observed device deficiency, together with an assessment

- report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the clinical investigation plan (CIP)
- report to the ethics committee (EC) serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or CIP or by the EC
- report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
- supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

### **SAE summary report table**

Section 8 of the SAE reporting guideline provides information on a summary report table, which is intended to be updated and transmitted to participating national Competent Authorities each time a new reportable event or a new finding to an already reported event occurs. The table is provided in the Appendix of the guideline. In addition to the table, some national Competent Authorities may request individual reports or more detailed information. An electronic version of the table can be downloaded from the European Commission website, [http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/sae\\_r....](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/sae_r....) The guideline states that English is the recommended language for the reporting form, which should be sent by e-mail preferably in Excel or an equivalent format to the participating national Competent Authorities.

### **Clinical study procedures and training**

The SAE reporting guidance introduces the need to report certain types of device deficiencies, provides guidance on reporting and includes a new summary table for reporting SAEs. These guidelines are not legally binding; however, they reflect positions taken by representatives of interested parties in the medical device sector, including national competent authorities. Sponsors of medical device clinical investigations should update their clinical study procedures to implement the recommendations in the guideline and conduct adequate training of clinical and regulatory staff, investigators and clinical sites to ensure that the procedures will be uniformly understood and followed.

### **References**

1. Clinical Evaluation: A Guide for Manufacturers and Notified Bodies (MEDDEV 2.7.1 Rev.3, December 2009); [http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2\\_7\\_1rev\\_3\\_en.pdf](http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf).
2. Guide for Competent Authorities in making an assessment of clinical investigation; notification (MEDDEV 2.7/2, December 2008); [http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/guidelines2008\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/guidelines2008_en.pdf).
3. Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC and 93/42/EEC (MEDDEV 2.7/3, December 2010); [http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2\\_7\\_3\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf).

4. Guidelines on Clinical Investigations: a guide for manufacturers and notified bodies (MEDDEV 2.7/4, December 2010); [http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2\\_7\\_4\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_4_en.pdf).
5. Appendix 1: Clinical Evaluation of Coronary Stents (MEDDEV 2.7.1, December 2008); [http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/cetf\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/cetf_en.pdf).
6. M.E. Donawa, "Revised European Guidance on Clinical Evaluations, Part 1," *European Medical Device Technology*, 1, 3, 16–20 (March 2010), [www.emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-1](http://www.emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-1).
7. M.E. Donawa, "Revised European Guidance on Clinical Evaluations, Part 2," *European Medical Device Technology*, 1, 4, April 2010, [emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-2](http://www.emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-2).

**Published in *European Medical Device Technology*, March 2011, Volume 2, No. 3**

**Source: <http://www.emdt.co.uk/article/serious-adverse-event-reporting-during-european-device-clinical-investigations>**