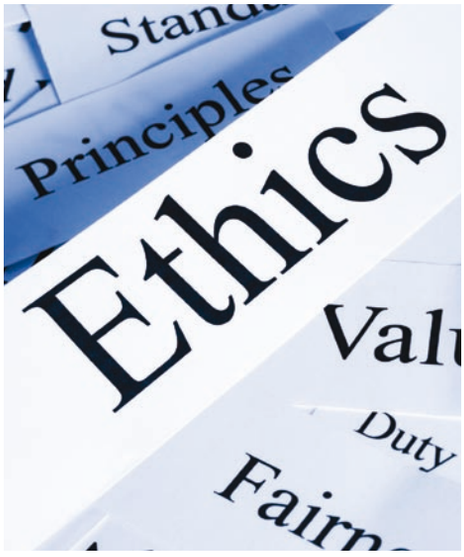
Revised Medical Device Clinical Study Standard Introduces Sweeping Changes

Manufacturers planning to conduct medical device clinical studies should be aware of the final draft international standard (FDIS) for medical device clinical studies, ISO/FDIS 14155:2010.

Importance of the standard

EN ISO 14155:2003 Quality Standard for Clinical Investigation of Medical Devices for Human Subjects is a European harmonised standard. Manufacturers can use this standard to demonstrate compliance with the requirements for clinical investigations detailed in the medical device directives. Part 1 of the standard provides general requirements, whilst Part 2 describes the contents of clinical investigation plans (CIPs). This version of the standard has undergone sweeping changes that encompass its title, format and contents. It is currently in the process of being voted upon by standards body members of the International Organization for Standardization (ISO).

Its importance to readers lies in the fact that, if adopted, it is destined to become a European harmonised standard and, in addition, the preferred standard for conducting medical device clinical studies in the United States, Japan and other countries. This is because of the generally recognised improvements over the current version, the probable wide acceptance by regulators and the harmonisation of clinical study requirements in the newly revised



Active Implantable Medical Devices Directive (AIMDD; 90/385/EEC) and Medical Devices Directive (MDD; 93/42/EEC).

Overview of the revisions

The revised standard has a new title, "Clinical investigation of medical devices for human subjects — Good clinical practices," which reflects its closer relationship with international good clinical practice regulations and guidelines. It is now a single document in that Part 2, Clinical investigation plan, has been incorporated into the standard as a normative annex. It is also about twice as long as the previous version. There are nine clauses instead of 15 and eight annexes instead of four. The eight annexes include two normative annexes, one for the clinical investigation plan and the other for the investigator's brochure (IB). Six informative annexes cover case report forms, the clinical investigation report, essential clinical investigation documents, an adverse event classification tree, the relationship with the MDD and the relationship with the AIMDD.

The scope of the standard has been revised and expanded. It states that ISO 14155 addresses good clinical practices for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. It also states that the principles set forth in the standard apply to all other clinical investigations and should be followed as far as possible, considering the nature of the clinical investigation and the requirements of national regulations. That is to say, the standard should not only be used when clinical studies are needed for the generation of

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clinical study data for regulatory purposes, but also when studies are conducted for other reasons, such as postmarket surveillance or even marketing purposes.

While some of the clauses of the revised standard have the same titles as the current version, such as justification for a clinical investigation and ethical considerations, the standard has been reorganised to include newly titled clauses on clinical investigation planning, clinical investigation conduct, clinical investigation suspension, termination and close out, responsibilities of the sponsor, and responsibilities of the principle investigator and the annexes.

It is important to note that several new requirements have been added to the standard, primarily based on provisions of the "Guideline for Good Clinical Practice" developed by the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. These new requirements concern Ethics Committees (ECs), sponsor responsibilities, informed consent for vulnerable subjects, study monitoring, electronic data management and risk management. The standard has also undergone editorial changes to the format, clause titles and the revision of some sections. In addition, some concepts have been reinforced and expanded. In general, there is more guidance on clinical investigation operations in comparison with the 2003 version of the standard.

The text is much clearer. Some definitions have been revised. In some cases, new definitions have been added: audit, blinding/masking, comparator and others. There is also increased emphasis on control of clinical study documents. For example, Clause A.1.2, Identification of the clinical investigation plan, requires the version/issue number and reference, if any, with the page number and the total number of pages on each page of the CIP. The same approach to page numbering is required for the IB in Clause B.1.2.

Ethics committees

The revised standard, in Clause 8.2.2(a), clarifies that the sponsor is responsible for preparing the documents required for EC submission. This was not specifically stated in the 2003 version of the standard.

Another important clarification has been made with regard to information to be submitted to the EC. In informative Annex B of the 2003 version of the standard, information that "can be of relevance for the ethics committee" was listed, such as an assessment of the scientific merit and justification of the clinical investigation project and of the investigational plan proposal. The revised standard in Clause 4.5.2, Initial EC submission, provides clearer indications of the specific documents that should, as a minimum,

be submitted to the EC. This information includes the CIP, IB or equivalent documentation; informed consent form and any other written information to be provided to subjects; procedures for recruiting subjects and advertising materials; and a copy of the CV of the principal investigator(s) for which the EC has oversight.

Clause 4.5.3, Information to be obtained from the EC, describes the type of information that should be contained in the EC approval. It states that the sponsor must obtain documentation of EC approval/favourable opinion identifying the documents and amendments on which the opinion was based. This is an important and useful change. The failure to clearly identify the documents upon which the opinion is based can lead to delays during the process of submitting clinical study documentation to regulatory authorities if the sponsor or investigator has amended some documents submitted to the EC and has doubts about the specific version of documents, upon which the EC opinion was based.

Clause 4.5.4, Continuing communication with the EC, indicates the information that must be provided to the EC, if required by national regulations, the CIP or the EC, whichever is more stringent. This information includes serious adverse events, requests for deviations, progress reports including safety summary and deviations, amendments to any documents already approved by the EC and other information. Readers should refer to the standard for the full list of information that should be provided.

Sponsor responsibilities

The responsibilities of the sponsor have been significantly expanded and are detailed in Clause 8, Responsibilities of the sponsor. An important area that has been expanded concerns the role of quality systems in the conduct of clinical investigations. Clause 8.1, Sponsor, General, of the 2003 version of the standard specifies only that the sponsor must ensure documentation demonstrating compliance of the investigator, sponsor and monitor with Part 1 of ISO 14155, the applicable CIP and subsequent amendments, together with all applicable regulatory requirements, by means of a quality system.

Clause 8.1, Responsibilities of sponsor, Clinical quality assurance and quality control, of the revised standard requires that the sponsor apply quality assurance and quality control principles to the processes of the clinical investigation. Specifically, the sponsor must implement and maintain written clinical quality procedures. The purpose of the procedures is to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with this standard, the CIP, any subsequent amendment(s) and any other applicable standards and regulatory requirements.

An important new requirement, which some may consider a clarification of existing sponsor responsibilities, is specified in Clause 8.2.2, Documents and materials preparation. This clause requires that prior to the start of the study, the sponsor must prepare the documents, such as those required for EC submission, the CIP

and IB, and submit any required applications to begin the clinical investigation to the appropriate regulatory authorities for review, acceptance or permission.

The monitoring activity has been appropriately placed within Clause 8, Responsibilities of sponsor, instead of in a separate clause on monitor responsibilities, as was the case in the 2003 version of the standard. Not only has the monitoring activity been moved, but it has been notably expanded into several subclauses that provide requirements on the qualifications of the monitor, assessment of the investigational site, initiation of the investigation site, routine on-site monitoring visits, close-out activities and monitoring reports.

Safety evaluation and reporting

In Clause 8.2 of the 2003 version of the standard, the sponsor must ensure that all adverse events and all adverse device effects are reported to and reviewed by the clinical investigator(s). Where appropriate, all serious adverse events and all serious adverse device effects must be reported to the relevant authorities, ECs and/or safety monitoring committee(s). In addition, during the clinical investigation the sponsor must inform in writing all principal clinical investigators about all serious adverse events and all serious adverse device effects occurring in (multicentre) clinical investigations that have been reported to the sponsor. It is also stated that this information must be sent to the clinical investigator(s) based on perceived risk.

Clause 8.2.5, Safety evaluation and reporting, in the revised standard states that the sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation. It expands the safety evaluation and reporting requirements in very important ways, listing eight actions that must be taken instead of the two specified in the 2003 version of the standard. A discussion of all requirements in this clause is beyond the scope of this article; however, an important activity concerns a new category of safety data on device deficiencies. That is, Clause 8.2.5(b) requires that the sponsor review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect. Device deficiency is a new concept in the management of clinical studies and fills a gap regarding an important source of data on medical devices used in clinical studies.

Publication of the standard

Prudent manufacturers will keep informed on the availability of ISO/FDIS 14155:2010, the publication of the final standard, the European harmonisation status of the standard, and its acceptance as a US FDA–recognised standard. The revision of ISO 14155 marks an important point in the evolution of medical device requirements and will have a profound effect on the conduct of medical device studies worldwide.

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