REGULATORY FOCUS

GCP Convergence Improves Transportability of Medical Device Clinical Data

By Harmonization-by-Doing Working Group 4

The safety, performance and effectiveness of medical devices are often evaluated by well-controlled clinical investigations before marketing authorization. The integrity of these clinical studies is ensured by compliance with voluntary standards or government regulations known as Good Clinical Practices (GCPs). Four GCPs are most applicable to US and Japanese marketing approvals: US Food and Drug Administration (FDA) regulations and guidance, Japanese GCP ordinances and notifications, ISO14155:2011 *Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice*[1] and ICH E6 (R1) *Guideline for Good Clinical Practice*.[2]

Consistency among GCPs is very important to allow data from a clinical investigation conducted in one country to be used for regulatory marketing approval in another country (this is called data transportability). Consistency also may reduce the need for duplicative GCP audits of sponsors, IRBs and investigational sites by different authorities. However, the various GCPs are not identical, which in some cases may impede acceptance of foreign clinical investigation data. Both standards and regulations are evolving and recent revisions further affect consistency among GCPs and the transportability of clinical data obtained under them.

This article discusses the impact of recent revisions to these GCPs on transportability of medical device clinical data obtained from a GCP-compliant study. It also updates a previous study of similarities and differences among GCPs.[3] The previous study concluded there were no substantive differences among GCPs with respect to fundamental criteria for ethical human studies, especially as they apply to the US and Japan. The effects of the recent revisions on this conclusion are included in this article.

Table 1: Revisions to the Japanese GCP Affecting the GCP Comparison

• more flexibility to use an institutional review board (IRB) outside the clinical trial site
• use of the same investigational product label in a multi-national clinical investigation allowable if agreed to by the IRB
• more flexibility for content and documentation of the clinical investigation plan (protocol) and case report form
• more flexibility for shipping of investigational devices
• reduced requirements for signature or seal of principal investigators on the clinical trial contract
• clarified requirements for documenting competence of test facilities and supporting reliability of results
• clarified requirements for retention of communication records
• reduced requirements for clinical trial contracts
• disclosure of IRB membership, SOPs and minutes

Previous GCP Comparison Study

The previous study was a joint effort by clinical and regulatory experts in the US and Japan as part of the work of Harmonization-by-Doing (HBD), a cooperative effort to move Japan and the US toward international regulatory harmonization.[4] HBD Working Group 4 performed a line-by-line evaluation and comparison of the four GCPs mentioned above.

Although that study identified numerous differences in wording, organization, 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: 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 categorized as substantive, non-substantive or administrative.

Importantly, the study found no substantive differences among the GCPs studied with respect to the four fundamental criteria. This means compliance with any one of the GCPs provided similar protections and requirements. There were no contradictory requirements among the four GCPs. Therefore, compliance with more than one GCP (or all GCPs) in the same investigation is possible.

Several non-substantive and administrative differences among GCPs were identified. This means that some documentation above and beyond what is required by one GCP may need to be collected to improve data transportability. The study report discussed how these differences could be addressed with additional documentation, such that the data could be relied upon by regulatory authorities outside the country or region where the study was conducted. The additional documentation was identified in the previous paper and is updated in tables contained in this article. The sponsor of a trial should also consult with the regulatory authorities before the study to confirm sufficiency of additional documentation.[5]

Since the original comparison study was completed, the GCPs have been revised. The Japanese ordinances and notifications (Japanese GCP or JGCP) have been revised, additional US guidance documents have been issued in draft or final form and ISO14155 underwent a major revision. The following briefly highlights these revisions and discusses their effect on the earlier GCP comparison study results and, consequently, their impact on transportability of clinical data.

Japanese GCP Revisions

The Japanese GCP ordinance originally issued on 23 March 2005[6] was revised on 31 March 2009. Also, the Japanese GCP notification originally issued on 20 July 2005 was revised on 24 December 2009, and again on 24 January 2012 with additional notifications. An additional revision was issued in draft form in May 2012. These revisions are summarized in **Table 1**. The revisions reduce several earlier differences from the US GCPs, as well as other international GCPs.

Table 2: Revisions to the US GCP Affecting the GCP Comparison

• registration of IRBs o As of 15 January 2009, amendment to Part 56, Institutional Review Boards (21 CFR 56.106) requires each IRB in the US that reviews FDA-regulated studies to register.
• issued guidance on registration in a public database of clinical studies o Applicable clinical studies must be publicly registered (www.ClinicalTrials.gov) and informed consent documents must include a specific statement that refers to the trial's description on the website.
• other guidance issued (since 2005) o Numerous issued guidance documents clarify emergency research, the process for inspection or auditing of clinical investigators and sites, the process for inspection of IRBs, the process for clinical trial data monitoring committees, data integrity of emergency use devices when patients withdraw, responsibilities of investigators including delegation of tasks, reporting of adverse events to IRBs, use of centralized IRBs, periodic review by IRBs and requirements for electronic records.
• draft guidance o Draft guidance documents explain exculpatory language in informed consent, risk-based clinical monitoring, design considerations for clinical investigations, financial disclosure by clinical investigators, electronic source verification, IRB continuing review, feasibility and initial clinical studies, clinical trial data monitoring committees and evaluation of gender differences in clinical trials.

US GCP Revisions

In the US, new requirements have been added to US regulations and additional guidance documents have been issued.[7,8,9] These additions were evaluated to determine whether they affected the differences between JGCP and US GCP identified in the earlier paper (see **Table 2**).

ISO14155 Revisions

ISO14155, the international standard for medical device clinical trials, was extensively revised and reissued on 1 February 2011. The standard is now more consistent with ICH guidance. Whereas ICH E6 applies to clinical trials of medicines, ISO14155 is specific to medical devices. Revisions to ISO14155 can be generally categorized as shown in **Table 3**.

Impact of GCP Revisions on GCP Comparison Results

Since these revisions touched on some of the differences identified in the original GCP comparison study, the working group of US and Japanese GCP experts reconvened to assess their potential significance. They considered whether each revision created a new difference among the GCPs, reduced existing differences, increased existing differences or altered the categorization (substantive, non-substantive or administrative) of differences. Each revision was associated with the appropriate section of the previous analysis and the results are summarized in **Tables 4** and **5**. The revised assessment may assist sponsors planning to conduct a clinical investigation in Japan or the US, or a multinational clinical investigation involving the US and Japan, thereby improving transportability of data for marketing approval in both countries and beyond.

The GCP experts observed numerous differences in wording, organization and depth of topic among the revised GCPs. However, they determined there still are no substantive differences with respect to the four fundamental criteria in the original study (rights, safety and welfare of trial subjects; scientific integrity of trial methods; accuracy of the data; and reliability as a basis for regulatory decision making). There are no contradictory requirements among GCPs, so compliance with more than one GCP (or all GCPs) is still possible. Compliance with any one of the GCPs provides similar protections with respect to the four fundamental criteria.

The revisions did, however, affect differences considered non-substantive in the previous study. For example, JGCP as revised on 24 December 2009 reduced one of the barriers in the labeling of study devices by allowing an English label to remain on the study device at Japanese sites in a multinational clinical investigation, along with the required Japanese label. **Table 4** shows the revised non-substantive differences.

The revisions also affected differences considered administrative in the previous study. For example, the 24 December 2009 revision to JGCP eliminated the requirement that investigational devices be delivered to medical institutions without use of a medical device dealer or third party; devices now may be shipped via courier (e.g., FedEx) rather than hand-delivered to institutions. This revision eliminated a difference identified in the original GCP comparison study. **Table 5** shows the revised administrative differences.

Facilitating Data Transportability in Japan, US

These observations suggest it is possible to conduct a GCP-compliant clinical investigation in either Japan or the US, or a multi-center study involving both countries, with the expectation there will be no substantive differences in acceptability with respect to the four fundamental criteria. To achieve full transportability, however, it may still be necessary to address the non-substantive and administrative differences by providing documentation necessary to bridge small gaps. By using the tables of non-substantive and administrative differences and consulting with regulatory authorities, sponsors usually can identify the specific additional documentation.

For example, **Table 4** identifies the financial disclosure information required in the US. Its purpose is to show that investigators do not have a financial conflict of interest that may cause them to bias the clinical investigation results. For investigational sites outside the US, gathering additional information demonstrating a lack of conflict of interest and lack of investigator bias in the clinical investigation results could address the needs of the US and other regulatory authorities. Hence, using **Tables 4** and **5** in this way to identify and address the need for additional information may be helpful.

Adherence to ISO14155 provides an additional basis for transportability of clinical data. Of note, a working group involving participants with extensive GCP experience from several countries, including the US and Japan, drafted the revision of ISO14155; it represents a current consensus standard for medical device clinical studies, inside and outside the US and Japan. Some form of recognition of this standard by regulators in several countries is expected.

Table 3: Revisions to ISO14155 Affecting the GCP Comparison

- emphasis on subject well-being, rights, safety and role as active participants
  - ISO 14155: 2011 enhanced requirements for medical care for subjects during and after the clinical investigation; communication with subjects (informed consent, changes affecting the subject's well-being and safety and rights in the event of termination); vulnerable populations; and payments/compensation available for subjects.
- significant emphasis on the increased role of risk assessment
  - ISO 14971:2007, Application of risk management to medical devices, is defined as "indispensable" in the application of ISO 14155:2011.
- role of the Institutional Review Board/Institutional Ethics Committee (IRB/IEC)
  - ISO 14155: 2011 is less prescriptive regarding the operation, responsibilities and roles of IRBs/IECs, and it refers to requirements per national or regional regulations. However, the implied role and responsibilities of the IRB/IEC regarding the types of documents the IRB/IEC must review, references to voting lists and who may vote and references to procedures for vulnerable populations are expanded from the 2003 version.
- more focus on conflicts of interest
  - ISO 14155:2011 adds requirements for documenting conflicts of interest and financial arrangements between those involved in the clinical investigation.
- changes to general conduct of the clinical investigation
  - ISO 14155:2011 adds details about the qualification of investigators, the informed consent process, monitoring, auditing and document maintenance and retention, and it adds references to data monitoring committees, closing an investigation and suspending or terminating an investigation.
- Emphasis on the integrity of the clinical investigation
  - ISO 14155:2011 adds references to maintaining an audit trail, ensuring the credibility of the trial results, publishing negative and positive results to guide future research and registering the clinical trial and the results in some jurisdictions.
- Alignment/harmonization with other GCP regulations
  - Revisions better align ISO 14155:2011 with clinical investigation regulations, in line with current global harmonization efforts.

Table 4: Nonsubstantive Differences

JGCP and US GCP differ with respect to…	To address this difference, additional documentation may be needed to demonstrate that…
Specifying medical experts to advise sponsor on the clinical trial[1]	A medically qualified person is available to advise the sponsor regarding the trial, with involvement in developing the protocol and direct responsibility for reviewing data regarding patient outcomes.
Indemnification or compensation for trial-related injuries[2]	There are provisions for patients to be compensated for any trial-related injuries.
Disclosure of potential or actual financial conflicts of interest[3]	Conflicts of interest are identified and managed so they do not bias or otherwise adversely affect the trial.
Required content of informed consent documents[4]	The informed consent process is adequate according to each investigative site's requirements and government regulations.
Scope of nontherapeutic provisions of informed consent documents[5]	The informed consent document is appropriate for the trial patient population.
Medical credentials of investigator[6]	The principal and sub-investigators are trained, experienced, and legally qualified or authorized to make medical decisions pertaining to subjects in the trial and fulfill their study responsibilities.
Investigator responsibility for ensuring patient follow-up[7]	The subjects understand instructions on device use and instructions are followed according to the protocol.
Informing other physicians of patient's participation in trial[8]	The investigator attempts to inform the subject's other physicians as relevant and as the subject permits.
IRB types, membership, organization, operation and documentation requirements[9]	IRB organization, operation and documentation are compliant with applicable government regulations; IRB is free from influence by any other entity and able to make independent judgments with regard to the safety and ethics of proposed clinical investigations.
Definition of reportable adverse events and timing of reporting[10]	Adverse events are reported in a reasonably timely manner to appropriate parties.
Labeling investigational product with device trade name, indications and instruction for use in package insert[11]	The product identification and proper instructions for use in the clinical trial are available to the principal investigator and the investigational devices are properly used.
Requirement for auditing[12]	A quality system at the sponsor and investigator sites ensures data quality and integrity and the protection of human research subjects in the trial.

JGCP Article 4 Paragraph 2; *FDA Guidance for Industry: Guideline for the Monitoring of Clinical Investigations*, January 1988 with minor editorial and formatting changes November 1998

1. JGCP Article 14 Paragraph 1; 21 CFR 50.25.
2. 21 CFR 54.4 and 21 CFR 812.110(d), *FDA Guidance for Industry: Financial Disclosure by Clinical Investigators*, 20 March 2001.
3. JGCP Article 71 Paragraph 1; 21 CFR 50.25, 812.40 and 812.100; *FDA Guidance for Sponsors, Investigators, and Institutional Review Boards: Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c)* February 2012.
4. JGCP Article 7 Paragraph 2 and Article 70 Paragraph 4; US 21 CFR 50.53 and 50.24
5. JGCP Article 2 Paragraphs 3 and 11, Article 4 Paragraph 2, Article 10 Paragraph 1(5) and Article 16 Paragraph 2; 21 CFR 812.3 (i) and 812.43 (a).
6. JGCP Article 65 Paragraph 1; 21 CFR 812.100.
7. JGCP Article 65 Paragraph 2.
8. JGCP Article 46 Paragraph 1 and Article 47; 21 CFR Part 56, *FDA Guidance for Institutional Review Boards (IRBs): Frequently Asked Questions – IRB Registration*, July 2009.
9. JGCP Article 2 Paragraph 18, Article 28, Article 39 and Article 68; PAL Enforcement Regulation Article 273, modified by Article 275; 21 CFR 812.3(s), 812.150(a)(1) and (b)(1).
10. JGCP Article 24 Paragraphs 1, 2 and 7; 21 CFR 812.5.
11. JGCP Article 31; 21 CFR 812.140 and 812.46.

Documentation of compliance to GCP is important. Monitors and auditors typically verify source data and assess compliance with GCP, as directed by the sponsor. The sponsor should inform monitors and auditors (as well as investigators and Ethics Committees) of the additional documentation that may need to be collected throughout the clinical investigation to address non-substantive and administrative differences. If the data will be used for approvals in several countries, informed consent documents should obtain the subjects' permission to disclose their data to regulatory authorities in these other countries. In addition, sponsors should ensure compliance with national laws on protection of confidential personal information.

Table 5: Administrative Differences

JGCP and US GCP differ with respect to…	To address this difference, additional documentation may be needed to demonstrate that…
Budget details[1]	Written agreements outline responsibilities and budget arrangements between sponsor and investigator.
Involvement of head of hospital as document signatory[2]	The trial-related documents are appropriately handled, e.g., trials disapproved by the IRB are not approved by the institution.
Investigator brochure[3]	The relevant information is provided to the investigators and IRB.
IRB appeal process[4]	The IRB reviews relevant information and has authority for the final decision.
Notification to patient if informed consent document is changed[5]	The trial subjects receive updated safety information pertinent to their participation and are given an opportunity to consider their continued participation.
Title, protocol number and date on protocol[6]	The version of the protocol in effect at any point in the trial is clear.
Method of identifying investigator to regulatory authority[7]	The institutions and investigators participating at any point of the trial are detailed in the final report of the clinical trial.
Method of reporting emergency deviations[8]	Local regulations are followed and deviations are reported in final report of the clinical trial.
Need for case report forms in multicenter trials[9]	The primary and supplemental data (if applicable) are collected in a systematic manner.
Timing of device delivery[10]	The time of device delivery has no effect on trial, conformity with IRB/ethics committee or regulatory requirements.
Details of suspension or termination of trial[11]	The appropriate notification (format, content, and timing) is provided.
Duration of record retention[12]	There is no impact on the clinical trial and records are kept for the period required by each country to ensure traceability of safety and performance of the product.
Differences in the titles and contents of essential documents	The validity of the trial methods and data integrity can be assessed.

JGCP Article 13 Paragraph 1(13); 42 USC section 1320a-7b. Anti-kickback Statute.

1. JGCP Article 55 Paragraph 2 and Article 13 Paragraph 1.
2. JGCP Article 8; 21 CFR 56.109 (e) and 21 CFR 812.110(b).
3. JGCP Article 51; 21 CFR 56.109 (e).
4. JGCP Article 74; 21 CFR 50.25 (b)(5).
5. JGCP Article 7; 21 CFR 812.25.
6. JGCP Article 33 Annex 2; 21 CFR 812.150 (b)(4).
7. JGCP Article 66 Paragraph 1; 21 CFR 812.150(a)(4) and 812.35(a).
8. JGCP Article 2 Paragraph 13 and Article 67; 21 CRF 812.140(3).
9. JGCP Article 11, Article 25 and Article 35 Paragraph 7; 21 CFR 812.1.
10. JGCP Article 32; 21 CFR 812.150(b)(2 and 3).
11. JGCP Article 34, Article 53 and Article 61; 21 CFR 812.140(b)(6) and (d).

Of course, 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. Likewise, the clinical practice patterns of physicians and ethnic makeup of the patient population may differ among countries and may affect patient outcomes; therefore, enrollment from various regions may be required in the study design. Early consultation with the relevant regulatory authorities may facilitate development of a clinical investigation design that is mutually acceptable to those authorities.

Conclusion

Given a clinical investigation design that is appropriate and acceptable to various regulatory authorities, this study shows that non-substantive and administrative differences among GCPs can be addressed with supplemental information and should not be a barrier to transportability and acceptance of clinical investigation data from elsewhere.

References

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2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E6 *Good Clinical Practice: Consolidated Guideline*; 1996. (Note: While the ICH E6 guideline is specifically applicable to drug and biological products, it has been applied as a GCP reference standard for some device studies, and was therefore included in this analysis.)
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4. US Food and Drug Administration. "Japan - US Harmonization-by-Doing HBD Pilot Program Initiative." www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/InternationalInformation/ucm053067.htm. Accessed 6 November 2012.
5. The term "regulatory authority" is intended to encompass both national regulatory authorities and independent conformity assessment bodies/agencies (e.g., PMDA) that perform marketing authorization reviews on behalf of those authorities.
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Acknowledgements

The authors thank GCP experts Kazuo Yano, Michael Gropp, Izumi Fukuzawa, Mari Shirotani, Makoto Akabori, Kira Cooper and Susan Dunsmore for their contributions to this project. The authors express appreciation for the hard work of WG4 committee chairs Kentaro Azuma and Carole Carey.

Disclaimer

This article represents the analysis and personal views of the authors and does not represent official US FDA correspondence or guidance or official Japanese Ministry of Health, Labour and Welfare (MHLW) correspondence or guidance. The Harmonization-By-Doing program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the US and Japan.