

CHAPTER 1

GOOD CLINICAL PRACTICE AND THERAPEUTIC PRODUCT DEVELOPMENT

This chapter provides the background information necessary to understand the universal basis of the inspectional strategies for clinical trials. Consequently, to be able to understand the purpose and background of an inspection, it is very important to comprehend Good Clinical Practice (GCP) and its applicability in real situations in clinical trials.

GCP will not teach or direct medical doctors on how to run a clinic, but rather will guide all parties involved in clinical research (the sponsors, the investigator, and the ethics boards) on what practices and procedures will ensure patient safety and data credibility.

It is very important that all personnel involved in clinical trials are properly trained and updated on GCP and understand the end implications of noncompliant activities in clinical research.

Together with GCP the reader should understand the FDA drug development process, where the regulator, observing GCP, outlines country-specific procedures and requirements to ensure compliance.

Also, this book discusses the applicability of GCP in postmarketing studies that have become increasingly necessary for the continuous evaluation of safety and efficacy of a marketed therapeutic product. The new approach of regulators worldwide seeking more postmarketing research took a definite turn with implementation of the FDAAA (FDA Amendment Act) in 2007, where the agency was provided with more enforcement power to direct sponsors holding a market authorization to sell a drug product, to conduct Phase IV clinical trials to further support safety and efficacy.

Initially, to ensure compliance to standards and regulatory requirements, all parties in clinical research have to implement quality assurance (QA) processes as needed. This book discusses, in a concise manner, what QA means for all clinical research parties involved and how to implement an efficient QA program to act preemptively on a regulatory inspection.

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The main topics discussed in this chapter are:

- Good Clinical Practice in clinical research
- Clinical development of therapeutic products in the United States
- Phase IV studies and GCP
- Quality assurance in clinical research

1.1 GOOD CLINICAL PRACTICE IN CLINICAL RESEARCH

1.1.1 Definition

Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

The main elements of GCP are (1) the **subject's** rights, welfare, and confidentiality and (2) **data** validity, integrity, and credibility.

1.1.2 GCP Compliance

Compliance with GCP provides public assurance that the rights, safety, and well-being of trial subjects are protected in consistency with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Patient safety and data credibility are the main objectives not only to GCP as a guideline, but to the FDA and other regulatory authorities as their requirements for clinical investigations on human therapeutic products.

1.1.3 GCP Objectives

The objective of GCP is stated by the document as follows:

“To provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.”

This definition applies also to all other countries that adhere to these guidelines.

These standards were adopted by most countries worldwide that have regulatory bodies that want to be integrated into the global mutual clinical data flow for submission purposes.

The FDA is observant of ICH/GCP guidelines (meaning that the FDA CFR precedes the guideline, but does not disagree with the principle).

It must be noted that although these guidelines should be followed by any party when generating clinical trial data that are intended to be submitted to

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regulatory authorities for market approval purposes, it also should be applicable to **any investigation where human subjects are participants.**

GCP should be considered applicable to **any investigation where human subjects are participants.**

1.1.4 Principles of ICH GCP

Clinical Trial Conduct Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

Risk Assessment Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

Subject's Rights and Safety The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

Background Information All available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

Clinical Trial Protocol Clinical trials should be scientifically sound and described in a clear, detailed protocol.

Note that the content structure of the protocol should be consistent to a standard format to allow easy search reading and understanding.

Ethics Review and Approval A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion. Mainly, all documents reviewed and approved by the IRBs have to be included in the approval letter to identify precisely the study, the protocol, and other related documents.

Ethics review boards have to be duly constituted according to GCP and local requirements and should follow standard operating procedures to demonstrate adherence.

Note that any ethics board that is not constituted and does not function according to regulatory requirements and GCP cannot issue a valid approval. From the investigator's compliance point of view (see Form 1572¹) it is like running a clinical trial without approval.

¹FDA Form 1572, Statement of the Investigator. Electronically available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualForms/Forms/UCM074728.pdf>.

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Medical Care of Trial Subject GCP is very clear that clinical trial personnel have to be qualified to perform the duties required. Therefore, “the medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.” Also if you refer to the Declaration of Helsinki this premise is consistent.

Qualifications of Clinical Trial Personnel “Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).”

Informed Consent Process The informed consent process goes far beyond the consent document per se. The process itself is part of the scrutiny during an inspection. It must be demonstrated that the consent was obtained freely, without prejudice or duress: “Freely given informed consent should be obtained from every subject prior to clinical trial participation.”

Data Management Once a study commences, the clinical trial data has to be collected **with extreme care and precision**. “All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.” The process of data management has to be described in detail in the sponsor’s standard operating procedures, which also are going to be inspected.

Patient Confidentiality Patient health records are covered by strict regulations. All data that is collected for clinical trials purposes must be treated as private and confidential. “The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).” The patient information and consent form should be written in accordance with local requirements and GCP to assure the participants that their identity will always be protected. Note that confidentiality of patient records and how the information is handled varies from country to country according to their laws, and the sponsor has to be very much aware of the differences.

Investigational Product Manufacturing, Handling, and Storage The sponsor is responsible for the investigational product that is being studied. “Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.”

Quality Assurance Sponsors and Institutional Review Boards should implement standard procedures to ensure that the activities carried out are in compliance with GCP and regulatory requirements. As you can observe, GCP does not establish requirements for the investigator to implement SOPs. The issue of investigators and SOPs will be discussed later.

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However, it is not enough to have written procedures of SOPs, since once procedures are written and implemented, a **quality assurance process** should be put in place to ensure that those activities have been carried out as per procedures and that if deviations have been observed, they are corrected and the activity well documented.

GCP requires that “systems with procedures that assure the quality of every aspect of the trial should be implemented.” Investigators should follow the procedures that are described in the protocol for a clinical investigation.

However, due to the inspectional findings where investigators fail to comply with their own responsibilities as investigators (described in brief in the signed Form 1572), written standard operating procedures are being sought. This issue is also going to be discussed further since written SOPs may not assure that the investigator will not repeat noncompliant activities. Therefore, a robust QA program has to be implemented when procedures are written and adopted.

Other regulatory bodies consider SOPs for investigators a requirement (Health Canada).

1.1.5 GCP Applicability

Good Clinical Practice applies to the three main parties involved in a clinical trial: (1) the sponsor of the clinical investigation, (2) the principal investigator (PI), and (3) the Institutional Review Board (IRB) or Ethic Review Board or Committee (see Figure 1.1)

In the case where the principal investigator initiates the clinical trial (academic clinical trials not sponsored by industry), he/she also bears the responsibilities of the sponsor. This is procedurally defined as a dual role sponsor – investigator. The dual role is discussed in-depth later to allow institutions that foster this type of human research to understand the scope of FDA regulatory applicability.

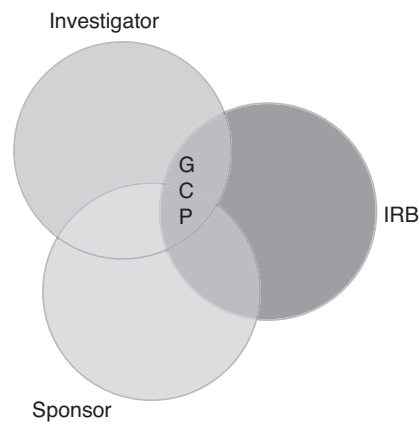


Figure 1.1 Parties in a clinical trial.

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The role and responsibilities of the clinical research sponsor are discussed first since the sponsor is the initiator of a clinical study.

1.2 ROLE OF THE SPONSOR OF A CLINICAL INVESTIGATION

The **sponsor** of a clinical trial is an individual, corporation, manufacturer, agency, or scientific institution that assumes the sponsor's responsibilities as described in Good Clinical Practice and the applicable regulatory requirements. For FDA purposes, the sponsor is the individual or company that identifies himself or itself as such in Form 1571².

1.2.1 GCP: Responsibilities of a Sponsor of a Clinical Trial

When a sponsor initiates the development of an investigational product in humans, he/she assumes the following responsibilities:

1. *Provide for Quality Assurance (QA) and Quality Control (QC)*. The clinical trial sponsor has to confirm and demonstrate that all clinical trial activities are conducted in accordance with GCP and regulatory requirements.

The sponsor should:

- (a) *Implement QA and QC*. The sponsor is responsible for implementing and maintaining quality assurance (audit capabilities) and quality control (monitoring clinical trials) systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- (b) *Secure Agreements with Parties*. The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing as part of the protocol or in a separate agreement.

The potential agreements within parties in clinical trials are between:

- Sponsor – investigator
- Sponsor–contract research organization/third party contractors
- Sponsor– clinical trial laboratory testing facility
- Investigator – institution
- Investigator– site management organization (SMO—not directly included in GCP or regulations)

²Form 1571—FDA Investigational New Drug Application. Available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualForms/Forms/UCM083533.pdf>.

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Site management organizations are identified as new players in the clinical research industry, providing services to the investigator site as coordinators and other clinical trial site-specific services. Note that these organizations, new in the clinical research setting, are not mentioned yet in GCP or regulatory requirements, and therefore are not subject to regulatory inspections. It is very important to address that, although SMOs are necessarily not inspected by the regulator, the sponsor should inspect the SMO that provides services for the investigator's site and determine that it is fully compliant with GCP and regulations. Also, the sponsor has to know in detail the agreement between the investigator site and the SMO to guarantee accessibility to records and quality of the activity contracted.

- (c) **Provide for Monitoring.** Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.
2. **Hire a Contract Research Organization (CRO).** In the last two decades, the industry faced an increased number of clinical trials and locations of investigational sites. Also, with the adoption of GCP and the increase in regulatory demands, sponsors had to seek out third party service providers for clinical research activities to remain compliant and to complete projects in a timely manner. GCP is very clear on the relationship between a sponsor and a sponsor's service provider.
- (a) **Transfer Trial-Related Duties.** A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing. **The transfer should be done in writing in the format of a contract agreement where the transferred duties must be detailed.** Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.
Transfer of duties does not mean in any case transfer of responsibilities. Note that the sponsor is always ultimately responsible for the quality and integrity of the trial data.
 - (b) **Ensure QA and QC of CRO.** The CRO should implement quality assurance and quality control. CRO compliance to GCP and regulatory requirements is the same as for the sponsor; therefore, it has to implement QA and QC.
 - (c) **CRO Shares Sponsor's Responsibilities.** All references to a sponsor in GCP also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor, and therefore assumes responsibility for the activities contracted.
3. **Provide for Medical Expertise.** Clinical trials, although not a replacement for medical treatment, have to always consider the health, safety, and well-being

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of the subjects involved. Medical decisions on efficacy and/or safety have to be done in an ongoing manner from the part of a sponsor of a clinical study. Therefore, the sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. Since it may become impractical for a company/sponsor to keep on staff full-time medical experts, then, if necessary, outside consultant(s) may be appointed for this purpose.

4. *Develop Trial Design.* The design of the clinical trial is the sponsor's responsibility. The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the Protocol and Case Report Forms and planning the analyses to analyzing and preparing interim and final clinical trial reports.
5. *Provide for Trial Management, Data Handling, and Recordkeeping.*
 - (a) *Clinical Trial Management Personnel Qualifications.* Adequately qualified personnel are the key to a successful study. The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.
 - (b) *Independent Data Monitoring Committee.* Due to the complexity and size of clinical trials, continuous safety surveillance of the subjects has to be provided to ensure that the sponsor reacts to safety concerns appropriately. The sponsor should consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and should maintain written records of all its meetings.
 - (c) *Electronic Data.* GCP established the grounds for many aspects of data management when electronic systems are utilized; nevertheless, regulators defined specific requirements that are to be implemented strictly to assure compliance.

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- (i) *Perform System Validation.* Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).
- (ii) *Use Standard Operating Procedures.* Maintain SOPs for using these systems.
- (iii) *Institute an Audit Trail.* Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

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- (iv) **Provide System Security.** Maintain a security system that prevents unauthorized access to the data.
- (v) **Determine Access Privileges.** Maintain a list of the individuals who are authorized to make data changes.
- (vi) **Provide for Data Backup.** Maintain adequate backup of the data.
- (d) **Blinding.** Maintaining the blinding in a clinical trial is essential to reduce bias on the observations on the part of the blinded parties. The sponsor should safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).
- (e) **Source Data.** Source data should exist for all information collected in a clinical trial CRF. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should ensure access to the source at any time.
- (f) **Unique Subject Code.** The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject. Also, since we should have one code for a subject, we should have one subject for a code. In other words, we cannot re-enroll subjects who previously participated in the study(ies) without particular exemptions (extensions, open label phases, etc.) since they are not going to contribute with new data, and long or repeated exposure to the investigational product may be of a higher unknown risk.

1.2.2 Essential Documents for the Clinical Trial

GCP states that “the sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial.” The sponsor should have an organized system, the Trial Master File (TMF) for filing, searching, and retrieving those essential documents. The sponsor also should maintain an electronic Trial Master File that contains all the essential documents for the clinical trial either electronically generated or scanned from the original paper documents. Accessibility privileges and all other assurances for the integrity of the filing system should follow the criteria for electronic systems in clinical trials. Also, the sponsor must keep the original paper documents as a source.

Retention of the Essential Documents for the Clinical Trial The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

Archiving of the Essential Documents for the Clinical Trial After Discontinuation of Development If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s) (in Canada the record retention is for 25 years).

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Notification If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

Transfer of Data Ownership In these times when mergers and acquisitions of pharmaceutical and biotech companies occur frequently, it is important that there is evidence of ownership of (and responsibility for) the data for the investigational products that continue development. Transferring data ownership also entitles the transfer of sponsors' responsibilities before the eyes of the regulator. GCP states that "any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s)."

Records Retention Access to records by the parties of a clinical study will allow the regulator through compliance inspections, to confirm the adherence to requirements. A comparison with original records at the investigator site and at the sponsor's site will only be possible if the records are retained for a minimum established period. The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor (in Canada the record retention is for 25 years).

Also, the sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention (e.g., in the clinical trial agreement) and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed. The sponsor is responsible for ensuring access to source documents and other clinical trial documents at the investigator site to auditors and regulatory inspectors for the stipulated period of time.

1.2.3 Investigator Selection

Clinical trial success depends on selecting the right investigator with the right resources and facilities. The selection process should be detailed in procedures that are very explicit on the sponsor's selection criteria.

GCP establishes that the sponsor is responsible for selecting the investigator(s)/institution(s).

Investigator's Qualifications GCP states that "each investigator should be qualified by training and experience." It is very important to note that the investigator is responsible for the medical care of subjects; therefore, when selecting an investigator, he/she should be qualified and able to provide that medical care (licensed to practice in the province, state, or region), and at the same time be able to conduct the study at the site.

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Resources at the Investigator's Site The investigator should have personnel to assist him/her in the undertaking of a clinical trial since it entails various activities that are time consuming and extensive. The investigator must comply with GCP, regulatory requirements, and specific study requirements at all times, and a person who acts as a coordinator for those activities may be required. Also, the investigator site should have, if required by the protocol, a study nurse and co/subinvestigators who will have certain responsibilities delegated to them in order to achieve the study's objectives in a timely and compliant manner. GCP states that "the investigator should have adequate resources to properly conduct the trial for which he/she is selected." If organization of a coordinating committee is to be achieved and/or selection of coordinating investigator(s) is to be done in multicenter trials, their organization and/or selection are the sponsor's responsibilities.

Protocol and Investigator's Brochure The sponsor has the responsibility to write and have the protocol and Investigator's Brochure available for the investigator to peruse before committing to the study.

GCP states that "before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided."

Agreement with the Investigator/Institution It is essential that the sponsor secure a written agreement with the investigator/institution before the clinical trial is initiated.

The sponsor should obtain the investigator's/institution's agreement for the following: (1) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC; (2) to comply with procedures for data recording/reporting; (3) to permit monitoring, auditing, and inspection; and (4) to retain the trial-related essential documents until the sponsor informs the investigator/institution that these documents are no longer needed.

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

Although GCP states the four essential elements of compliance in the agreement between an investigator and sponsor (compliance to regulatory requirements and GCP and IRB approved protocol; compliance to protocol procedures for data recording/reporting; permitting monitoring and audit; and document retention), it is important to emphasize that the sponsor should include specific conditions for the implementation of the clinical trial at the site and consequences for violations, deviations, or noncompliant activities.

1.2.4 Allocation of Responsibilities

GCP states that, prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions. This activity is usually performed by the

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assigned project manager/project leader, who, with the guide of the protocol and the Investigator's Brochure, will estimate and allocate clinical trial functions to ensure compliance and project control.

1.2.5 Compensation to Subjects and Investigators

Compensation to Subjects for Trial-Related Injuries A subject compensation clause is applicable when regulatory authorities establish that requirement and when the patient is financially responsible for his/her medical care. It is essential that this issue is discussed properly in the patient information and consent form. GCP establishes that "if required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/institution against claims arising from the trial — compensation for trial related injuries — except for claims that arise from malpractice and/or negligence."

It is important to note that any claims that arise from malpractice and/or negligence against the site are the investigator's responsibility and he/she should have knowledge of that to make sure his/her professional insurance covers clinical trial situations. In the same way, the sponsors are responsible for their part in any claim.

GCP states that "the sponsor's policies and procedures (SOPs) should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s)."

Other Types of Compensation to Trial Subjects It is generally accepted that healthy volunteers who participate in Phase I studies be compensated for their participation in the study. However, depending on the regulatory body, patients in Phase II or III trials might not be entitled to monetary compensation. It is important to note that the compensation should not be construed as a benefit. The GCP guidance states that "when trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s)."

1.2.6 Financing

Previously, we discussed the GCP guideline where there should be a written agreement between the sponsor and the investigator on the compliance terms of the clinical study — the Clinical Trial Agreement (CTA). Also, the sponsor and the investigator must agree on the financial terms of the study. Those financial terms can be part of the CTA, but not necessarily. The parties may have an independent financial agreement that also has to be available for inspection. GCP states in this matter that "the financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution."

It is important to note that investigations of a site within an institution may be subject to institutional overhead. Financial agreements between the sponsor and investigator will set the basis for the amount of overhead charged.

1.2.7 Notification/Submission to Regulatory Authorities

Drugs, biologicals, and medical devices intended to be tested in humans are regulated products. Sponsors must ensure that they request and obtain regulatory authorization to start the development of an investigational product in humans. The scope of the regulated product may vary from country to country, but the applicability of the principle is the same.

The GCP principle states that “before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.”

1.2.8 Confirmation of Review by IRB/IEC

The sponsor does not communicate with the IRB/IEC directly. However, in a January 2010 draft guidance, the FDA suggested that the sponsor should submit annual safety reports directly to IRBs since they have access to a broader base of information. All communications and interactions within the IRB/IEC are done through the investigator.

According to GCP regarding IRB/IEC, it is the sponsor’s responsibility to obtain the following from the investigator/institution:

- ***IRB/IEC Identification.*** The name and address of the investigator’s/institution’s IRB/IEC.
- ***IRB/IEC Compliance Statement.*** A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
- ***IRB/IEC Approval Document of the Clinical Trial Documents.*** Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s), and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.
- ***Protocol Amendments Approvals.*** If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.
- ***Continuous IRB/IEC Review and Approval.*** The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

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1.2.9 Information on Investigational Products

This part refers to the sponsor's responsibility to have a complete preclinical development dossier that will support the application to develop the investigational product in humans, and to write and update an Investigator's Brochure.

GCP states that "when planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied."

Safety and efficacy information together with the risk assessment of the investigational product will eventually change as development evolves. It is important to reassess risk as new data becomes available and inform the investigator and the patient if that information is relevant.

GCP states that "the sponsor should update the Investigator's Brochure as significant new information becomes available."

1.2.10 Manufacturing, Packaging, Labelling, and Coding Investigational Products

Characterization, Manufacturing, and Labeling of the Investigational Product The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

Storage Conditions The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

Packaging of the Investigational Product Investigational products are shipped and stored and therefore handled before being provided to the eligible subjects. The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

Coding and Decoding of the Investigational Product In clinical trials that are designed to be blinded to reduce bias in data collection and reporting, the process to access the identification of the blinded product is called **Decoding**. Decoding procedures should be followed in case of patient emergency as stated in the protocol. The decoding procedure and the unblinding of a patient investigational product should not compromise the blinding of the study. Decoding is performed through the use of code breakers that are paper format or electronic. Access to codebreakers should be 24/7. Any decoding, including involuntary decoding, should be properly documented.

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GCP states that “in blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.”

Investigational Product Changes and Bioequivalence Studies “If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.”

1.2.11 Supplying and Handling Investigational Products

The sponsor has the responsibility to supply investigational product to the investigational site (investigator/institution) in a timely manner and in compliance with GCP and regulatory requirements.

Supply The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

Procedures for Investigational Product Handling The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe (1) receipt, (2) handling, (3) storage, (4) dispensing, (5) retrieval of unused product from subjects, and (6) return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

Investigational Product Records The sponsor should provide and maintain records for the handling of the investigational product. The sponsor should maintain records that document (1) shipment, (2) receipt, (3) disposition, (4) return, and (5) destruction of the investigational product(s).

Investigational Product Retrieval or Recall The sponsor should maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

Investigational Product Disposition The sponsor should maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition. That system should be explained in the protocol and followed by the investigator.

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Investigational Product Stability Ongoing stability testing will ensure that the investigational product remains stable during the clinical trial. GCP states that “the sponsor should take steps to ensure that the investigational product(s) are stable over the period of use.”

Investigational Product Samples The sponsor should maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

1.2.12 Record Access

Access to records should be available at any time to source verify data entered in the Case Report Forms, to audit for compliance, and to allow access to regulatory inspectors.

GCP states that “the sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.”

Verification of Patient Consent to Record Access The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

1.2.13 Safety Information

As principles of the Declaration of Helsinki, it is important that the sponsor ensures patient safety and well-being at all times. The risk and benefit assessment of an investigational product is started when the sponsor initially submits the request for authorization to regulatory authorities to run the first clinical trial in humans.

However, safety is of concern at all times, and the sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

Safety Issues Any unexpected and serious adverse event, if confirmed, may affect adversely the safety of the subjects in a study.

Communication of Safety Issues GCP states that “the sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could:

- affect adversely the safety of subjects,
- impact the conduct of the trial, or
- alter the IRB/IEC’s approval/favorable opinion to continue the trial.”

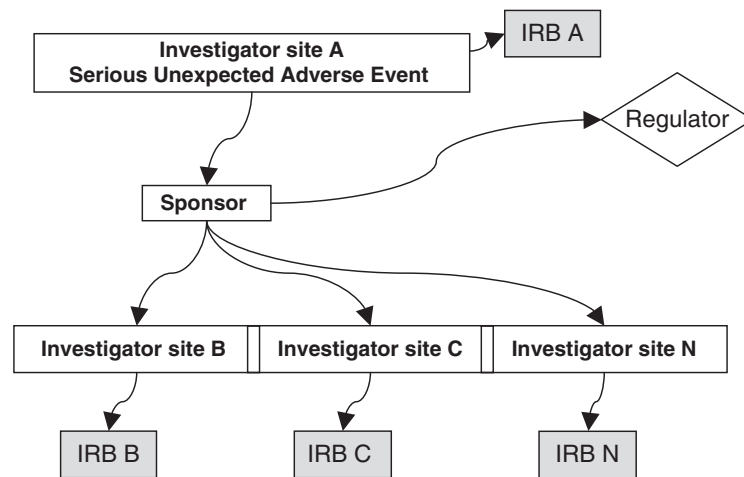


Figure 1.2 SAE reporting flow chart.

1.2.14 Adverse Drug Reaction Reporting

Serious Unexpected Adverse Drug Reactions These reactions are serious in nature and severity and never previously reported in the Investigator’s Brochure or any other safety record. Those reactions may affect the risk–benefit assessment and therefore should be communicated immediately. The sponsor must report them as soon as it becomes aware of the event, following GCP and regulatory requirements.

The sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected. (see Figure 1.2.)

SAE Reporting Compliance SAE reporting process and timeliness should comply with (1) applicable regulatory requirement(s) and (2) ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Safety Updates and Periodic Reports This reporting is in addition to the serious adverse event reporting and clinical trials reports. GCP stipulates that “the sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).” This reporting should be mostly generated by the Independent Data Monitoring Committee or Data Safety Monitoring Boards appointed by the sponsor and who have the responsibility to follow all safety issues for the investigational product in question and conduct an ongoing safety assessment.

1.2.15 Monitoring

The monitoring of a clinical trial is a sponsor responsibility and should be conducted periodically to confirm patient safety and data quality. One of the biggest issues facing

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the sponsor is to determine how often is often enough. Sponsors should have SOPs that very clearly and concisely describe the process and frequency of monitoring clinical trials.

Monitoring of a clinical trial is a sponsor's responsibility.

Purposes: GCP states that the purposes of trial monitoring are to verify that (1) the rights and well-being of **human subjects** are protected; (2) the reported trial **data** are accurate, complete, and verifiable from source documents; and (3) the conduct of the trial is in **compliance** with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Selection and Qualifications of Monitors

Selection of Monitors The sponsor appoints the monitors of a study. Although there are no specifics to the relationship between the monitor and the sponsor, he/she can be either a full-time employee of the sponsor, a contractor, or a CRO.

Background and Qualifications of Monitors GCP indicates that "monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented." Mostly, a monitor can be a person with a degree in science, nursing, medicine, or other health-related discipline.

Clinical Trials Specific Training and Education Besides the required background, GCP states that "monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s)." Having internal full-time monitors allows the sponsor to thoroughly train and instruct them on the company's SOPs and protocol requirements, although having contractors or CROs performing monitoring activities will accelerate resource-wise the study completion.

Extent and Nature of Monitoring GCP indicates that the sponsor should ensure that the trials are adequately monitored. However, there is no indication on what is considered adequate, leaving it up to the sponsor to determine, according to the protocol design, resources, and compliance procedures, the frequency and extent of monitoring for a clinical trial site.

The guidance also states that "the sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial." To comply with this the sponsor should have SOPs that detail the process for estimating and allocating monitoring capabilities as well as monitoring procedures and reporting.

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Monitoring Strategies There are some common strategies that have been accepted and utilized in the last several years by sponsors of clinical trials:

- On-site monitoring (most common and accepted)
- Central monitoring (fax, email, web based)
- Statistically controlled sampling of data monitoring

GCP specifies that “in general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.”

Monitor’s Responsibilities The monitor’s responsibilities are defined by the scope of the compliance requirements to oversee all clinical trial activities at the investigator site.

GCP details that “the monitor(s) in accordance with the sponsor’s requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site.”

- 1. Communication Link with Site:** The monitor acts as the main line of communication between the sponsor and the investigator. The monitor is the eyes and ears of the sponsor and the link between the investigator site and the sponsor. Also, during monitoring visits the monitor has to verify the documentation and products as described below.
- 2. Investigator Site Qualifications, Resources, and Facilities.** Verifying that the investigator has adequate qualifications and resources and they remain adequate throughout the trial period; that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- 3. Investigational Product(s)**
 - (a) Storage.** Storage times and conditions of the investigational product(s) are acceptable, and supplies are sufficient throughout the trial.
 - (b) Supply.** The investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
 - (c) Instructions for Use.** Subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
 - (d) Accountability.** The receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
 - (e) Drug Disposition.** The disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

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- 4. *Protocol Adherence.*** Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
- 5. *Informed Consent.*** Verifying that written informed consent was obtained before each subject's participation in the trial.
- 6. *Up-to-Date Version of Investigator's Brochure, Documents, and Trial Supplies.*** Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- 7. *Training of Investigator Site.*** Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
- 8. *Protocol and Clinical Trial Agreement Compliance.*** Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
- 9. *Patient Eligibility.*** Verifying that the investigator is enrolling only eligible subjects.
- 10. *Subject Recruitment Rate.*** The monitor has to report the subject recruitment rate.
- 11. *Source Data Availability.*** Verifying that source documents and other trial records are accurate, complete, up-to-date, and well maintained.
- 12. *Investigator Reports.*** Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- 13. *Source Data Verification.*** Checking the accuracy and completeness of the CRF entries, source documents, and other trial-related records against each other. The monitor specifically should verify the following:
 - (a) *Data.* The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
 - (b) *Therapy.* Any dose and/or therapy modifications are well documented for each of the trial subjects.
 - (c) *Safety.* Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
 - (d) *Patient Visit Compliance.* Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
 - (e) *Withdrawals/Dropouts.* All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.
 - (f) *Error Capture and Resolution.* The investigator is informed of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the

1.2 ROLE OF THE SPONSOR OF A CLINICAL INVESTIGATION 21

investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

- (g) *Adverse Event Reporting*. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).
- (h) *Essential Documents*. Determining whether the investigator is maintaining the essential documents
- (i) *Protocol Deviations*. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Monitoring Procedures Although specific procedures are not defined in GCP guidelines, the sponsor should establish (1) the SOPs on monitoring clinical trial sites to achieve full compliance, and (2) that the monitor adheres to those procedures as well as study-specific monitoring requirements.

Monitoring Report The monitoring report is a clinical trial document that must be generated at the end of each monitoring visit to a site. This document will evidence the visit and status of the site. A copy of the document must remain in the Trail Master File. The investigator, although not provided with a copy, should be informed in the form of a letter or other communication tool of the findings to the site. A visit is also considered a phone contact, email, or other type of communication with the site where trial-specific issues were discussed. The monitoring report should be provided to the monitor in the form of a template with all specific GCP/regulatory compliance requirements.

GCP recommends the following regarding a monitoring visit:

- *Written Report*: The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.
- *Contents of the Report*. Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted. Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.
- *Report Review*. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

1.2.16 AUDIT

The sponsor is required to implement a quality management system that will allow internal quality assurance inspections to confirm compliance to SOPs, GCPs, and regulatory requirements.

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GCP requires that the sponsor performs quality inspections considering the following principles.

- *Independence.* The site/sponsor auditors (QA) must be independent from clinical operations (QC monitoring) and that independence must be established in the company's SOPs.
- *Evaluation.* The main objective of an internal audit is to evaluate the trial conduct, compliance with the protocol, company's SOPs, and adherence to GCPs and regulatory requirements.

Selection and Qualifications of Auditors Auditors or internal inspectors are employed by the sponsor to perform internal quality assurance functions that will ensure compliance. The sponsor should make certain that (1) inspectors are independent from clinical functions (QC) and (2) the auditors are qualified by training, and experience to conduct audits properly. All auditor qualifications should be documented in the form of background, training, and certifications.

Auditing Procedures The sponsor should have, within the quality management system, SOPs on:

- Clinical trial audit scope (what to audit)
- Clinical trial audit procedure (how to conduct an audit)
- Clinical trial audit frequency (how often to audit)
- Clinical trial audit reporting (how to report findings)

Site Selection Criteria for Inspection Also, the sponsor should have criteria for selecting sites/trials for audit. Those criteria should be based on the GCP criteria as follows:

- *Submission Priority.* Trials should be selected according to the importance of the trial in the submissions to regulatory authorities
- *Subject Number.* Trials that provide most of the safety and efficacy data, because they enrolled the most patients, should be audited.
- *Type of Study.* Pivotal studies provide most of the safety and efficacy data due to design and size.
- *Complexity of Trial.* Studies with a high degree of complexity should be inspected for adherence to the protocol.
- *Risk to Subject.* Studies that involve a higher risk to subjects should be inspected to verify that patient safety was not compromised at any point.
- *Problems Identified in Previous Inspections.* Studies conducted at sites that had problems in prior inspections should be reinspected to verify that remedial procedures were implemented.

Reporting of Findings

- All the noncompliant activities should be documented by the auditor in writing and copies should be obtained of necessary supporting documents.
- The audit report should be a confidential document, and the regulatory authorities should not request a copy as GCP requires one “to maintain the independence and value of the audit function.”
- There are two cases where the regulator can seek access to QA inspection reports: (1) If the quality assurance systems per se appear not to be compliant to GCP/regulatory requirements due to serious findings by authorities, or (2) during legal proceedings.

Audit Certificate The audit certificate is a document that confirms, when filed in the sponsor’s Trial Master File, that a GCP quality audit has been conducted at a particular site.

GCP states that “when required by applicable law or regulation, the sponsor should provide an audit certificate.”

1.2.17 Noncompliance

It is the sponsor’s responsibility to identify and remediate SOP, GCP, and regulatory noncompliant activities (see Figure 1.3).

Any serious or persistent noncompliant activity or violation deserves termination of the investigator site and notification to regulatory authorities.

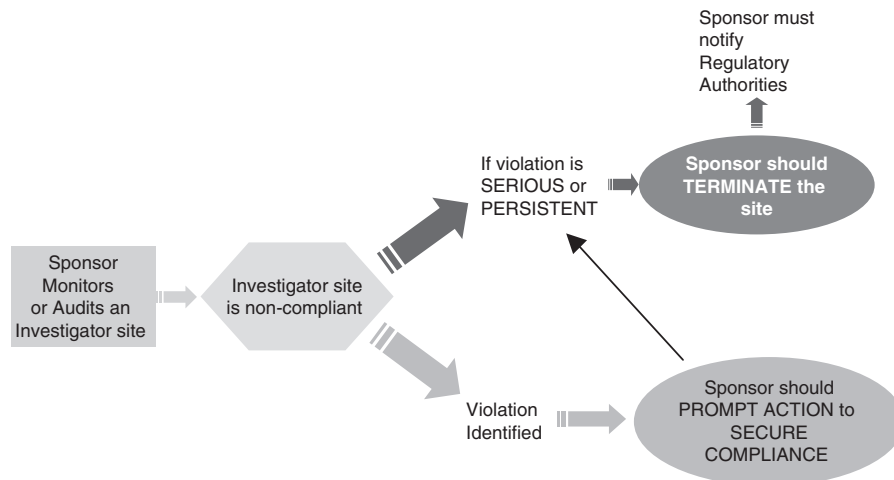


Figure 1.3 Noncompliance.

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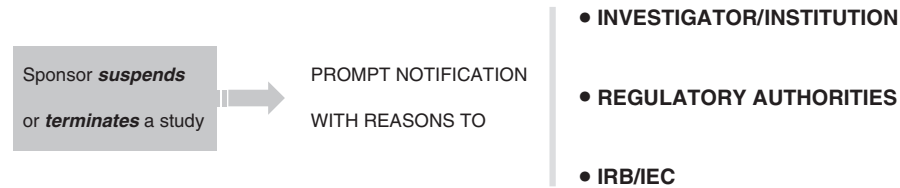


Figure 1.4 Termination or suspension of a trial.

1.2.18 Premature Termination or Suspension of a Trial

Termination or suspension of a study has many implications, especially to a patient's safety. Upon the sponsor's decision to terminate or suspend a study, the investigator/institution, regulatory authorities, and IRB/IEC should be notified promptly, stating the reasons. (see Figure 1.4.)

1.2.19 Clinical Trial/Study Reports

- *Responsibility.* The sponsor bears the responsibility of writing the Clinical Trial Report in the format required by the regulatory authorities.
- *Submission.* Every written report must be submitted to the regulatory authorities.
- *Trial Data.* Every clinical trial must have documented the results in a Clinical Trial Report.
- *Report Completion.* The report must be written for completed and for prematurely terminated studies.
- *Marketing Applications:* For marketing applications, the report must meet either the standards of the *ICH Guideline for Structure and Content of Clinical Study Reports* or country specific regulatory requirements.

1.2.20 Multicenter Trials

Drug development in the pharmaceutical industry has increased in complexity. The design of protocols includes centers located nationally or internationally to achieve enrollment in shorter times. Since many investigators will enroll patients, the sponsor must ensure the following:

- *Protocol Adherence.* The study should be conducted in strict compliance with the agreed protocol that was previously approved, if required, by regulatory authorities, and given approval/favorable opinion by the IRB/IEC. If every investigator introduces changes or deviates from the protocol, the study cannot be analyzed since the number of variables introduced becomes unknown, the safety of patients becomes compromised, and the study would not represent the objectives of the protocol.

1.3 ROLE OF THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC) 25

- *Data Collection.* Data is going to be collected in Case Report Forms (CRFs). All investigators will collect data in preestablished CRFs. Supplemental CRFs should be provided for investigators who provide additional data.
- *Management of Study Investigators.* GCPs states that “the responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.”
- *Investigators’ Guidance.* All investigators should be given instructions on (1) following the protocol, (2) complying with a uniform set of standards for the assessment of clinical and laboratory findings, and (3) completing the CRFs.
- *Investigators’ Interaction.* GCP states that “communication between investigators is facilitated.” It is very important that the sponsor ensures that the communication does not compromise the blinding of the study (if blinded) or promote bias in patient assessments.

1.3 ROLE OF THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

1.3.1 Responsibilities

Ethics review of research involving human subjects is a requirement stated in the Declaration of Helsinki.

The Institutional Review Board or Independent Ethics Committee has the mandate to safeguard the **Rights, Safety, and Well-being** of all trial subjects. GCP notes that “special attention should be paid to trials that may include vulnerable subjects.” Subjects like children, the elderly, or patients with mental limitations cannot provide consent and are considered vulnerable.

The IRB/IEC should perform the following *activities* for *ethics review*.³

Document Gathering The following documents should be collected by the IRB/IEC before reviewing a proposed study:

- Trial protocol(s)/amendment(s)
- Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial
- Subject recruitment procedures (e.g., advertisements)
- Written information to be provided to subjects (the Informed Consent Form template)
- Investigator’s Brochure (IB)
- Available safety information
- Information about payments and compensation available to subjects

³Information Sheets. Guidance for Institutional Review Boards and Clinical Investigators. 1998 Update—A Self-Evaluation Checklist for IRBs can be found at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidanceInformationSheetsandNotices/ucm118063.htm>.

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- The investigator's current curriculum vitae and/or other documentation evidencing qualifications
- Any other documents that the IRB/IEC may need to fulfill its responsibilities

Review of Documentation GCP states that the IRB/IEC should:

- **Review** a proposed clinical trial within a *reasonable time*;
- **Document** its views in writing, clearly identifying the trial, the documents reviewed, and the dates; and
- **Issue a Decision** on the conduct of the trial for the investigator site with (1) an approval/favorable opinion; (2) modifications required prior to its approval/favorable opinion; (3) disapproval/negative opinion; and (4) termination/suspension of any prior approval/favorable opinion (if deemed necessary in the light of new information regarding safety and compliance).

1.3.2 Considerations for Review

- *Investigator's Qualifications.* As documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.
- *Continuous Review.* The IRB/IEC should conduct a continuous review of each ongoing trial (to assess safety and ethics issues in a continuous manner), or at least once a year or depending on the degree of risk to subjects.

1.3.3 Additional Information to be Provided To Subjects

The IRB/IEC may request additional information to be given to subjects when, in the judgment of the IRB/IEC, that information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

Nontherapeutic Trials When subjects who provided consent through legally acceptable representatives are enrolled in nontherapeutic trials (where no benefits can be expected to a subject, as in a bioequivalence study), the IRB/IEC has to determine if the proposed protocol and/or other documentation adequately addresses relevant ethical concerns and is compliant with regulations.

Emergency Situations When a study is designed to take place in an emergency setting, the design of the study and the protocol has to indicate that, in the case when consent is not possible directly from the subject or legally appointed representative, the IRB/IEC should determine if the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials. This GCP guideline should be applied carefully in conjunction with regulatory requirements. Note that this type of study may affect the population at large within the investigator site, and public consultation may be further needed to address specifically this ethical issue.

1.3 ROLE OF THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC) 27

Payment to Study Subjects Payment to study subjects is a fact, although it remains controversial as to the amount and conditions of payment. To address any possible ethical issue, the IRB/IEC should review the following:

- Amount of payment to subjects
- Method of payment to subjects

This review should provide assurance that it does not represent coercion or undue influence on the trial subjects.

The method of payment should be **prorated** and **unconditional**. Prorated means proportional to the subject's participation. This is to avoid a subject remaining in a study with the sole purpose of collecting money. If a subject remains in a study just to collect payment and an adverse event develops, that may mean unnecessary exposure to an unsafe product if the subject remains for financial reasons. Unconditional means not wholly contingent on completion of the trial by the subject.

Payment Information in the Consent Form To avoid misunderstandings regarding financial compensation to study subjects, GCP determines that "the IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment is prorated should be specified."

Composition, Functions, and Operations

- 1. Reasonable Number of Members.** GCP states that the IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include (a) at least five members, (b) at least one member whose primary area of interest is in a nonscientific area, and (c) at least one member who is independent of the institution/trial site.
- 2. Independence of the Members.** Only those IRB/IEC members who are **independent of the investigator and the sponsor** of the trial should vote/provide opinion on a trial-related matter. The issue of the investigator sitting on an IRB/IEC is resolved as GCP states that "the investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC." That must be documented clearly in the minutes of the meeting. The other issue is having the sponsor hold an IRB/IEC within the family of companies that decides on its own studies. That scenario has to be evaluated in detail since employees of the sponsor cannot sit and deliberate on a study without being in conflict of interest.
- 3. Membership.** A list of IRB/IEC members and their qualifications should be maintained. That list should be available to the investigator, the sponsor, and the regulator upon request.

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- 4. Function According to Standard Operating Procedures.** The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).
- 5. Decision with Quorum.** An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.
- 6. Voting Privileges.** Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.
- 7. Nonmembers.** An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

IRB/IEC Standard Operating Procedures The IRB/IEC should establish, document in writing, and follow its procedures.

SOPs required as in GCP guidelines

- 1. Composition.** An SOP determining its composition (names and qualifications of the members) and the authority under which it is established.
- 2. Meeting Scheduling.** An SOP on the scheduling process for IRB/IEC meetings.
- 3. Member Notification of Meetings.** An SOP on methods of notifying its members of a meeting.
- 4. Meeting Conduct.** An SOP on how the IRB/IEC meetings should be conducted.
- 5. Initial and Continuous Review.** An SOP to determine the process for the initial and continuous review of a trial.
- 6. Frequency of Review.** An SOP to determine the frequency of continuing review of a trial, as appropriate.
- 7. Expedited Review.** SOPs that determine the process for expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.
- 8. Enrolment Dependent on IRB/IEC Approval.** An SOP that specifies that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial. *Admission to a trial means that a subject signed consent and is going to provide either data or take active investigational product under a protocol.*
- 9. Protocol Deviations.** The IRB/IEC should have procedures specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, **except (a) when necessary to eliminate immediate hazards to the subjects or (b) when the change(s) involves only logistical or administrative aspects of the trial** (e.g., change of monitor(s), telephone number(s)).

1.4 ROLES AND RESPONSIBILITIES OF THE CLINICAL TRIAL INVESTIGATOR 29

- 10. Investigators Reporting.** An SOP specifying that the investigator should promptly report the following to the IRB/IEC:
- (a) *Deviations.* Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects.
 - (b) *Changes.* Changes in the protocol or information in the safety data increasing the risk to subjects and/or affecting significantly the conduct of the trial.
 - (c) *Adverse Drug Reactions.* All adverse drug reactions (ADRs) **that are both serious and unexpected.**
 - (d) *New Information.* Any new information that may affect adversely the safety of the subjects or the conduct of the trial.
- 11. IRB/IEC Notifications.** The IRB/IEC should have SOPs to ensure that the investigator/institution notified promptly and in writing concerning (a) its trial-related decisions/opinions, (b) The reasons for its decisions/opinions, and (c) procedures for appeal of its decisions/opinions.

Records It is very important to demonstrate compliance to the regulator. Therefore, the IRB/IEC should provide records of their activities. The GCP establishes that “the IRB/IEC should retain all relevant records” as, for example, written procedures, membership lists, lists of occupations/affiliations of members, submitted documents by the investigator, minutes of meetings (complete and appropriate), and correspondence (with the investigators) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide its written procedures and membership lists.

1.4 ROLES AND RESPONSIBILITIES OF THE CLINICAL TRIAL INVESTIGATOR

The clinical trial investigator is responsible for the clinical trial at the site and has to comply with GCP and regulatory requirements in an extent that demonstrates that patient safety and data integrity is assured.

GCP establishes several requirements for compliance that are going to be the basis for essential aspects of a regulatory inspection.

1.4.1 Investigator’s Qualifications and Agreements

- *Qualifications.* The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial; should meet all the qualifications specified by the applicable regulatory requirement(s); and should provide evidence of such qualifications through up-to-date

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curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

- *Training in Use of the Investigational Product.* The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.
- *GCP and Regulatory Compliance.* The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- *Monitoring and Inspection.* The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- *Clinical Trial Personnel List.* The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

1.4.2 Adequate Resources

The following are considered resources in a clinical trial:

- *Prospective Subjects.* The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed upon recruitment period.
- *Time to Conduct the Study.* The investigator should have sufficient time to properly conduct and complete the trial within the agreed upon trial period.
- *Qualified Personnel.* The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- *Training of Personnel.* The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

1.4.3 Medical Care of Trial Subjects

The Declaration of Helsinki considers that the duty of a clinical investigator is foremost the medical care of the subjects involved.

- *Medical Decision in a Trial.* A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- *Medical Care After Adverse Event.* During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically

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significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

- *Communication with Primary Physician.* It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
- *Reason for Subject Withdrawal.* Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. This point is very important because the reasons for withdrawal may be unreported adverse events or lack of efficacy, which, for private reasons, the subject may not wish to share with the study personnel. These outcomes are very important for the conclusion of the study.

1.4.4 Communication with IRB/IEC

The investigator is the party in a clinical trial who communicates directly with the IRB/IEC. Therefore, the investigator is responsible for the following activities:

- *Obtain Written Approval/Favorable Opinion for the Protocol.* Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent forms consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
- *Provide IRB/IEC with Investigator's Brochure.* As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.
- *Continuous Submission of Documents.* During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

1.4.5 Compliance with Protocol

- *Conduct Study in Compliance with Protocol.* (1) The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, (2) by the regulatory authority(ies), and (3) which was given approval/favorable opinion by the IRB/IEC.
- *Confirmation of Agreement.* The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

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- *Protocol Deviations.*

- (1) *Implementation.* The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, **except** (a) where necessary to eliminate immediate hazard(s) to trial subjects, or (b) when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).
- (2) *Documentation.* The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- (3) *Communication.* As described previously, the investigator may implement a deviation from, or a change of, the protocol to eliminate immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. Following the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted (a) to the IRB/IEC for review and approval/favorable opinion (after the fact), (b) to the sponsor for agreement and, if required, (c) to the regulatory authority(ies).

1.4.6 Investigational Product(s)

The sponsor is responsible for providing the investigational product, and the investigator bears the responsibility to store, dispense, and account for the investigational product according to the protocol at the trial site.

GCP requires the following from the investigator:

- *Accountability.* Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
- *Delegate Accountability to Pharmacist.* Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
- *Recordkeeping.* The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the **product's delivery** to the trial site, the inventory at the site, the use by each subject, **and the return** to the sponsor or **alternative disposition of unused product(s)**. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

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- *Storage.* The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
- *Use Controlled.* The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
- *Subject Instruction and Follow-up.* The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

1.4.7 Randomization Procedures and Unblinding

Randomization of treatment groups as well as blinding are performed to ensure an equitable number of subjects are exposed to a particular treatment arm and that data is collected in an unbiased manner. Therefore, the investigator has the responsibility to follow randomization procedures and keep the blinding in the study, if applicable.

GCP states that the investigator should (1) follow the trial's randomization procedures, if any; (2) ensure that the code is broken only in accordance with the protocol, and (3) if the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

1.4.8 Informed Consent of Trial Subjects

The investigator bears the responsibility for obtaining consent from subjects before any clinical trial procedure or data collection for trial purposes is initiated.

The consent process has to be followed and documented according to regulatory requirements.

GCP requires the following:

- *Compliance.* In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.
- *IRB/IEC Approval.* Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.
- *Revision.* The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form and written information should receive the IRB/IEC's approval/favorable opinion in advance of use.
- *Reconsent of Subjects.* The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

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- *No Coercion.* Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
- *No Release of Liability.* None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
- *Subject Fully Informed.* The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favorable opinion by the IRB/IEC.
- *Language.* The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
- *Time to Decide.* Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative with ample time and opportunity to enquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- *Signature Prior to Participation.* Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
- *Witness.* If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form, and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
- *Elements of the Informed Consent Form.* Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

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1. That the trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subject's responsibilities.
6. Those aspects of the trial that are experimental.
7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
10. The compensation and/or treatment available to the subject in the event of trial-related injury.
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. The anticipated expenses, if any, to the subject for participating in the trial.
13. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or may withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
14. The monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
16. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
17. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

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19. The expected duration of the subject's participation in the trial.
 20. The approximate number of subjects involved in the trial.
- *Copy of Signed Consent.* Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
 - *Consent Through Legal Representative.* When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
 - *Nontherapeutic Trials.* Except as described above, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.
 - *Conditions for Nontherapeutic Trials.* Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:
 1. The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
 2. The foreseeable risks to the subjects are low.
 3. The negative impact on the subject's well-being is minimized and low.
 4. The trial is not prohibited by law.
 5. The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
 6. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

1.4.9 Records and Reports

Proper documentation in clinical trials is very important to demonstrate compliance with and adherence to regulatory requirements. The investigator may be required to generate specific reports to document clinical trial activities and collect data for the sponsor. The following are the GCP requirements for records and reports:

- *Accuracy, Completeness, Legibility, and Timeliness of the Data Reported.* The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports (any delays may compromise the safety of patients).
- *Source Data.* Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
- *Data Correction or Resolution.* Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by the sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections. Note that no changes to data are allowed if not authorized by the investigator.
- *Record Retention.* The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see table Essential Documents for the Conduct of a Clinical Trial part 8 of the ICH/GCP guideline) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
- *Retention Times.* Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements (e.g., in Canada it is 25 years) or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents are no longer need to be retained.
- *Financial Agreements.* The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
- *Access to Records.* Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

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1.4.10 Progress Reports

The investigator may need to provide progress reports to the sponsor and to the IRB/IEC from time to time to update the safety and enrollment status.

1. The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.
2. The investigator should promptly provide written reports to the sponsor, the IRB/IEC, and, where applicable, the institution on any changes significantly affecting the conduct of the trial and/or increasing the risk to subjects.

Safety Reporting

1. All serious adverse events (SAEs) (Unexpected) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.
2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
3. For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

1.4.11 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

1. If the investigator terminates or suspends a trial without prior agreement of the sponsor (a) the investigator should inform the institution where applicable, and (b) the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension.
2. If the sponsor terminates or suspends a trial (a) the investigator should promptly inform the institution where applicable, and (b) the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC with a detailed written explanation of the termination or suspension.

3. If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial,
(a) the investigator should inform the institution where applicable, and (b) the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.
4. Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and the regulatory authority(ies) with any reports required.

1.5 CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS

The contents of a trial protocol should generally include the following topics. However, site-specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

1.5.1 Contents of Trial Protocol

1. *General Information*

- (a) Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- (b) Name and address of the sponsor and monitor (if other than the sponsor).
- (c) Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- (d) Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- (e) Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- (f) Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- (g) Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

2. *Background Information*

- (a) Name and description of the investigational product(s).
- (b) A summary of findings from nonclinical studies, that potentially have clinical significance, and from clinical trials that are relevant to the trial.
- (c) Summary of the known and potential risks and benefits, if any, to human subjects.

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- (d) Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
 - (e) A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
 - (f) Description of the population to be studied.
 - (g) References to literature and data that are relevant to the trial and that provide background for the trial.
- 3. *Trial Objectives and Purpose.*** A detailed description of the objectives and the purpose of the trial.
- 4. *Trial Design.*** The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include the following:
- (a) A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
 - (b) A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.
 - (c) A description of the measures taken to minimize/avoid bias, including (i) randomization and (ii) blinding.
 - (d) A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).
 - (e) The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
 - (f) A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial, and entire trial.
 - (g) Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
 - (h) Maintenance of trial treatment randomization codes and procedures for breaking codes.
 - (i) The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and considered source data.
- 5. *Selection and Withdrawal of Subjects***
- (a) Subject inclusion criteria.
 - (b) Subject exclusion criteria.
 - (c) Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying (i) when and how to withdraw subjects from the trial/investigational product treatment; (ii) the type and timing of the data to be collected for withdrawn subjects; (iii) whether and how subjects are to be replaced; and (iv) the follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6. Treatment of Subjects

- (a) The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- (b) Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- (c) Procedures for monitoring subject compliance.

7. Assessment of Efficacy

- (a) Specification of the efficacy parameters.
- (b) Methods and timing for assessing, recording, and analyzing efficacy parameters.

8. Assessment of Safety

- (a) Specification of safety parameters.
- (b) The methods and timing for assessing, recording, and analyzing safety parameters.
- (c) Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.
- (d) The type and duration of the follow-up of subjects after adverse events.

9. Statistics

- (a) A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- (b) The number of subjects planned to be enrolled. In multicenter trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification, should be given.
- (c) The level of significance to be used.
- (d) Criteria for the termination of the trial.
- (e) Procedure for accounting for missing, unused, and spurious data.
- (f) Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
- (g) The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

10. Direct Access to Source Data/Documents. The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

11. Quality Control and Quality Assurance

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12. *Ethics*. Description of ethical considerations relating to the trial.
13. *Data Handling and Recordkeeping*
14. *Financing and Insurance*. Financing and insurance if not addressed in a separate agreement.
15. *Publication Policy*. Publication policy, if not addressed in a separate agreement.
16. *Supplements*

1.5.2 Investigator's Brochure

Introduction The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide investigators and others involved in the trial with information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight for the clinical management of study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk–benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

The GCP guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate, depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to investigators and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator-sponsored trial, the sponsor–investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor–investigator, then he/she should provide the necessary information to

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the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor–investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in the guideline.

General Considerations The IB should include:

1. *Title Page.* This should provide the sponsor’s name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.
2. *Confidentiality Statement.* The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator’s team and the IRB/IEC.

Contents of the Investigator’s Brochure The IB should contain the following sections, each with literature references where appropriate:

1. *Table of Contents*
2. *Summary.* A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.
3. *Introduction.* A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.
4. *Physical, Chemical, and Pharmaceutical Properties and Formulation.* A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(s)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.
To permit appropriate safety measures to be taken during the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.
Any structural similarities to other known compounds should be mentioned.
5. *Nonclinical Studies.* The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the

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methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- (a) Species tested
- (b) Number and sex of animals in each group
- (c) Unit dose (e.g., milligram/kilogram (mg/kg))
- (d) Dose interval
- (e) Route of administration
- (f) Duration of dosing
- (g) Information on systemic distribution
- (h) Duration of postexposure follow-up
- (i) Results, including nature and frequency of pharmacological or toxic effects, severity or intensity of pharmacological or toxic effects, time to onset of effects, reversibility of effects, duration of effects, dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

- (a) *Nonclinical Pharmacology*. A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).
- (b) *Pharmacokinetics and Product Metabolism in Animals*. A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.
- (c) *Toxicology*. A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
 - Repeated dose
 - Carcinogenicity
 - Special studies (e.g., irritancy and sensitization)
 - Reproductive toxicity
 - Genotoxicity (mutagenicity)
6. *Effects in Humans.* A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from clinical trials, such as from experience during marketing.
- (a) *Pharmacokinetics and Product Metabolism in Humans.* A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination)
 - Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form
 - Population subgroups (e.g., gender, age, and impaired organ function)
 - Interactions (e.g., product–product interactions and effects of food)
 - Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s))
- (b) *Safety and Efficacy.* A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.
- The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).
- (c) *Marketing Experience.* The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions).

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The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7. *Summary of Data and Guidance for the Investigator.* This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.