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A New Standard for Medical Device Investigations

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Sweeping changes to ISO 14155

The International Standards Organization's standard, "ISO 14155: Clinical investigation of medical devices for human subjects," has governed the conduct of medical device trials since 1996. Now, the standard is undergoing sweeping changes. The first and most evident change is the standard's new title: "ISO 14155: Clinical investigations of medical devices in human subjects – good clinical practices." Harmonized with the ICH E6 GCP guidelines, "good clinical practices" was added to the title to signal ISO's intention to establish this as the standard to be followed for international medical device investigations, with equal footing alongside ICH E6.

The standard takes into account the mechanical, physical and engineering nature of devices through the normative reference to "ISO 14971: Application of Risk Management to Medical Devices." The content of investigator's brochures for medical device trials reflects a mechanical device rather than a chemical drug. In addition, the requirements for recording and reporting device deficiencies alongside adverse events complements the essential requirements of EU Directive 93/42/EEC on medical devices (MDD) and EU Directive 90/385/EEC on active implantable medical devices (AIMD).

The standard states that its "principles...apply to all other clinical investigations..." of medical devices, including studies not intended for regulatory submission. However, the standard does not apply to *in vitro* diagnostic devices.

An International Standard Written by International Experts

The new standard is achieving broader international acceptance. It is expected to be recognized as a consensus standard by the FDA and adopted by regulatory authorities in China, India and South Korea. Essentially the same rules will apply in every country that adopts the standard. A team of experts from the U.S., Europe and Japan wrote the new standard, with contributions from about 20 other countries. The team consisted of industry representatives, consultants and regulators to ensure that the new standard would be achievable and consistent with country regulations and accepted ethical and organizational practices. It did not come easily; the working group and editing committee met 14 times, with a dozen or so teleconferences between the meetings.

This standard will be an economic leveler. From the regulatory perspective, it will be neither easier nor more difficult to conduct a trial in one country vs. another. For example, in the past, it was cheaper and faster to conduct first-in-man implant studies in Europe because of limited regulatory control.

All Studies Are Created Equal

It can be hard for Americans to grasp that there is no risk-based categorization of clinical trials in the standard. In contrast to 21 CFR 812: Investigational Device Exemptions, the concept of significant vs. non-significant risk studies does not exist. All the rules apply equally to all clinical investigations.

Format and Approach

The Part 1 and Part 2 standards from 2003 are now combined into a single, comprehensive, 65-page document. The strategy is to approach clinical investigations from a project management perspective. A look at the layout gives an idea of the breadth and depth of the standard.

First, there are four administrative sections:

1. Scope
2. Normative references
3. Terms and definitions
4. Ethical considerations

"Normative" is ISO-speak for "required," i.e., not just a recommended good practice. One small sentence in the Normative references section also elevates ISO 14971 to a required standard. Being listed as a normative reference means that the sponsor is, de facto, non-compliant with ISO 14155 if they are not compliant with ISO 14971. Scattered throughout the ISO 1415 document are the many ways in which Risk Analysis Reports are integrated into clinical investigations.

The administrative sections are followed by three project planning sections:

5. Clinical investigation planning
6. Clinical investigation conduct
7. Suspension, termination and close-out

The project management sections are notable for their substantial increase in detail and instructive language. If you have never done a clinical study before, you will find these sections a welcome reference.

Another example of a requirement included to meet MDD and AIMD essential requirements is the need for a Clinical Evaluation Report (like a Report of Previous Investigations in drug studies). This report is to be produced according to the principles of the ISO Global Harmonization Task Force (GHTF) Study Group 5 to justify the design of the clinical protocol.

The project planning sections are followed by two sections on responsibilities:

8. Responsibilities of the sponsor
9. Responsibilities of the principal investigator

Sponsor and principal investigator responsibilities closely follow FDA's new guidance, "Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects," and ICH E6 GCP guidelines. In addition, the principal investigator at each site is required to review and sign the Clinical Investigation Report.

Much of the detail is laid out in five annexes:

- Annex A (normative) – Clinical investigation plan
- Annex B (normative) – Investigator's brochure
- Annex C (informative) – Case report forms
- Annex D (informative) – Clinical investigation report
- Annex E (informative) – Essential clinical investigation documents
- Annex F (informative) – Adverse event classification decision tree

Annexes A and B are required for compliance. The remaining annexes are explanatory, hence the qualifier "informative" annex. They contain extremely valuable information on organizing case report forms, writing a final report, and understanding the relationships between adverse events and effects.

Extensive Other Changes

The new standard expands each section to include sufficient narrative to teach a new sponsor how to conduct a clinical investigation. This controversial move is meant to educate as well as to set a performance bar.

Notable examples of substantive additions and changes include:

- Clearer definitions of adverse events, adverse device effects, and unanticipated device effects
- A definition for device deficiencies, along with recording and reporting requirements
- Requirements for recording and reporting adverse device effects in persons other than subjects
- Implied requirement for a clinical research quality management system
- Requirement for a Risk Analysis Report
- Requirement for a Clinical Evaluation Report to justify the study design
- Required content for a protocol (clinical investigation plan)
- Required content for the investigator's brochure
- Suggested content and organization for case report forms
- Discussion of data monitoring committees
- Requirement for document and data control
- Requirement for electronic data systems
- Auditing recommendations
- Procedures for suspension or premature termination of a trial
- Procedures for working with vulnerable populations
- An extensive list of the documents essential for a clinical trial
- Omission of the annex discussing how to perform a literature review
- Two alternative schemes for adverse event classification

The Publication Plan

ISO published the standard in January 2011. It can be purchased at www.iso.org. The next step is for each member Standards Body to adopt the standard into its own system. Thus, in the U.S., the standard will be re-issued as an American National Standards Institute (ANSI) standard of the same number.

Oddly enough, a member Standards Body is free to modify the standard before issuing it under its own name. The French version, for example, may thus turn out different than the British version.

Soon after publication by ISO, the international standard will be harmonized in Europe via publication in the European Commission Official Journal. It will take force in Europe immediately, with no phase-in period, so sponsors should begin updating their international procedures now.

Author

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