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Achieving Robust GCP Compliance with ISO 9001

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Introduction

Good Clinical Practice (GCP), as set forth by the International Conference on Harmonization (ICH), is the international quality standard for the conduct of clinical trials. EMA guidelines, WHO recommendations, CDISC standards and other applicable governmental regulations and guidances also apply. GCP provides assurance that the rights of study participants are protected and the resulting data are accurate, complete and credible.[1] However, while GCP includes numerous requirements, it does not describe a quality management system (QMS) to ensure compliance with those requirements in a robust manner.

ISO 9001, the international standard for quality QMSs, fills this gap. In fact, it requires compliance with statutory and regulatory requirements, such as GCP.[2]

This article discusses the process of implementing a GCP QMS according to the ISO 9001 standard.

Process Stakeholders, Actors and Customers

ISO 9001 looks at the world as a network of processes. In ISO 9001terminology, an "actor" is a person, entity or automated system that carries out one or more steps in a process. One actor can play roles in multiple processes. Actors other than systems are "stakeholders" in the process, as are other people and entities that have an interest in its performance, because they contribute inputs to it, influence it or receive outputs from it. Stakeholders that receive outputs from a process are called "customers" of that process.[2 section 4.2 and annex A.3]

Clinical research is a complex activity, with numerous actors, stakeholders and customers:

- Study sponsors
  - Study management
  - Quality management
  - Safety management
  - Etc.
- Clinical sites
  - Site management
  - Principal investigator
  - Research team
  - Etc.
- Patients and study participants
- Solution providers:
  - CRO(s)
  - Biostatisticians and other product and service providers
  - Central laboratories and other centralized services
  - Etc.

- Regulatory authorities
- IRB/ethical review committee

A QMS must consider the role and perspective of every stakeholder in every process.

This article will discuss only study sponsors and their solution providers, but the same principles apply to other clinical research stakeholders, including research sites.

Quality Policy Statement

An ISO 9001 Quality Policy Statement sets forth the purposes of a QMS, its scope, its stakeholders and its objectives (e.g., GCP compliance).

ISO 9001 requires a holistic rethinking of processes from a QMS perspective, not just from a binder full of standard operating procedures (SOPs). Implementation requires substantial resources, with significant implications across an organization, including the visible commitment and involvement of executive management.[2 section 5]

Understanding the Organization and its Environment

ISO 9001:2015 (the latest version) requires an organization to develop a clear understanding of itself and its environment, including internal and external stakeholders, and its strengths, weaknesses, opportunities and threats (SWOT). This information informs the design of a QMS. For example, a study sponsor must understand that investigators are both service providers and potential customers. A change in the environment (e.g., adoption of eRegulatory Binders by sites) changes the requirements of a QMS for GCP compliance.

Documentation

Compliance with GCP documentation requirements also satisfies ISO 9001 requirements.

Process Identification and Analysis

Process mapping is a widely used tool that enables systematic compliance with ISO 9001 requirements.

Basic components of process mapping include the following:

- **Process.** Overall workflow that transforms inputs into outputs from starting point to endpoint(s)
- **Task.** Step in a process performed by a person, entity or system
- **Flow** c**hart.** Diagram that visually displays interrelated information, such as steps in a process, in an organized fashion, such as sequentially or chronologically
- **Event.** Trigger that causes a process to start, end or follow a different route
- **Gateway.** Complex trigger in which an outcome or decision can route the process to different options, depending on events and conditions.
- **Actor.** A person, entity or system that performs one or more tasks in a process

Process mapping proceeds in the following steps:

- Identify the process you want to document.
- Gather information from process participants via interviews, observation or SOP content.
- Identify the start and endpoints of the process.

- Break the process into distinct tasks, identifying events, gateways and actors.

Process mapping is often used for process improvement, in which a process is revised to improve speed, quality, cost, flexibility, safety and other factors.[3] While GCP focuses on the desired state of full compliance, ISO 9001's perspective is that process improvement can refine the processes that ensure full GCP compliance.

After mapping, the processes can be combined into a high-level process map in the following tiers:

- **Strategic.** Processes that define policies and organizational elements, such as quality policy, risk management, management review and commercial strategies
- **Operational.** Processes for the productive activities of the organization, such as protocol design, research sites selection and vendor auditing
- **Support.** Processes that are not directly part of the productive activity, such as training, document management and equipment maintenance

Risk Management

Risk management is a close cousin to quality management. The most recent version of ICH GCP (R2) incorporates principles of risk management related to regulatory compliance, data integrity and patient rights.[4,5] ISO 9001 (2015) establishes the broader goal of business excellence, which requires minimizing risk and identifying opportunities for internal improvement and external positioning of the organization.

Process mapping does not address the risks inherent in a process. However, risk management is inherent in process improvement. There are five steps in risk management: identification, evaluation, treatment, monitoring and review. Some tools for risk management include trend analysis, root cause analysis, fishbone diagramming and probability/severity charting.

Quality Objectives

ISO 9001 states that organizations must define quality objectives for the functions, relevant levels in the organization and processes necessary for the QMS itself.[2 section 6.2]

An ISO 9001 quality objective is a "S.M.A.R.T." (specific, measurable, achievable, relevant, time-based) and desired or intended quality improvement goal:

- **Specific.** Objectives must be clear and specific, i.e., aimed at a concrete opportunity for improvement, and not be a general statement. For example, a specific quality objective might be: "Reduce Asian site complaints about study drug deliveries by 30 percent this year" and not "Reduce complaints from international sites."
- **Measurable.** If accomplishment of an objective cannot be measured, it cannot be said to have been achieved. In the example above, setting a 30 percent reduction goal makes it measurable.
- **Achievable.** Achievable objectives motivate performance and are likely to be accomplished. The opposite is true for unrealistic objectives. In the example above, a 30 percent reduction is realistic.
- **Relevant.** Resources should be applied to prioritized objectives that are most likely to make important improvements in quality. In the example above, timely deliveries of the study drug will significantly reduce protocol violations and protect the health of study participants.

- **Time-Based.** Objectives must have a planned completion date and should probably have interim steps with their own dates for planning and progress-tracking. In the example, above the completion date is this year.

Relationships with Process Customers

As stated above, process stakeholders who receive outputs from a process are called "customers" of that process. Customers can be internal (e.g., within the clinical operations department of the CRO that performs the process). Customers can also be external (e.g., within a different department, such as medical affairs) or in an entirely different organization (e.g., the study sponsor).

Process customers do not have to be customers in the normal business sense. For example, clinical research sites are process customers for the study sponsor process that generates protocols.

GCP assigns ultimate responsibility to the study sponsor for its own work and that of any product and service providers with proper delegation and supervision.

ISO 9001 requires documentation of process-customer requirements in which:

- Customer requirements are clearly specified.
- Any differences between the customer's initial statement of requirements and the final statement of requirements are specified.
- The customer and process owner both accept (e.g., with a signature) the final requirements as satisfactory and achievable in a verifiable manner.

Clinical Trial Design

GCP compliance and high-quality study results require clinical study processes to be designed with quality in mind (i.e., Quality by Design [QbD]).

A typical clinical study might include the following GCP design documents:

- Clinical protocol
- Adverse event management manual
- Biological samples management manual
- Instructions for handling the investigational drug
- Monitoring plan
- Data management plan
- Statistical analysis plan

ISO 9001 requires the study sponsor (or CRO) to establish, implement and maintain a design process that ensures the study is carried out in accordance with legal and regulatory requirements, process customer requirements and internal quality criteria. ISO 9001 requires study sponsors to ensure that that product or service providers follow ISO 9001 principles, even if they are not ISO 9001 certified.

The design process should document the following elements:

- All steps in the design process
- Specifications for each design activity
- Mechanisms of customer participation in the design process
- Design, verification, validation and approval activities

- Instructions for verifying and documenting that the design process meets its requirements

In the EU, governmental GCP inspections require maintenance of design document drafts.

Suppliers and Subcontractors

As noted above, under GCP, a study sponsor may delegate any of its trial-related duties and functions to a CRO or other service provider; but the ultimate responsibility for the quality and integrity of study conduct and data still resides with the sponsor. The same delegations can occur from the CRO to subcontractors, thus generating a chain of delegation. The sponsor still maintains ultimate responsibility, regardless of the number of delegation levels.

These supervised delegations are consistent with ISO 9001, provided suppliers are informed of their GCP and ISO 9001 responsibilities, evaluated (generally in the context of risk assessment) and supervised in a proper and well-documented manner.

Operational Processes

Compliance with GCP requirements, in conjunction with applicable governmental regulations and guidances, is consistent with compliance with ISO 9001.

Process Measurement and Monitoring

ISO 9001 sets forth process monitoring, measurement, analysis and evaluation as improvement mechanisms for evaluating the performance of the organization and the satisfaction of internal and external customers. These improvement-oriented aspects comprise the fundamental conceptual difference between ISO 9001 and GCP.

Key Performance Indicators (KPIs) measure the processes of an organization and serve as instruments for quality improvement.[6]

KPIs are based on the following three concepts:

- **Metric.** A measure of an organization's activities and performance, accompanied by a scale for evaluation (e.g., patient enrollment rate in a study)
- **Indicator.** A metric that provides a meaningful signal about some aspect of study performance that affects the likelihood of study success.
- **Attribute (Factor).** A common measurable property of a set of things being measured.

Clinical research processes should be measured based on the following elements:

- Associated risks
- Monitoring reports
- Audit reports
- Process customer complaints

In the case of a composite metric, the contribution of each contributing metric should be weighted based on its impact.

A single metric in isolation is of limited value. Metrics become more useful for managing and improving processes when they can be compared over time or, for example, across different clinical studies, different research sites or different responsible personnel.

Audits

GCP audits assess the compliance of a clinical study with respect to the protocol, SOPs, GCP and applicable regulatory requirements.[1,7]

ICH E6 (R2) states: "If or when sponsors perform audits ..." In contrast, ISO 9001 states: "The organization must carry out internal audits" to achieve, maintain and improve quality.[8]

ISO 9001 thus requires organizations (sponsor or CRO) to carry out audits at planned intervals to provide information on whether its QMS is meeting its objectives. ISO 9001 requires an annual audit plan that includes internal audits of the QMS.

Certification

In contrast to GCP, ISO 9001 provides for certification by an accredited certification body.

QMS Management Review

Unlike GCP, ISO 9001 provides a role for management. Specifically, top management must review the organization's QMS at regular intervals to ensure its continued suitability, adequacy, effectiveness and fulfillment of the organization's strategic objectives.

This management review must include the review, analysis and assessment of the following elements:

- Status of QMS and operational process improvement actions generated by previous reviews
- Internal and external changes that may affect the QMS
- Customer and other stakeholder comments
- The degree to which quality objectives have been achieved
- Nonconformities and corrective actions
- Results of process monitoring and measurement (KPIs)
- Audit results
- Results of monitoring of external providers
- Adequacy of QMS resources
- Effectiveness of actions implemented to mitigate risks and exploit opportunities
- Opportunities for improvement
- Any other element that is relevant to the QMS

Management's findings must document decisions and actions related to the following aspects:

- Opportunities for improvement
- Needed changes QMS
- Resources required for implementation

Nonconformities and Corrective Actions

ISO 9001 covers GCP protocol deviations and other nonconformities, as well as deviations from process customer requirements.

Continuous Improvement

GCP mentions continuous improvement only in passing, in connection with communication of risks in the risk management process during the conduct of a clinical study.[1, section 5.0.5] In contrast, ISO 9001 establishes continuous improvement as a primary objective for the QMS itself.

Conclusion

GCP and ISO 9001 are complementary standards. Whereas GCP primarily specifies the characteristics of high-quality clinical studies, ISO 9001 primarily specifies how an organization can develop operational processes and a QMS for achieving that level of quality, as well as other organizational objectives. As a result, while GCP sees imperfections as deviations from the standard that must be avoided or mitigated, ISO 9001 assumes that operational processes are imperfect, especially when objectives and conditions have changed, and focuses on how to avoid and mitigate deviations, along with improving process efficiencies.

References

1. ICH Harmonized Guideline Integrated Addendum to ICH E6(R2): Guideline for Good Clinical Practice.
2. ISO 9001:2015. Quality Management Systems – Requirements.
3. (a) Howard K. Kalman. PIQ, Vol.15 (4), 57-73 (December 2002). (b) *The Map to Success: Using Process Mapping to Improve Performance* (ISBN 1 903433 02 9). Published by Audit Scotland (May 2000).
4. "Reflection Paper on Risk-Based Quality Management in Clinical Trials." EMA/INS/GCP/394194/2011.
5. FDA Guidance for Industry. Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (2013).
6. D. Parmenter, *Key Performance Indicators - Developing, Implementing and Using Winning KPIs*. (4th edition, 2020). John Wiley & Sons
7. Revision of the Engage Auditing Guideline. An Optional Guideline for GCP Compliance and Quality Management Systems Auditing. EFGCP 2005.
8. ISO 19011:2018. Guidelines for Quality and/or Environmental Management Systems Auditing.

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