Good Clinical Practice for Medical Device Trials

Background
The medical device manufacturing industry is becoming a major player in health-care delivery. Physicians treat many illnesses and conditions, such as cardiovascular and neurological diseases, with medical devices as often as with medicine. In 2008, for the first time, the FDA received more reports of adverse events from these devices than from pharmaceuticals.

Medical device manufacturers can conduct clinical trials more easily in Europe where currently regulatory barriers to clinical testing have less constraints. Consequently, new innovative medical devices typically come to market in Europe first. Approval for marketing these devices in the US follows in five to ten years, then an additional five to ten years for Japan, which has the longest regulatory pathway.

A medical device clinical trial can cost between $5 and $10 million in the United States or Western Europe and more in Japan. The cost of the same trial conducted in Eastern Europe will be considerably lower, and in India, China, or Korea, it may be 1/10 as expensive. Manufacturers are turning to Asian countries for their high-risk, first-in-human studies and even for their pivotal studies because these countries contain a huge available human population with limited alternatives for healthcare. Also, the regulatory barrier to starting a device clinical trial in India, China, or Korea is almost nonexistent.

Problem
Regulations for conducting medical device clinical trials around the world have varied widely. Complications that arise between trials conducted under different protocols make bringing a device to market difficult in a stricter country. Data may be considered questionable given different requirements. The time required to determine acceptability and perhaps repeat trials may delay the device's approval, frustrating patients as well as manufacturers. In addition, the safety of human subjects participating in the clinical trial and ultimately patients is in question in countries with lax regulations and resultant uncontrolled clinical settings. Less rigorous studies cannot ensure consistent performance quality thus potentially jeopardizing the health the devices are meant to protect. Standards to harmonize these trials will ensure safety, effectiveness/performance, and quality, as well as help to promote commerce, and may ultimately ease suffering.

Approach
In 1993, the European Committee for Standardization (Comité Europeen de Normalisation, CEN) published standard EN 540, a precursor of the international standard ISO 14155. Like the International Organization for Standardization (ISO), CEN is an international nonprofit organization providing a platform for cooperating, volunteer organizations to develop consensus standards. In 1996, ISO and CEN joined forces to create the first version of ISO 14155, which repeated EN 540 standards. Almost immediately, the two organizations formed parallel working groups (WGs) to expand the standard. WG4 of ISO's TC (technical committee) 194 developed more elaborate general requirements in ISO 14155 part 1, while CEN's WG elaborated part 2, requirements for

the clinical investigation plan. In 2003, the organizations published both.

ISO 14155 includes the following:

- Step-by-step methodology, record-keeping, and reporting requirements
- Ethical and legal approval requirements
- Steps to construct a protocol
- Risk assessment
- Case report (data collection) forms
- Instructions for preparing a final report

ISO 14155 defines procedures for conducting clinical investigations of medical devices that will

- Protect human subjects
- Ensure proper scientific conduct in the clinical investigation
- Assist sponsors, monitors, investigators, ethics committees, regulatory authorities, and bodies involved in assessing medical device conformity

The requirements that ISO 14155 specifies ensure that the clinical investigation establishes the medical device's performance by mimicking normal clinical use. An ISO 14155 trial will reveal adverse events under normal use and allow researchers to assess acceptable risks while considering the device's intended performance.

In their last meeting before publishing ISO 14155 part 1, the TC 194 WG 4 members documented outstanding points which they believed needed work in a revision. Consequently, immediately after publishing the 2003 version, ISO voted a new work item to continue evolving the general requirements.

ISO and CEN both work to make development, manufacture, and supply of products and services safer, cleaner, and more efficient. Their standards also ease trade between countries and make that commerce fairer. ISO 14155 confronts several ethical and fair trade issues by leveling the playing field for all countries in conducting device trials.

In particular, medical tourism creates conflicts and safety concerns. Those countries where devices become available because of more lax requirements benefit financially, but with safety risks for their population. For example, many thousand American patients with enough money to travel purchase a package tour to Europe or India that includes surgery (for a spinal disc, for example), hospital stay, airfare, hotel stay, and follow-up visits. Whether one argues that citizens of these countries benefit first from new, innovative devices or that they serve as the proving ground for the rest of the world, ethical issues abound.

Outcome

Experts from the United States, Europe, and Japan have agreed on a standard that, at minimum, met the regulatory requirements that already exist in their respective countries. This standard helped to level the field among countries. The standard raises ethical, record-keeping, and reporting expectations to the level considered the norm in the

pharmaceutical industry, a related medical sector.

ISO 14155 standards will serve several groups involved in developing and regulating medical devices:

- Medical device manufacturers who sponsor clinical trials to gain human data about the safety and performance of new devices
- Physicians and other healthcare practitioners who serve as investigators and implement and oversee trials
- Hospital institutional review boards or ethics committees who review the trial protocol (investigation plan) to protect the welfare of human subjects
- Regulators such as the FDA who approve applications to conduct a clinical trial, review the final data to assess safety and performance of a new medical device, and approve or deny applications for commercialization

For patients, ISO 14155 helps provide access to innovative technology in a more timely and safe manner.