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Part 1: Introduction

Proper documentation is critical to the success of a clinical study. Every aspect of the study must be documented in order to obtain useful data and demonstrate compliance with Good Clinical Practice (GCP) guidelines and with all applicable regulations.

This module provides an overview of GCP documentation requirements, requirements in federal regulations, and sponsor required documentation.

Documentation Requirements in Good Clinical Practice Guidelines

Essential documents for the conduct of a clinical study are defined in ICH GCP 8.1 as follows:

"… those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements."

Essential documents may be audited or inspected by quality assurance monitors or by regulatory authorities to confirm the validity of the study and the integrity of the data collected.

GCP guidelines list the essential documents (ICH GCP E6 Section 8) that, at a minimum, must be maintained for every clinical study. These documents are to be maintained by the site and the sponsor, and are classified according to the stage of a study at which they are normally created. These documents may be maintained in multiple locations, depending on whether they are stored with regulatory files or as participant documents. The sponsor and the investigator/institution should maintain a record of the location(s) of their respective essential documents, including source documents. Additional documents may be developed and maintained by the sponsor or the sponsor(s) representatives.

Part 2: Documentation Requirements in GCP and Federal Regulations

BEFORE

Before a Study Begins

The following essential documents must be created and kept on file at study sites before a study begins:

- Signed protocol and amendments, if any.
- IRB-approved Informed Consent Form and any other written information that will be given to prospective study participants to enable them to make an informed decision about enrolling in the trial.
- Sample case report forms, either electronic or paper.
- Participant recruitment advertisements, if any.
- Documentation that the Institutional Review Board (IRB) is set up in accordance with GCP and that all necessary IRB approvals have been obtained.
- Decoding procedures for blinded trials to document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment, if applicable.
- Documentation of study personnel's qualifications (e.g., curriculum vitae, professional licenses).
- Documentation of financial agreements and any other arrangements between the parties involved in conducting the study (e.g., investigator(s), institution(s), sponsor, contract research organization).
- Insurance statement, where required, to document that compensation to subject(s) for trial-related injury will be available.
- If the study involves the use of an investigational drug, instructions for handling, dispensing, and tracking the investigational product, as well as shipping records, and a sample of the label to be attached to the investigational product container.
- Investigator's Brochure, when applicable.
- Evidence of notification, approval, or authorization of the protocol and its supporting documentation by regulatory authorities (if required)
- Evidence of approval or certification of facilities that are performing medical or laboratory tests required by the study protocol.
- Normal value(s)/ range(s) for medical, laboratory, and/or technical procedures and tests included in the protocol.
- Reports of site initiation visits and qualification visits by quality assurance monitors.

IN PROGRESS

While a Study is in Progress

The following are essential documents that should be added to the file while a study is in progress:

- Amendments to the Protocol and changes to the case report forms (CRFs), recruitment materials, Informed Consent Form, and Investigator's Brochure.
- Documentation of approval of amendments by the Institutional Review Board (IRB) and regulatory authorities (if required).
- Copies of all reports, including interim and annual reports, sent to the IRB and other regulatory authorities.
- Informed consent forms signed by study participants.

- Signed, dated, and completed CRFs and documentation of any CRF corrections with the signature sheet.
- Documentation of investigational products and trial-related materials shipment.
- Relevant communications, such as letters and meeting notes, that document agreements or discussions about issues including protocol violations, adverse events, the conduct and administration of the study, and all safety information notifications and communications.
- Relevant communications other than site visits, such as letters and meeting notes.
- Reports of interim visits by quality assurance monitors.
- Curriculum vitae for new investigators and sub-investigators.
- Source documents.
- Participant screening log, enrollment log, and identification code list.
- Documentation that investigational drugs, if used in the study, have been handled and accounted for as required in the protocol.
- Records of location and identification of retained tissue samples, if any.
- Staff signature log, documenting signatures and initials of all persons authorized to make entries and/or corrections to CRFs.
- Updates to CVs, license etc.

AFTER

After a Study is Completed or Terminated

The following are essential documents that should be added to the file after a study is completed or terminated:

- Documentation that investigational drugs, if used, were handled, accounted for, and returned or destroyed as required in the protocol.
- List of all participants enrolled in the study at the site (completed subject identification code list).
- Reports of closeout visits by quality assurance monitors.
- Final reports to Institutional Review Boards and regulatory authorities.
- Clinical study report, which documents the study's results, if applicable.

Part 2: Documentation Requirements in GCP and Federal Regulations

Documentation Requirements in Federal Regulations

21 CFR 312.62 requires investigators to:

- Maintain adequate records of the disposition of investigational drugs.
- Maintain adequate case histories for all participants in studies that involve the use of investigational products.
- Retain records for 2 years after the date a marketing application is approved for the drug for the indication for which is it has been investigated by the U.S. Food and Drug Administration (FDA) or for 2 years after the study is discontinued and the FDA is notified.
- Records of all NIH–sponsored studies must be maintained for at least 3 years after the study ends per NIH policy and for a longer time if required by regulations or local institutional policies. This requirement applies to all research projects, including studies of investigational drugs, behavioral studies, and survey–based studies.

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Records of all CTN–sponsored studies must be maintained for at least 3 years after the study ends per NIH policy and for a longer time if required by regulations or local institutional policies. This requirement applies to all research projects, including studies of investigational drugs, behavioral studies, and survey–based studies.

Of note, most facilities where CTN research is conducted are covered entities that must comply with the HIPAA Privacy Rule. Covered entities are required to account for disclosures (must retain documentation) 6 years from the date of creation on which the accounting is requested. (Reference the Clinical Research and the HIPAA Privacy Rule.)

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Part 3: Examples of Other Sponsor-Required Documents

In addition to the essential documents included in the GCP guideline, the sponsor may require other documentation. The following lists examples of other documentation that may apply to clinical trials.

Certificate of Confidentiality

A Certificate of Confidentiality provides an additional level of protection for the privacy of participants in alcohol and drug abuse research studies. (For more detailed information on Certificates of Confidentiality, go to the Confidentiality and Privacy module.)

Quality Assurance Documents

Quality assurance documents may include the following:

- Research site Initiation Activation Form, which indicates that a site is ready to start study enrollement.
- Site visit logs, to record visits to the research site by quality assurance monitors and other personnel.

Training Documents

A training plan and verification of compliance with the training plan, including:

- Al training documentation form for each staff person
- Documentation of required assessments training per the study training plan.
- Documentation of study–specific training.
- Pertinent certifications for clinical staff implementing a study intervention.

Behavioral Therapy Documents

Many CTN studies involve behavioral interventions. Behavioral studies may require essential documents different from, or in addition to, those required by GCP guidelines. These documents may include therapy manuals and materials, audio and videotapes of treatment sessions, and other documents specific to the

behavioral intervention that is being studied.

Source Documents

Source documents are original documents, data, or records that are created during a clinical study, that relates to the medical treatment and the history of the participant, and from which study data are obtained. Source documents are one type of essential document that is required by GCP guidelines.

The purpose of source documents (GCP 8.3.13) is to:

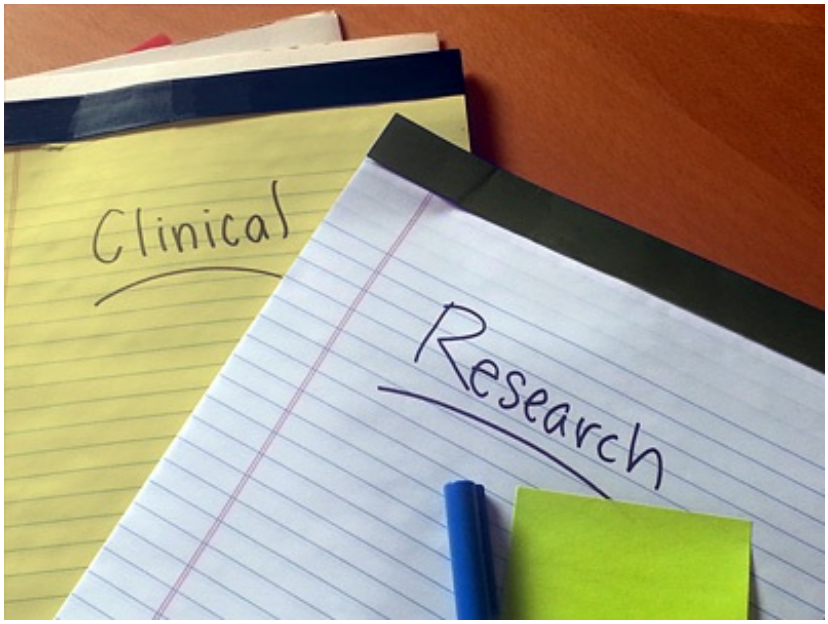
- Document the existence of study participants.
- Substantiate the integrity of the study data collected.

Any document in which information, an observation, or data generated relevant to a study is recorded for the first time is a source document. Thus, a scrap of paper, a Post–It ® note, or an electronic mail message may be a source document if it is the original form on which information relevant to a study is recorded.

Examples of Source Documents

The following are examples of source documents:

- Adverse event and concomitant medication logs
- Reports of diagnostic test results
- Signed and dated Informed Consent Forms
- Participant diaries
- Appointment calendars
- Progress notes
- Paper case report forms (CRFs) on which data are entered directly onto the CRF, rather than extracted from another source document.



Progress Notes

These source materials must be readily available and retrievable for quality assurance monitoring and for auditing, for example, by the study sponsor (NIDA) or for inspection by the U.S. Food and Drug Administration (FDA).

The purpose of progress notes is to document participants' involvement in the study and the study–related care they receive. Both research and clinical staff may complete progress notes.

Progress notes are source documents; and may not be recorded in the study database or sent to the sponsor. Often, progress notes are used on–site to monitor the progress of the study. Another important purpose of progress notes is to substantiate the data recorded in the case report forms (CRFs).

Progress notes should be concise but should provide enough information that the participant's study–related activities, and the order in which events occurred, can be easily understood.

Progress notes are of two types, both considered to be essential study documents:

- Clinical notes record information related to the experimental treatment that the participant received during the clinical phases of the study.
- Research notes record information related to the participant's involvement in the research phases (e.g., follow-up assessment visits) of the clinical study.

Click here for a list of information that should be documented in both clinical and research progress notes.

Click here for a summary of Good Medical Record practices that should always be observed when writing progress notes.

Case Report Forms

GCP defines a Case Report Form (CRF) as follows:

"A printed, optical, or electronic document designed to record all of the protocol–required information to be reported to the sponsor on each trial subject" (ICH GCP 1.11)

Thus, a CRF may be a printed document that a study team member completes in the clinic or an electronic document that is sent directly from a laboratory to the data management center.

The purpose of CRFs is to gather study data in a standardized format so that the data can be entered into a computerized database and analyzed. The CRFs record all of the information needed to complete the data analyses used to assess the outcomes of the study.

A CRF is a source document only when study data are entered directly onto the CRF, rather than extracted from another source document (e.g., progress notes).

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CTN–Specific Essential Documents

CTN investigators are required to maintain a Certificate of Confidentiality, QA, Training, Behavioral Therapy, Source, Progress Note, and CRF documents for CTN studies. Additionally, contact information should be maintained for the following CTN study personnel:

- Key personnel at the Lead Node.
- Key personnel at the Participating Node.
- Key personnel at the NIDA Center for the Clinical Trials Network (CCTN).
- The NIDA Study Medical Officer and other parties who must be contacted when expedited reporting of an adverse event is necessary.

Read more...

Part 4: Documenting the Use of Investigational Drugs

21 CFR 312.62 requires investigators to maintain adequate records of the disposition of investigational drugs, including dates, quantities, and use by participants. The investigator must also maintain records of receipt.

The following equation may help in understanding the process of accountability for drug disposition:

Although this equation may look simple, in practice accounting accurately for the disposition of an investigational drug can be quite complicated. The investigator must account for every unit of the investigational product (e.g., tablet, capsule, inhaler).

Let's take a closer look at what is involved in accounting for every unit of an investigational product.

Documentation of the "Amount of Drug Received"

Documentation of the "amount of drug received" must account for:

- The total number of capsules, tablets, etc. in every dosage (e.g., 5 mg, 10 mg).
- Multiple lot numbers.
- The type of packaging in which the medication is delivered (e.g., bulk supply, individual kits).

Documentation of the "Amount of Drug Used"

Documentation of the "amount of drug used" must account for:

- The amount of medication that each study participant is individually exposed to.
- The total amount of medication consumed by all study participants.
- The amount of medication that is returned by participants (i.e. unused).
- The amount of medication that is wasted (e.g., lost, dropped down the kitchen sink).

Verification of the "Amount of Drug on Hand"

Inventory must be taken at regular intervals to verify the "amount of drug on hand." Any discrepancies must

be documented.

To ensure proper accountability, a carefully designed plan (or standard operating procedure) must be in place at the beginning of the study to document the disposition of the investigational product at each site. This plan must be adhered to throughout the study and, if necessary, modified to ensure 100% accountability. The investigator's records of drug disposition must agree with the data submitted to the sponsor.

Summary of Key Points

- Every aspect of a clinical study must be documented in order to obtain useful data and demonstrate compliance with Good Clinical Practice (GCP) standards and with all applicable regulations.
- GCP guidelines specify the essential documents that must be maintained for every clinical study. These documents are classified according to whether they are normally created before a study begins, while a study is in progress, or after a study is completed or terminated.
- Federal regulations require investigators to retain records for 2 years after approval of the investigational drug by the U.S. Food and Drug Administration (FDA) or for 2 years after the study is discontinued and FDA is notified.
- Sponsors may require specific documentation in addition to the list of essential documents specified by GCP.
- Source documents are original documents created during a clinical study, from which study data are obtained. The purpose of source documents is to document the existence of study participants and substantiate the integrity of the study data collected.
- Progress notes document participants' involvement in the study and the study–related care they receive. Progress notes are used to monitor the progress of the study and substantiate the data recorded in the case report forms (CRFs).
- The purpose of CRFs is to gather study data in a standardized format so that the data can be entered into a computerized database and analyzed. All of the information needed to complete the data analyses used to assess the outcomes of the study is recorded in the CRFs.