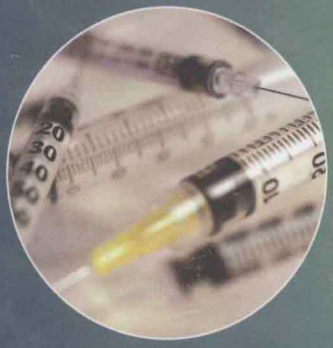
CLINICAL TRIALS AUDIT PREPARATION

A Guide for Good Clinical Practice (GCP) Inspections



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A Guide for Good Clinical Practice (GCP) Inspections

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PREFACE

GCP inspections of clinical trial sites are the challenges that clinical research faces in demonstrating data credibility and patient safety. However, I found in my clinical research experience that audits are a tedious but nevertheless necessary activity to assure that all parties do their job right.

Being a clinical scientist and third party auditor allowed me to understand the struggles in clinical research (CR) and quality assurance (QA). Although CR and QA are independent activities (we do not talk to each other unless necessary) they have interdependent tasks. The auditor should know the challenges of the clinical research associate/monitor, and vice versa. Understanding the objectives of each other's tasks will allow the clinical work to proceed smoothly.

In the last 15 years since ICH GCP was issued as an International Guidance for clinical research, the pharmaceutical research-based industry as well as academic research institutions had to realign all their activities to remain "compliant" to regulations. The setting of clear and uniform standards raised the bar for clinical research and development (R&D); however, it also increased the cost to staggering levels.

During my preregulatory inspections of clinical trial sites and sponsors as well as GLP labs, a constant issue was always present—the dread of the inspected facility of the possible findings and their consequences.

Many times while performing inspections I was asked "Are we in compliance?" or "Do you see something serious?" My logical thought was "Will I be able to find all possible sources of noncompliance before the FDA inspector comes?" Could I provide assurance to my client that everything was OK?

Obviously, some of my clients are happy to see me and eager to walk though the inspection, learning and uncovering all possible issues. However, others dislike my presence, thinking that I will point a finger at people who did things wrong and who thus may lose their jobs. At that point I feel isolated and unwanted, but badly needed.

The best part is at the end of the inspection, when we all sit down to dissect the results and the clinical teams start to understand the meaning of the findings and accept suggestions to achieve compliance. Finally, we all shake hands and, with a smile, we go home after long days of document hunting and endless reading.

The writing of the report is another story. When I write my inspection report, it does not look like a Form 483; it is a "catharsis" for my client. I summarize hundreds of findings in a tabulated manner where the last column is "Suggested Remedial Action." I point out the noncompliance and how to get back on track. That is a relief to my clients, since action can be taken immediately to ensure future compliance.

Of course, it would be childish to suggest that all noncompliance can be remediated: some noncompliance issues are based on the complete misunderstanding of the requirement or regulation, and on strong opinions based on old school medicine.

With this book I was given the task of putting together the world of the regulator, the sponsor of clinical research, and the investigators. As a professional development instructor and former university teacher, I understand that we cannot start speaking of a particular topic without first seeing the big picture, and where that topic fits in and the implications and future consequences of the issue discussed. I do not take anything for granted until it is explained and understood. Therefore, it was very important that with the first chapters I review compliance to what, and then compliance by whom, and finally how to achieve compliance. Understanding the drug development process is also a must, since the reader needs to be on the same page to understand the inspection process. The processes described in this book are part of the FDA BIMO compliance programs 7348.810 and 7348.811 that are publicly available.

The challenge in writing this book was to present the subjects objectively to avoid the boredom inherent in a dry topic as GCP compliance. Therefore, I covered the responsibilities of the parties in clinical research according to GCP and 21 CFR 312, and other applicable requirements and utilized examples as much as possible. The biggest challenge was that every time I thought I had finished, new things happened in the clinical research world that I had to include, and every review was an update until I said this is it, for now. I am already thinking of the next edition and how things will change in the coming years.

We have to move forward in clinical research and in how therapeutic products are developed. Ten to twelve years for development and billions of dollars is too much for a failure rate of more than 75%, and changes are coming soon. Read the FDAAA (http://www.fda.gov/oc/initiatives/advance/fdaaa/accomplishments.html) for current insight.

Having the privilege to work in basic scientific research, medicine, clinical research and development and being a scientist, I was able to present clearly issues from product discovery to market and write about them from the compliance point of view.

Another topic that I consider extremely informative is the analysis of warning letters. As we go through the regulatory findings we can easily see where the failures in compliance are and what may be missing. I do suggest that all clinical research professionals read the FDA warning letters to clinical investigators, sponsors, and institutional review boards as they appear in the FDA website, since they point out issues that arose after detailed review of data and documents; this will increase the reader's pool of regulatory knowledge.

Lastly, I formulated several key questions in understanding GCP compliance to clarify topics that may pop up when reading the guidance.

The footnote references are a pivotal part of this book; the reader has been provided some of the documents referred to in the footnotes in the appendixes.

My last bit of advice is that before implementing processes or procedures (SOPs), read the code of federal regulations applicable to your activity or product. Also, go to the source, and never rely on interpretations or guidance that may be only the opinion of one party. See the whole picture, and then you will understand why.

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January 2010

INTRODUCTION

Clinical trials are conducted in humans to determine safety, tolerability, and efficacy of potential therapeutic products. Those trials have to be conducted in compliance with specific regulatory requirements and Good Clinical Practice to demonstrate that patient's rights, safety, and well-being, as well as data credibility are ensured.

Internal sponsor audits together with FDA regulatory inspections of clinical trial activities are essential to assure compliance with SOPs, GCPs, and established regulatory requirements.

This book intends to summarize specific aspects of drug development as well as present in a clear and concise manner the principles of drug development and Good Clinical Practices.

It is very important that the clinical research stakeholder (sponsor, investigator, or member of an Institutional Review Board) understands the basic principles of the GCP guideline, since it highlights the spirit of the requirements for clinical trials. The FDA, although it did not implement ICH/GCP into its regulations, is fully observant.

Following the principles of GCP will allow stakeholders to focus their activities in a compliant fashion. Understanding the regulatory requirements established in the FDA code of federal regulations, particularly 21 CFR 11, 50, 54, 56, 312, 314, 320, 601, 812, and 814, will allow the research professional to establish proper processes and procedures to ensure compliance for FDA regulated trials.

This book will guide the reader through the extensive foundation of knowledge that is necessary to understand and be prepared for the task of conducting clinical investigations in human subjects.

Since its implementation, the FDA Bioresearch Monitoring Program has been in charge of GCP inspections of clinical trial investigative sites, sponsors, Institutional Review Boards, and Contract Research Organizations. The processes and procedures that the inspector follows are publicly available in the *FDA Compliance Program Guidance Manual*. However, this book assists readers to understand how the process works, who is inspected and why, and what are the consequences of an inspection. An in-depth analysis of warning letters gives the reader an insight of what is essentially going wrong, and where stakeholders have to improve.

BACKGROUND HISTORY ON CLINICAL RESEARCH STANDARDS

Clinical research and development has undergone extensive changes in the last decades, adapting to a continuously changing regulatory framework. With the need to expand the applicability of clinical trial data gathered internationally, it was

recognized that common grounds should be established for global research and development of therapeutic products.

Large R&D-oriented pharmaceutical companies initially implemented their own R&D standards and internal processes aimed at local regulatory requirements for submission purposes. In the last few decades, before new guidelines were set into place, clinical trials were mostly conducted at a local level, and the industry had to spend additional resources and time to satisfy every country-specific requirement. There was no unified standard for the conduct of clinical trials; therefore, standards were set up independently by regulatory bodies to be consistent with the Declaration of Helsinki.[1]

The Declaration of Helsinki was adopted by the 18th World Medical Association Assembly in 1964 and outlined the basis for the ethical principles for medical research involving human subjects, serving as the main document for the conduct of medical research. The fundamentals of the declaration were set in the Nuremberg Code[2] after the Nuremberg tribunal exposed medical research crimes committed during the Second World War.

In the United States, on April 18, 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report,[3] which identified the basic ethical principles that underlined the conduct of biomedical and behavioral research involving human subjects and developed guidelines that should be followed to assure that such research is conducted in accordance with those principles.

Both documents focused on subjects' rights and safety as the main concern; however, they were inadequate on setting a standard for data quality, accuracy, and integrity.

It is reasonable to understand that data quality was not the objective of those documents since they are mostly an extension of the Nuremberg Code, which focused purposely on subjects' rights and safety.

Therefore, after observing a great procedural and implemental disparity in clinical research, the need was identified for a process that will be internationally accepted to set the guidelines for the conduct of human research, taking into account both aspects of clinical research: subject's rights and safety, and data quality, accuracy, and validity.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use issued the *ICH Harmonised Tripartite Guideline for Good Clinical Practice E6(R1)*[4] on June 10, 1996. In this document the industry and stakeholders, for the first time, have an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. This document addresses both aspects of clinical research: patients' rights and safety and data quality, accuracy, and integrity.

[1] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. See Appendix Cat the end of this book.

[2] See Appendix D at the end of this book for a copy of the Nuremberg Code.

[3] See Appendix E for a copy of this report.

[4] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guideline for Good Clinical Practice E6(R1)*, June 10, 1996.

GLOSSARY

The glossary in this book is aligned with the definitions provided in the ICH/GCP document.[5]

Adverse Drug Reaction (ADR): In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; that is, the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the *ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the *ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

Applicable Regulatory Requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate: A declaration of confirmation by the auditor that an audit has taken place.

Audit Report: A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trail: Documentation that allows reconstruction of the course of events.

Blinding/Masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware,

[5] *Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance*, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), April 1996 ICH.

and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the *ICH Guideline for Structure and Content of Clinical Study Reports*).

Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials): Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee: A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

Coordinating Investigator: An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

Contract Research Organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, X rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see point 8 in *Essential Documents for the Conduct of a Clinical Trial*).

Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness: A person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and nonmedical members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

Informed Consent: A process by which a subject voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical): Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB): An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator/Institution: An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements."

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report: A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Multicentre Trial: A clinical trial conducted according to a single protocol but at more than one site and therefore carried out by more than one investigator.

Nonclinical Study: Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee): The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record: See **Source Documents**.

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guideline the expression "regulatory authorities" includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): Any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic

negatives, microfilm or magnetic media, X rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor–Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor–investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Subinvestigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also **Investigator**.

Subject/Trial Subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

Trial Site: The location(s) where trial-related activities are actually conducted.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial.

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