Clinical Investigation of Medical Devices: Promoting Convergence

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Abstract
The safety, performance and effectiveness of medical devices are evaluated by clinical investigation before they enter the market. The integrity of the data is ensured using international standards like ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, or ICH E6 Guideline for Good Clinical Practice (GCP) or other GCPs. A clinical investigation design should be made which is appropriate and acceptable by many regulatory authorities that acts as a "gateway" for data transportability and removes all trade barriers. This article brings out the differences between ISO GCP and ICH GCP. Also, it discusses the need for harmonising various GCP standards. Since consistency is essential among GCPs to avoid duplication of work and to allow data from a clinical investigation to be used in another country for marketing approval (data transportability); so it is important that the standards are harmonised.

Keywords: Clinical Investigation Plan, Harmonisation-by-Doing, ISO14155, Convergence, Good Clinical Practices

Introduction

Regulations for conducting medical device (MD) 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[1]. Reciprocal acceptance of Good Clinical Practices (GCPs) would facilitate multinational studies and promote the use of clinical data to support regulatory submissions in multiple countries [2].

Objectives

- To bring out the differences between international standards like ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practices (GCP) or ICH E6 GCP.
- To discuss the advantages of harmonisation of these guidelines for the benefit of the medical device industry and public health.

ISO 14155:2011

ISO 14155:2011 addresses good clinical practice 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.
The principles set forth in ISO 14155:2011 also apply to all other clinical investigations and should be followed as far as possible, depending on the nature of the clinical investigation and the requirements of national regulations. ISO 14155:2011 specifies general requirements intended to protect the rights, safety and wellbeing of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.[3]

ICH GCP

The ICH-GCP is a harmonised standard that protects the rights, safety and welfare of human subjects, minimises human exposure to investigational products, improves quality of data, speeds up marketing of new drugs and decreases the cost to sponsors and to the public. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and consistent with the principles of the Declaration of Helsinki, and that the clinical trial data is credible. [4,5]

Differences [6]

ISO 14155:2011	ICH GCP
ISO technical committee – regulators and (predominantly) medical device industry	Joint initiative – regulators and pharmaceutical industry
Goal – international standardisation of clinical investigations of medical devices	Goal – harmonise requirements in order to aid global drug development
ISO14155 assesses clinical performance	ICH GCP assesses efficacy
Investigator is qualified by education, training and experience	Investigator is a qualified physician or dentist
ISO 14155:2011: investigator brochure to contain a summary of relevant manufacturing processes and related validation processes	ICH GCP – in accordance with applicable Good Manufacturing Practice
ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects– GCP – not globally adopted	ICH GCP guidance introduced in 1996 – widely adopted in USA, Europe, Japan and many others
Adverse events • Adverse device effect – insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device • Device deficiencies – inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance • Adverse events not restricted to subjects – can also be users or other persons	Adverse event is related to the drug. Due to the systemic nature of drugs, all adverse events will need to be captured and analysed as potentially related to the drug.[7]
Reporting – ISO 14155:2011 doesn't differentiate the reporting of foreseeable adverse events and anticipated adverse device effects from unanticipated events / effects	Reporting serious reactions, product quality problems, therapeutic inequivalence / failure with drugs

Problems[6]
- ISO 14155 perceived as "weaker" than ICH GCP.
- ICH GCP too pharmaceutically-oriented for medical devices.
- Terminology:
  (i) Manufacture in accordance with GMP.
  (ii) Pharmacokinetics, metabolism, pharmacodynamics, dose response, efficacy, and other pharmacological activities…
- Safety reporting: not always applicable to devices – adverse drug reaction – devices fail in different ways to drugs.
- Lacking in some areas – training / data management / subject identification log.

Solution[8]
- Release of ISO 14155:2011 is a positive step towards harmonisation.
- Disparities still exist for significant trial concepts.
- Standards bodies may adapt the new guidance as they deem necessary.
- Objective to create one uniform measure to demonstrate a specific regulatory requirement has not yet been realised.

Data Transportability of Clinical Trials

The transportability of medical device clinical data obtained from a GCP-compliant study has a great impact on the marketing approval of an MD[9]. Reports and regulatory discussions have suggested differences between GCP in the different countries that make it difficult to analyse and utilise clinical trial data from one GCP system in support of marketing approval in the other. Language and cultural barriers may add to the complexity. By understanding the nature of these differences, it may be possible to more accurately determine whether data from an alternate GCP provide similar assurances of valid scientific information and patient protection. GCP, as described in standards and regulations, governs the quality of clinical trials for medical products, including medical devices, but the differences between GCP requirements have not been well studied. Further study of these differences is needed to enhance the meaning of compliance with one set of GCP requirements versus another[2].

Benefit of GCP Convergence for Patients[10]
- Improve safety and timeliness of new devices.
- Encourage innovation of medical device therapies.

Convergence May[10]
- Promote multi-national studies.
- Provide similar assurances of valid scientific information and patient protection.
- Support reciprocal acceptance of clinical data to support regulatory submissions in multiple countries.

International Effort Towards Harmonization

Four GCPs are most applicable to US and Japanese marketing approvals: US Food and Drug Administration

and notifications, ISO14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice and ICH E6 (R1) Guideline for Good Clinical Practice. Clinical and regulatory experts in the US and Japan formed a group – Harmonization-by-Doing (HBD), a cooperative effort to move Japan and the US toward international regulatory harmonisation. HBD Working Group 4 performed a line-by-line evaluation and comparison of the four GCPs mentioned above. The convergence of US and Japanese medical device regulations and practices provides an opportunity to accelerate delivery of innovative medical devices to patients in need of medical treatment. [2]

Although that study identified numerous differences in wording, organisation, specificity and depth of topic coverage, in general, the GCPs were found to be quite similar. The differences were assessed with respect to four fundamental criteria: [9]

1) Rights, safety and welfare of trial subjects,
2) Scientific integrity of trial methods,
3) Accuracy of the data, and
4) Reliability as a basis for regulatory decision-making.

Differences were categorised as substantive, non-substantive or administrative.

Harmonization-by-Doing Programme's Working Group[4] (WG4)[11]

'Harmonization-by-Doing', commonly known as HBD, is an international effort to develop global clinical trials and address regulatory barriers that may be impediments to timely device approvals. This process is a cooperative effort to move both Japan and the US toward international regulatory harmonisation. Participants in this process include:
- U.S. Food and Drug Administration (FDA) Centre for Devices and Radiological Health (CDRH),
- Japan's Pharmaceutical and Food Safety Bureau (PFSB) of the Ministry of Health, Labour, and Welfare (MHLW)

and its review agency, the Pharmaceutical and Medical Devices Agency (PMDA),
- Duke Clinical Research Institute (DCRI),
- Japanese academic community, and
- Japanese and US medical device industry.

What is the HBD Initiative?[11]

The HBD initiative is a pilot project launched in December 2003 that seeks regulatory convergence between FDA and MHLW-PMDA premarket review of device cardiovascular technology. Instead of taking a theoretical approach to harmonisation, HBD will utilise parallel development, application submissions and review of actual medical device projects by FDA and MHLW-PMDA. The objective is to eliminate redundancies, added costs, and time delays inherent in sequential trials. The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective medical devices to benefit patients worldwide.

What are the Benefits of HBD?[11]

FDA and MHLW-PMDA share similar scientific concerns and reviewers pose similar safety and effectiveness questions. While there may be divergence in regulatory practices, the two agencies are willing to consider ways of approaching the differences in order to allow the availability of novel treatments and innovative, safe and effective medical devices to patients more quickly. Only through international collaboration can global market reviews be conducted in a timely manner. HBD provides:
- More robust clinical trials
- Improved clinical research infrastructure
- Better clinical trial data
- Better understanding of how the U.S. and Japanese experiences can complement one another
- A new approach to early market availability of new treatment and devices to benefit patients in both countries
- A mechanism to decrease lag time between U.S. and Japanese product approval
- An atmosphere of international collaboration between regulators, regulated industry, clinical researchers, patients and academia
- A continuous progression in global harmonisation The HBD concept is also a process that can be broadened in scope beyond premarket activities. It can also be applied to post-market clinical studies, collection of post-market data and patient registries.

Regulatory Approach[12]

It is a step-by-step process within the current regulatory framework as shown in Figure 1. "Aligning" the regulatory roadmaps – tools already exist in both countries as shown in Figure 2.

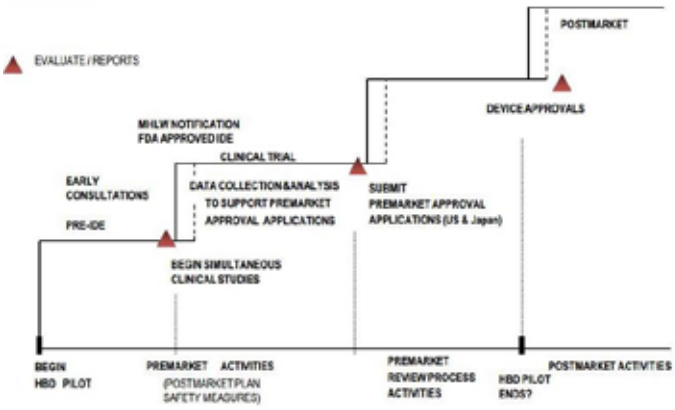

Figure 1: The Regulatory Approach

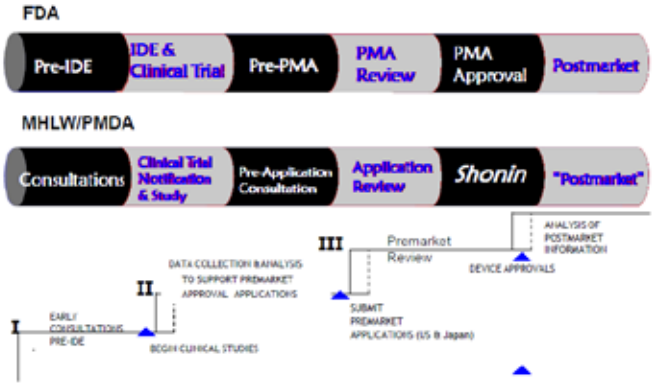

Figure 2: "Aligning" the Regulatory Roadmaps – Tools already exists in both countries

Global Clinical Trial Challenges[12]
- Pooling data (demographics, differences in practice of medicine, protocol-related factors).
- Review of foreign data (applicability to country's population and medical practice).
- Statistical methodology (comparing foreign data to native country data, adjustment for covariate differences).
- Identifying safety and effectiveness endpoints necessary for market approval.
- Cultural and language issues.
- Variations in medical practice and healthcare systems.
- Ethical issues concerning clinical research.
- How to communicate effectively with sites.
- Establishing realistic timelines and other logistics.

Challenges can be overcome with creative and well planned clinical trial designs.

Importance of Globally Standardised Clinical Trials [12]

- High scientific and ethical standards.
- More robust clinical trials and better data.
- Globally acceptable clinical data.
- Widely applicable conclusions – more interpretable and more informative safety and effectiveness data.
- Quicker and more cost-effective generation of clinical data.

Conclusion

Compliance with GCPs alone does not ensure transportability. The clinical investigation design, including the choice of patient population, sample size, endpoints, follow-up periods and statistical analysis plans must address the requirements of various regulatory authorities. Early consultation with the relevant regulatory authorities may facilitate development of a clinical investigation design that is mutually acceptable to those authorities. So, the intent of convergence is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective use of MD to benefit patients worldwide.

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