Adverse Event Reporting in European Premarket Clinical Studies

Sponsors of clinical studies that are unaware of the variations in adverse event reporting that occur during European medical device premarket clinical studies risk delays and unplanned resource expenditures.

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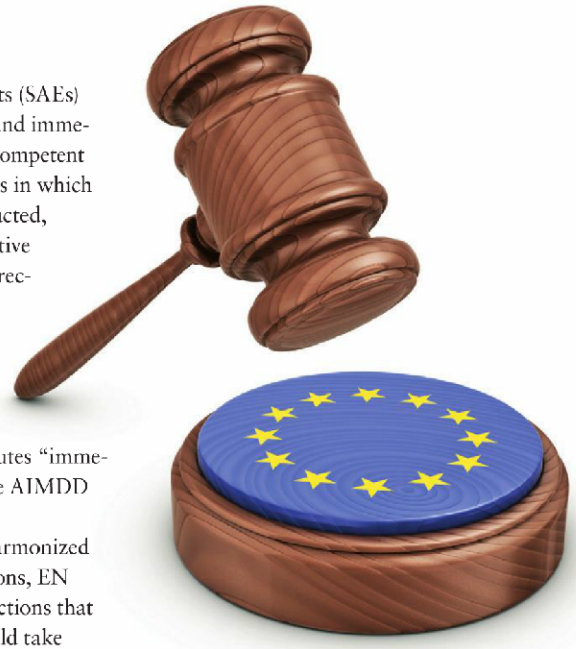

All serious adverse events (SAEs) must be fully recorded and immediately reported to all Competent Authorities of EU member states in which the clinical study is being conducted, according to Annex 7 of the Active Implantable Medical Device Directive (AIMDD) and Annex X of the Medical Devices Directive (MDD). However, no further detail on how these requirements should be met nor a definition of what constitutes "immediately" is provided in either the AIMDD or MDD.

Fortunately, the European harmonized standard for clinical investigations, EN ISO 14155:2011, specifies the actions that sponsors and investigators should take to manage and report adverse events that occur during medical device clinical studies, including device deficiencies that must be reported.

The European guideline on SAE reporting—"Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385 and 93/42/EEC"—also describes the recommended procedures for reporting SAEs and device deficiencies. In addition, it addresses the Competent Authorities, to whom reports should be submitted; reporting timelines; reporting of an adverse event in a third country when the third country and European clinical sites are covered by the same clinical investigation plan; and information on the reporting form that is included in an Appendix.

It should be noted, however, that this guideline was published in December 2010, which preceded the release of EN ISO 14155:2011. Thus, the definitions found in the guideline were based upon definitions in the final draft standard, which differ slightly from the final version of the standard. For this reason, companies should consider the definitions in ISO 14155:2011 as official and apply those definitions to their European clinical study procedures and documentation.

According to the European SAE guidelines, SAEs are to be reported simultaneously to all national Competent Authorities of the Member States in which the clinical investigation has commenced using the summary tabulation provided in the Appendix. The sponsor is to report the following:

- 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. These issues must be reported immediately, defined as no 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—including reportable device deficiencies—or a new finding or update to an already reported event. The events or findings must be reported immediately, specified in this case as no 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.

Device deficiencies must be reported if they did not lead to an adverse event but could have led to a medical occurrence if:

- Either a suitable action had not been taken
- Intervention had not been made, or
- Circumstances had been less fortunate

German Reporting Requirements

Sponsors of clinical studies conducted in Germany should be aware of the SAE reporting requirements in advance of the need for reporting. This is because the Federal Institute for Drugs and Medical Devices (BfArM), the German Competent Authority, has specific requirements for SAE reporting that will not be fulfilled if sponsors follow only the AIMD, MDD or European SAE guideline.

Reporting requirements for SAEs also apply to reportable device deficiencies, as specified in EN ISO 14155:2011 and the European SAE guideline. The forms that must be used to report SAEs to BfArM and the timeline for reporting depend upon the presumed cause of the SAE (device / procedure related or not) and whether or not the SAE has occurred in Germany or outside Germany.

The German SAE report form must be used when there may be a causal relationship between the SAE and the investigational medical device, a comparator device, a diagnostic or therapeutic procedure performed as part of the clinical study, or other conditions of the study, and the event occurred in Germany. If the event occurred outside of Germany, the MEDDEV 2.7.3 reporting form—called a summary table on the BfArM Web site—must be used. On the other hand, when it is possible to exclude a causal relationship between the SAE and the investigational medical device, a comparator device, a diagnostic or therapeutic procedure performed as part of the clinical study, or other conditions of the study conduct, the MEDDEV reporting form must be used and the reports submitted quarterly. There are additional requirements that some companies find quite confusing, however, with regard to the MEDDEV report form, which is an Excel file.

Regardless of causality, all SAEs that occur outside of Germany and the quarterly listings of SAEs that occur in Germany must be documented using the same Excel file, in a cumulative manner, using separate Excel sheets. That is, all SAEs that occurred outside of Germany must be documented on one sheet (sheet 1), irrespective of immediate or quarterly reports, whereas, quarterly listings of SAEs that occurred in Germany must be included on a separate sheet (sheet 2).

Swiss Reporting Requirements

Swissmedic, the Swiss Competent Authority for medical devices, has published an information sheet on the authorization, notification and reporting for medical device clinical studies. Section 7.2.3 of the information sheet lists the criteria for determining whether an event is serious and therefore reportable, guidance on determining whether or not the event could be related to the study device, timelines for reporting, the forms to be used for reporting, and other advice regarding the management of SAEs.

Timelines for reporting to Swissmedic are not exactly the same as those specified in the European SAE guideline in that SAEs and reportable device deficiencies—termed "Events (serious and not obviously unrelated)"—must be reported to Swissmedic within seven days. If such an event takes place in a Swiss study center, a special Swiss form should be used, which is available from the Swissmedic Web site. However, for SAEs occurring in multicenter studies, a report form in accordance with the European SAE guideline must also be submitted. This Excel table must be completed cumulatively over the course of the study.

Italian Reporting Requirements

Of the examples provided, the Italian Ministry of Health (Ministero della Salute), is the only Competent Authority that accepts the reporting of SAEs and reportable device deficiencies occurring in a premarket medical device clinical study in accordance with the European SAE guideline without any deviation or variation.

Need for Reporting Plans

Sponsors of European medical device clinical studies, especially studies conducted in more than one European member state, need to develop a Serious Adverse Event Reporting Plan as soon as possible in the study planning process. Plans should:

- Specify the reference regulations and standards
- Identify the countries where the study will be conducted
- Include relevant definitions
- Outline sponsor and investigator reporting responsibilities, reporting flow diagrams or explanations, and other information that will ensure that all parties understand the reporting requirements applicable to all countries where the study is being conducted.

Prudent sponsors will ensure that such a plan is developed before the first patient is enrolled in the clinical study.

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