MEDICAL DEVICE CLINICAL INVESTIGATIONS AND ISO 14155

EXECUTIVE SUMMARY

Medical device regulations around the world generally require manufacturers of most types of medical devices to supply data as part of the regulatory review process that supports claims regarding the safety, performance and effectiveness of their devices. For new or novel devices that may not have a predicated device, this data is typically derived from clinical investigations, studies or trials conducted by the manufacturer or an appointed third-party contract research organization (CRO) with specialized expertise in conducting such investigations.

However, the cost of a clinical investigation can run into the millions of dollars and often take a year or more to execute. Further, nuanced differences in regulatory requirements can render the data from a clinical investigation inadmissible or otherwise unacceptable by authorities in a given jurisdiction. These challenges require manufacturers to design and execute medical device clinical investigations that meet threshold requirements for safety and effectiveness while also addressing variations in how regulators define these requirements.

This UL white paper discusses the scope of clinical investigations applicable to medical devices, the role of ISO 14155, Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice (GCP) in the acceptance of clinical data by regulatory authorities. Beginning with an overview of the types of medical devices subject to clinical investigations, the paper next reviews some of the current challenges facing device manufacturers in conducting clinical investigations. Then, the white paper will present a brief history of ISO 14155 and the status of its acceptance by regulatory authorities around the world, before offering a detailed summary of the standard's key provisions. The paper concludes with some additional considerations for medical device manufacturers in designing clinical investigations that are aligned with regulatory requirements.

CLINICAL INVESTIGATIONS FOR MEDICAL DEVICES

According the U.S. Food and Drug Administration (FDA), a medical device is

"AN INSTRUMENT, APPARATUS, IMPLEMENT, MACHINE, CONTRIVANCE, IMPLANT, IN VITRO REAGENT, OR OTHER SIMILAR OR RELATED ARTICLE, INCLUDING A COMPONENT PART, OR ACCESSORY WHICH IS...INTENDED FOR USE IN THE DIAGNOSIS OF DISEASE OR OTHER CONDITIONS, OR IN THE CURE, MITIGATION, TREATMENT, OR PREVENTION OF DISEASE..."[1]

While other specific definitions of a medical device may differ somewhat, this definition clearly illustrates the wide range of products that fall within this general scope. Medical devices today include products as diverse as highly advanced medical technologies and life-saving emergency equipment, as well as surgical instruments, blood pressure cuffs and simple thermometers. According to one estimate, there are more than half a million different medical devices currently on the market.[2]

Modern medical devices have transformed the healthcare landscape in myriad ways. Ready access to medical devices has improved the quality, effectiveness and safety of medical care for billions of people around the world, reducing deaths and injuries related to medical conditions and contributing to ever-increasing average human lifespans. As a result, the medical device industry represents a major force in the global economy with worldwide sales of medical devices expected to surpass $500 billion (USD) by the end of the decade.[3]

Because of the potential risks associated with their use, medical devices are typically subject to clinical investigations to establish their safety and effectiveness prior to receiving approval from regulators and being placed on the market. The scope of a clinical investigation required for a given medical device can depend on several factors, including the level of risk posed by the device and the specific regulatory requirements of a jurisdiction. Post-market clinical studies may also be required to assess device effectiveness and to evaluate potential risks not identified in the pre-market assessment.

While clinical investigations of medical devices are essential, they can also be time-consuming. One study of the FDA's review of innovative medical devices estimates that clinical trials range in duration from three months to seven years, with a median duration of three years.[4] Of course, the duration of clinical investigations of medical devices does not include time required for initial research and product development, or the time required for medical device review and approval by regulatory authorities. These timeframes can represent significant challenges for medical device manufacturers seeking to introduce new and innovative medical devices to the market.

Another challenge facing medical device manufacturers is the cost of clinical investigations, which can range from $250,000 (USD) to as much as $10 million or more for a single product.[5] The cost factor can be especially daunting for small and mid-sized device manufacturers which make up the vast majority of medical device companies.[6]

The escalating costs of clinical investigations along with other factors have led many medical device manufacturers to explore alternative approaches. One approach is to conduct clinical investigations in countries outside of the U.S. where investigation expenses can be considerably less. Another option is the use of a third-party clinical research organization (CRO) that can offer in-depth knowledge and experience in conducting clinical investigations, and that can leverage investments in technology and other processes to transform the traditionally labor-intensive investigative process. Using a CRO is independent of where the investigation is conducted and can potentially lead to time savings, especially when this may be one of the first times the manufacturer has conducted a clinical investigation.

CLINICAL INVESTIGATIONS AND ISO 14155

ISO 14155 provides a detailed framework for the design, conduct and reporting of clinical investigations involving human subjects for the purposes of assessing the safety or performance of many types of medical devices (in-vitro diagnostic medical devices are excluded from the scope of the standard). Originally published in 1996, the standard has been extensively revised over the past 20 years to more effectively address the specific investigation requirements for medical devices, and to better align its requirements with those of the Good Clinical Practice (GCP) guidelines developed by the International Conference on Harmonization (ICH).

The current version of the standard, ISO 14155:2011, which replaced ISO 14155:2003 Parts 1 and 2, is now closely harmonized with GCP guidelines. These guidelines have served as the basis for regulatory requirements applicable to clinical investigations of pharmaceutical products and medical devices in many jurisdictions around the world. While some differences remain between GCP guidelines and ISO 14155 requirements (partially explained by ISO 14155's focus on clinical investigations with medical devices), data collected through clinical investigations conducted in according with ISO 14155 is being more widely accepted by regulators as part of the medical device pre-market approval application process.

This growing acceptance makes compliance with the clinical investigation requirements detailed in ISO 14155 an essential element in the efficient review and approval of medical devices by regulators and global market acceptance. At the same time, ISO 14155 can also provide device manufacturers with greater flexibility regarding the conduct of clinical investigations. For example, manufacturers can now more confidently collect data from studies conducted in countries where investigation costs are lower, as long as the investigation is conducted in accordance with ISO 14155 requirements. And device manufacturers can more easily consider outsourcing clinical investigation activities to a qualified CRO that has adopted ISO 14155 practices.

KEY ELEMENTS OF ISO 14155

ISO 14155:2011 consists of nine separate clauses and six annexes that provide specific requirements applicable to clinical investigations for medical devices. The following sections provide details on each of the key clauses.

ETHICAL CONSIDERATIONS (CLAUSE 4)

The essential ethical requirements of ISO 14155 are intended to protect the rights, safety and well-being of the human subjects that are part of a clinical investigation. Adherence to these core principles outweighs any other commercial or scientific concerns. Specific ethical provisions include:

- **IMPROPER INFLUENCE OR INDUCEMENT**

  Both the study sponsor(s) and investigator(s) must avoid any improper influence on, or the inducement of, any of the parties involved in the clinical investigation.

- **COMPENSATION FOR HUMAN SUBJECTS**

  Compensation for subjects participating in a clinical investigation is permitted if allowable under applicable national regulations. However, the amount of the compensation cannot be large enough to encourage participation or otherwise influence subjects.

- **OVERSIGHT COMMUNICATIONS**

  An independent ethics committee must be appointed to protect the rights, safety and well-being of investigation subjects. This sub-clause details requirements related to the initial and ongoing communication between the sponsors and investigators and that committee.

- **VULNERABLE POPULATIONS**

  The use of members of vulnerable populations as study subjects is not permitted, except when an investigation cannot be otherwise conducted. When vulnerable populations must be used, the investigation should be designed to address specific health problems of the vulnerable subjects, and offer study participants the potential of a direct health-related benefit.

- **INFORMED CONSENT**

  ISO 14155 requires all study participants to give their informed consent in writing prior to their involvement in the clinical investigation. The written consent must include an information form and a signature form. In some cases, informed consent can be provided by a legally authorized representative.

CLINICAL INVESTIGATION PLANNING (CLAUSE 5)

Prior planning for a clinical investigation is a key element of ISO 14155 requirements. The standard requires undertaking the following planning activities in advance of any clinical investigation:

- **RISK ANALYSIS**

  A risk analysis consistent with the requirements of ISO 14971 must be conducted to identify the potential risk and adverse effect to which investigation subjects may be exposed.

- **JUSTIFICATION**

  A justification for the design of the clinical investigation must be prepared based on the evaluation of pre-clinical data and the result of a clinical evaluation of the medical device.

- **CLINICAL INVESTIGATION PLAN**

  A clinical investigation plan (CIP) must be developed, consistent with the requirements detailed in Annex A of the standard.

- **INVESTIGATOR'S BROCHURE**

  The investigator's brochure provides the investigator(s) with sufficient device safety or performance data to justify human exposure during an investigation. Specific information is detailed in the standard's Annex B.

- **CASE REPORT FORMS**

  Case report forms must be developed to collect and record data for each subject during a clinical investigation. Details can be found in Annex C of the standard.

- **MONITORING PLAN**

  The clinical investigation sponsor must develop a monitoring plan based on an assessment of the extent and nature of monitoring appropriate to the study.

- **INVESTIGATION SITE SELECTION**

  Finally, the rationale for selecting a given site for a clinical investigation must be documented.

CLINICAL INVESTIGATION CONDUCT (CLAUSE 6)

Clinical investigations conducted under ISO 14155 cannot commence until written approval has been provided by the investigation's ethics committee and, if required, the relevant regulatory authorities where the clinical investigation is being conducted. Subsequent to those approvals, clinical investigation sponsors and investigators must address the following requirements:

- **INVESTIGATION SITE INITIATION**

  An initiation meeting or visit is required for each investigation site. A log of attendees, their functions and scope of authority must be created to document the meeting.

- **INVESTIGATION SITE MONITORING**

  Monitoring of investigation activities in accordance with clinical investigation plan must be conducted, per the monitoring plan detailed above.

- **ADVERSE EVENTS AND DEVICE DEFICIENCIES**

  All adverse events and deficiencies related to the medical device under investigation must be documented as they occur and in a timely manner. They then need to be reported, as per the requirements.

- **OTHER DOCUMENTS AND DOCUMENTATION**

  Amendments and changes to all required forms and documents must be properly documented and include a statement justifying the change. A log of subjects enrolled in the clinical investigation must be maintained. Substantial amendments to the investigation plan are subject to EC approval.

- **PRIVACY AND CONFIDENTIALITY**

  The privacy of each subject enrolled in a clinical investigation and the confidentiality of all subject-related information must be maintained throughout the investigation. All data must be secured against unauthorized access.

- **DOCUMENT AND DATA CONTROL**

  Documents and data generated during a clinical investigation must be produced and maintained in a manner that assures their control and traceability.

- **DEVICE ACCOUNTABILITY**

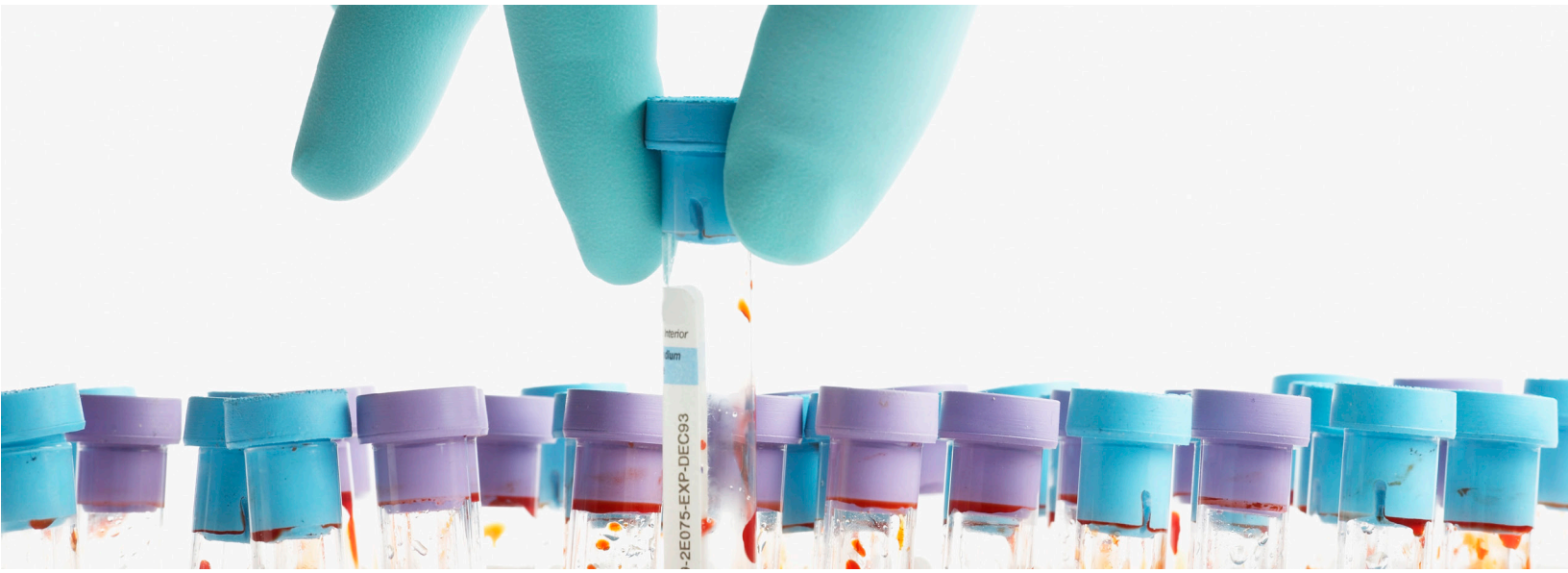
  Access to medical devices that are the focus of a clinical investigation must be controlled, and their use limited exclusively to the investigation in accordance with the CIP.

- **SUBJECT ACCOUNTABILITY**

  Human subjects enrolled in a clinical investigation must be documented and accounted for during the course of the study. In cases where a subject withdraws from a clinical investigation, the reason for their withdrawal must be recorded.

- **AUDITING**

  When deemed appropriate by an investigation's sponsor, an audit of the clinical investigation may be conducted by the sponsor or an appointed third-party to assess compliance with the CIP.



CLOSE-OUT OF CLINICAL INVESTIGATION (CLAUSE 7)

This clause of the standard addresses procedures for closing out a clinical investigation, including instances in which an investigation is suspended or terminated for significant reasons. Specific provisions of this clause include:

- **SUSPENSION OR PREMATURE TERMINATION**

  A clinical investigation may be suspended or prematurely terminated by the investigation sponsor, the principal investigator, the ethics committee or a regulatory authority. Reasons for suspending or terminating an investigation include unacceptable risks to study subjects, or serious or repeated deviations by the investigator from the CIP. The party terminating an investigation must document in writing the reasons for its action and report it as per the requirements.

- **ROUTINE CLOSE-OUT OF INVESTIGATION**

  The standard stipulates a number of reporting and notification actions to be conducted upon the completion of a clinical investigation. These actions are intended to ensure that all records and documents are complete, that all open issues related to the investigation have been resolved, and that any remaining clinical investigation materials have been properly disposed of.

- **CLINICAL INVESTIGATION REPORT**

  Upon the completion or termination of a clinical investigation, a final written report must be prepared that identifies the medical device that was evaluated in the investigation, a description of the methodology and the design of the investigation, and an analysis of the data. A copy of the report should be provided to the ethics committee and regulatory authorities. Further details regarding the clinical investigation report are found in Annex D of the standard.

- **DOCUMENT RETENTION**

  Copies of the final clinical investigation report and all relevant clinical investigation documents must be retained by the investigation sponsor and principal investigator as required under applicable regulatory requirements. A list of specific documents to be retained is detailed in Annex E.

RESPONSIBILITIES OF THE SPONSOR (CLAUSE 8)

This clause enumerates the principle responsibilities of the sponsor of a clinical investigation. In general, these responsibilities include the planning and conduct of the clinical investigation within prescribed quality assurance and quality control principles. The clause expressly permits a sponsor to contract with a CRO to perform the duties and functions related to a clinical investigation. However, in such cases the sponsor must retain responsibility for the quality and integrity of the clinical investigation data.

RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR (CLAUSE 9)

Clause 9 of ISO 14155 details the specific qualifications and responsibilities of the principal investigator in a clinical investigation. These responsibilities include the implementation and management of the day-to-day activities of the investigation in accordance with the CIP, ensuring the integrity of investigation data, and safeguarding the rights, safety and well-being of the human subjects involved in the study.

ACCEPTANCE OF ISO 14155 BY REGULATORS

According to the International Medical Device Regulators Forum (IMDRF), regulators in a number of major medical device markets will either accept data from clinical investigations that have been conducted in accordance with ISO 14155:2011, or have adopted clinical investigation requirements that are the equivalent of those in ISO 14155:2011.[7] Some examples cited by the IMDRF affirming the acceptance by regulators in major markets of ISO 14155:2011 for medical device clinical investigations include:

- **EUROPEAN UNION (EU)**

  EN ISO 14155:2011 is the European equivalent of ISO 14155:2011 and is an EU-harmonized standard. As such, compliance with its requirements provides a presumption of conformity with relevant essential requirements for clinical investigations applicable to medical devices under current EU directives.

- **JAPAN**

  According to Japan's Pharmaceuticals and Medical Devices Agency (PMDA), ISO 14155:2011 is an equivalent standard to Japan's GCP requirements as stated in Ministerial Ordinance No. 36 (2005) which addresses requirements for medical devices. (Note that on-site or so-called desktop inspections may still be required.)

- **BRAZIL**

  ISO 14155:2011 is one of the primary reference standards included in that country's Resolution RDC No. 10/2015, addressing requirements for clinical trials for medical devices. Brazil's National Health Surveillance Agency (ANVISA) also references ISO 14155:2011 in its guidance document as a standard to be applied to clinical trial audits.

- **AUSTRALIA**

  Under regulations applicable to medical devices by Australia's Therapeutic Goods Administration (TGA), clinical investigations conducted in accordance with the requirements of ISO 14155:2011 satisfy the requirements of Essentials Principle (EP) 14—Clinical Evidence.

Broader acceptance by ISO 14155 in other countries can be expected as regulators adopt integrate ISO 14155:2011 into existing regulations. However, it is important to note that individual national regulators may also impose additional requirements related to clinical trials beyond those found in ISO 14155. For these reasons, medical device manufacturers should thoroughly investigate specific clinical investigation requirements applicable to medical device approvals in their intended markets.

While many regulators are still looking for clinical investigations to be conducted on representative populations, as an international standard ISO 14155 is also likely to support efforts to conduct more clinical trials in regions where the cost to conduct such trials is less and where potential human subject populations and other factors are consistent with those characteristics of regions where a given device is intended for use. The widespread adoption of the standard's clinical investigation requirements will help to standardize the overall approach to clinical investigations, producing more reliable results and bringing greater transparency to the process. These benefits may also serve to address the concerns of individual regulatory authorities regarding the quality of data generated through foreign clinical investigations.

ACCEPTANCE OF ISO 14155:2011 IN THE U.S.

In the U.S., the situation regarding the acceptance of data from clinical investigations based on ISO 14155:2011 requirements is more nuanced. The FDA specifically requires that clinical investigations of medical devices comply with GCP principles. While ISO 14155:2011 more closely aligns with GCP principles than prior versions of the standard, there are still important areas where FDA requirements based on GCP are more stringent than comparable requirements in ISO 14155.

At the same time, in a 2015 draft Guidance on the use of clinical data from studies conducted outside the U.S., the FDA affirms that ISO 14155:2011 is based on

"GCP PRINCIPLES THAT ARTICULATE ETHICAL AND POLICY STANDARDS FOR OUS (OUTSIDE U.S.) CLINICAL TRIALS…(AND THAT) SHOWING COMPLIANCE WITH GCP IS ONE WAY SPONSORS OF DEVICE APPLICATIONS MAY BE ABLE TO SHOW THAT THEIR OUS DATA COMPLY WITH APPLICABLE FDA REQUIREMENTS CONCERNING HUMAN SUBJECT PROTECTION AND OTHER ASPECTS OF CLINICAL INVESTIGATIONS."[8]

FDA Guidance documents and draft Guidance documents are solely intended to present the agency's current thinking on a given topic, and do not have the force of law. However, references to ISO 14155:2011 in this and other FDA documents, FDA's list of recognized consensus standards[9] and proposed FDA regulations[10] suggest that clinical investigations that comply with the requirements of ISO 14155 may be more likely to receive objective consideration from FDA reviewers.

The FDA also actively encourages medical device manufacturers to discuss their anticipated clinical investigation design with FDA representatives through the agency's pre-submission process. Medical device manufacturers that contemplate seeking FDA approval for their products should consider the potential benefits of such a discussion to affirm their choice of study design and to identify any specific concerns in advance.

SUMMARY + CONCLUSION

Bringing new medical devices to market is about more than breakthrough technology or innovative design. It also requires the application of a rigorous clinical investigation process, as well as in-depth knowledge of the requirements of regulators regarding such studies. As a protocol for the structure and conduct of clinical investigations for medical devices, ISO 14155:2011 is gaining acceptance by both regulators and manufacturers seeking a structured and detailed approach to clinical investigations that also embodies the essential requirements of GCP guidelines. This acceptance will help to strengthen the overall quality and safety of clinical investigations and support the efforts of manufacturers to bring innovative and safe medical devices to market.

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END NOTES

[1] "Is the Product a Medical Device?" website of the U.S. Food and Drug Administration, updated September 12, 2014. Web. 27 November 2015. http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/ucm051512.htm.

[2]"The Global Future of Clinical Trials for the Medical Device Industry," blog posting by Forte Research, January 30, 2015. Web. 27 November 2015. http://forteresearch.com/news/global-future-clinical-trials-medical-device-industry/.

[3]"Global Medical Devices Market 2012-2020," Grace Market Data, May 2015, as reported by Business Wire, May 22, 2015. Web. 27 November 2015. http://www.businesswire.com/news/home/20150522005285/en/

[4]"Characteristics of Pivotal Trials and FDA Review of Innovative Devices," J.Rising and B. Moscovitch, February 2015, posted on the PLoS One Open Access Journal and available through the website of the U.S. National Library of Medicine, National Institutes of Health. Web. 27 November 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4317185/.

[5]"How Will Conducting a Medical Device Clinical Trial Outside the U.S. Impact Your FDA Approval?" J. Hogan, guest column posted to Med Device Online, June 8, 2015. Web. 27 November 2015. http://www.meddeviceonline.com/doc/how-will-conducting-a-medical-device-clinical-trial-outside-the-u-s-impact-your-fda-approval-0001.

[6]"The Medical Device Industry in the United States," Select USA website, maintained by the U.S. Department of Commerce. Web. 27 November 2015. http://selectusa.commerce.gov/industry-snapshots/medical-device-industry-united-states.html.

[7]"Statement Regarding Use of ISO 14155:2011 'Clinical investigation of medical devices for human subjects-Good clinical practice'," International Medical Device Regulators Forum, 26 March 2015. Web. 27 November 2015. http://www.imdrf.org/docs/imdrf/final/procedural/imdrf-proc-150326-statement-iso141552011.pdf#search="ISO 14155"

[8]"Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States: Draft Guidance for Industry and Food and Drug Administration Staff," U.S. Food and Drug Administration, Center for Devices and Radiological Health," April 22, 2015. Web. 27 November. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm443133.pdf.

[9]"Recognized Consensus Standards," website of the U.S. Food and Drug Administration, updated August 5, 2013. Web. 15 January 2016. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/results.cfm

[10]"Human Subject Protection: Acceptance of Data from Clinical Studies for Medical Devices," Proposed Rule, issued by the U.S. Food and Drug Administration, published in the U.S. Federal Register, February 25, 2015. Web. 27 November 2015. http://www.gpo.gov/fdsys/pkg/FR-2013-02-25/pdf/2013-04201.pdf.