Data integrity is vital in the conduct of clinical research because data is necessary for the evaluation, reconstruction, and validation of clinical findings, observations and other study activities. Record-keeping requirements for research records are outlined in the federal regulations and guidance documents. Specifically, 21 [CFR 312.62](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62) provides that investigators are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or used as a control in the investigation. The record-keeping requirements for investigators conducting research involving investigational devices are outlined in 21 [CFR 812.140](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1&subpartNode=21:8.0.1.1.9.7). The [International Conference on Harmonisation ICH, E6 Good Clinical Practice (GCP) Guideline](http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/guidancesinformationsheetsandnotices/ucm219488.htm) defines the essential documents that must be maintained before, during and after the conduct of the study. In 2016, the National Institutes of Health (NIH) issued a policy requiring all NIH funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials[[1]](#footnote-1) be trained in GCP consistent with ICH Guidelines. The principles of GCPs should be applied to these clinical trials.

In considering the Food and Drug Administration (FDA) regulations, NIH Policy and ICH GCP Guideline for record keeping, the University of Pittsburgh Education and Compliance Support for Human Subject Research (ECS-HSR) has established the following record-keeping requirements for FDA regulated research and clinical trials. Utilizing these standards will ensure data quality by creating audit trails and enabling verification that data are present, complete and accurate.

1. **DOCUMENTATION STANDARDS**

Research records should be kept for each research subject. The records should include the consent form as well as information relevant to the subject’s condition before, during and after the conduct of the study.

To achieve data quality the ALCOA-C principle should be applied to source documentation, which specifies the data should be:

**A**ttributable Is it obvious who wrote/did it and when?

**L**egible Can it be read?

**C**ontemporaneous Is the information current and in the correct time frame?

**O**riginal Is it a copy? Has it been altered?

**A**ccurate Are conflicting data recorded elsewhere?

**C**omplete Has the information been recorded in its entirety?

At a minimum, the following general standards must be followed:

* Keep handwritten notes and signatures legible. If necessary, the individual’s name may be printed underneath the signature.
* Sign and date all entries in real time.
* Make error corrections by 1) drawing a single line through the incorrect information, 2) initialing, dating, and stating a reason for the change (if necessary), and 3) inserting the correction. If the change is obvious, i.e., a transcription error that can be verified with the original source, then a rationale for the change is not required. If the change is not obvious, i.e., a diagnosis or symptom that was deleted after initial entry, then there should be a rationale for the change.
* Never obliterate entries that require correction.
* Never destroy original documents, even if they require error correction.
* Keep subject records secure yet accessible.
* Do not alter past-dated notes, chart notes/progress notes, e.g., by writing alongside or adding to prior entries.
* Only use dark ink.
* Never use whiteout.
* Never use pencil.
1. **INFORMED CONSENT**

Informed consent is the primary ethical requirement underpinning research involving humans; it reflects the basic principle of respect for persons. Informed consent is an ongoing process, not a single event.

According to the University of Pittsburgh Human Research Protection (HRP) Division, a licensed physician investigator must obtain consent for studies involving a drug, device or surgical procedure and must sign the investigator’s certification statement at the time of this involvement (refer to HRP Policies and Procedures, Chapter 13).

Signatures on the consent form must be personally dated by each person signing the form. If the consent form will be uploaded into the UPMC medical record system, each person signing the consent form must personally record the time of signing on the consent form.

In addition to obtaining a signed consent form, the process for obtaining informed consent must be documented in the research record. The consent process note should document that written informed consent was obtained prior to participation in the study, unless the IRB granted an exception for the evaluation of an emergency procedure. The consent process note may include the following additional information:

* A list of the persons who were present during the informed consent discussion,
* A statement that risks were presented,
* A notation, if applicable, that significant issues of concern to the subject were addressed,
* A statement that all questions were answered to the satisfaction of the subject, and
* A notation that a copy of the consent form was provided to the subject.

If re-consenting is required, the process for obtaining reconsent should also be documented in the research record.

All pages of the original signed consent form with original signatures, not photocopies, and documentation of the consent process must be maintained. Signed consent forms can be kept in a file separate from or with the subject research records, provided this process is consistently implemented for all subjects and any signed revised or addendum consent forms are maintained in the same manner. In addition, the consent forms and subject research records must be maintained as described in the Institutional Review Board (IRB) approved consent form and protocol.

1. **SOURCE DOCUMENTATION**

Source documents are the original recording of any observations made or data generated about a subject during participation in a clinical trial. These documents serve to substantiate the integrity of the study data, confirm the recorded observations, and confirm the existence of the subjects. The ICH GCP Guideline defines source documents as:

*Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).*

1. Signing/Initialing and Dating Source

If more than one person makes an entry on the same source document, each entry must be signed and dated. However, multiple entries to a source document made by the same person on the same day require only one signature and date on the page if there have been no interim entries made by other individuals. It is incumbent upon the individual signing the source document to ensure that there have been no entries other than his/her own. A single date on a source document with multiple entries is permitted if all entries were made on that same date.

Initials may be used in place of signatures on source documents provided that a signature key is maintained by the research staff. The signature key should include initials, signatures and credentials (if applicable).

1. Subject Identifiers

All source documents must be consistently labeled with at least one unique identifier to enable verification that the documents correspond to a particular subject. The labeling method should be consistent with the method described in the consent form and protocol.

1. Case Report Forms Used as Source Documentation

The ICH GCP Guideline defines a case report form (CRF) as, “A printed, optical, or electronic document designed to record all of the protocol required information [e.g., study data] to be reported to the sponsor on each trial subject.” There must be source documentation to substantiate all data recorded on the CRFs.

CRFs may be used as source documents if they represent data collected for the study and are where the data were initially recorded. An example of data initially recorded on the CRF may include verbal responses from the subject.

If data are transcribed from another source onto the CRF, the CRF is not considered to be the original source document and it cannot be used as source documentation. Examples of data that are routinely transcribed from other sources include: laboratory results, radiology reports, histories documented in referral letters, etc.

As a source document, the original CRF must be signed/initialed and dated by the individual recording the data on the CRF. If data are obtained at a later date, i.e., after the study visit and are recorded on the CRF as source documentation, it must be signed/initialed and dated at the time of entry.

A list of the CRFs that are considered source documentation should be maintained to ensure consistency throughout the study and to clearly indicate for potential reviewers (e.g., monitors, auditors and regulatory authorities) which CRFs are being used as source documentation. To ensure version control, it is recommended that a version/date be included in the footer of the CRF.

1. Computer Records Used as Source Documentation

When data is entered directly into a computer system that is 21 CFR Part 11 compliant, the electronic data in the computer system is the original source document. A paper record, e.g., a printout or print screen of the electronic data, is considered to be a copy.

An example of direct data entry is the collection of vital signs during a study visit and the immediate entry of this information into a computer system, without recording the vital signs on paper. If the vital signs were initially recorded on paper and then entered into the computer system, the data recorded on paper would be considered the original source and not the data in the computer system.

For questions regarding compliance with Title 21 Part 11 for systems stored on a server maintained by the University of Pittsburgh, contact the University of Pittsburgh Information Technology.

For questions regarding compliance with Title 21 Part 11 for systems stored on a server maintained by the University of Pittsburgh Medical Center, contact a representative of UPMC information technology management executive leadership. Of note, information contained within UPMC legacy computer systems (e.g., e-record systems developed prior to August 1997) is presumed to be noncompliant with Title 21 Part 11 unless verified prospectively by UPMC information technology management executive leadership.

1. **OTHER ELEMENTS AND CONSIDERATIONS FOR RESEARCH SUBJECT RECORDS**
2. Entry Criteria

Eligibility checklists should be developed to capture each criterion outlined in the protocol. Source documentation to address the presence and absence of the protocol’s inclusion and exclusion criteria must be present in the research record.

1. Communications

Verbal and written communications pertinent to research data collection must be documented in the research record in enough detail to support the data collected, such as actual or attempted contacts, emails, letters, etc. The communications must have appropriate identifiers to verify that they correspond to the specified subject, e.g., subject ID, date of communication and name of research team member documenting the communication.

1. Laboratory Tests

It is acceptable to write a note that broadly indicates that specimens were obtained for the protocol required tests. All laboratory reports must have the appropriate subject identifiers, date of specimen collection and specify where the test was performed.

A qualified investigator or sub-investigator should review laboratory reports and as documentation of this review, sign/initial and date the laboratory report or note the completion of this review in the research record. A clinical assessment should be documented for out-of-range values along with documentation of any action taken with respect to the assessment. It is recommended that out of range values be designated as “clinically significant” (CS) or “not clinically significant” (NCS).

1. Questionnaires

The actual data on a subject completed questionnaire does not need supporting source documentation because the questionnaire is the source document. However, documentation is required to demonstrate that the protocol required questionnaire was given to the subject in accordance with protocol requirements. This can be accomplished by a checklist or with documentation in the research record indicating the questionnaire was given to the subject to complete on a specified date. This is important in cases where the subject refuses or fails to complete the questionnaire.

If a questionnaire is not personally completed by the subject, documentation should be present to indicate who completed it and the reason it was completed by this individual. If questions are completed by research staff, the staff member should sign/initial and date those questions/sections and document in the research record the method for obtaining the information, e.g., personally interviewed subject.

1. Investigational Drug/Agent

Investigational agents should be dispensed only upon the written order of the investigator or upon the order of a licensed practitioner directly responsible to the investigator as stated on the Form FDA 1572. A copy of the order must be maintained in the research record.

By signing the Form FDA 1572, the investigator has certified that the investigational agent will be administered only to subjects under his/her personal supervision or under the supervision of sub-investigators responsible to him/her. Use of the investigational agent by the subject must be recorded in the research record along with any changes in the study intervention. The following are examples of changes in study intervention:

* + - Any change in investigational agent status must be documented with sufficient detail to support and provide an explanation for the change.
		- Entries regarding dose modifications must include the reason for the change and the actual dosage change.
		- Notes regarding the holding of the investigational agent must include the reason for the agent being held.
		- Notes regarding the reinstitution of the investigational agent must include the reason for reinstitution of the agent and the dosage.

If the services of the UPMC Investigational Drug Services (IDS) are utilized, IDS will ensure that procurement, receipt, storage, accountability, preparation, dispensing and labeling of investigational agents comply with state, federal (FDA) and institutional Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for handling such agents.

1. Investigational Device

An investigator shall permit an investigational device to be used only with subjects under the investigator’s supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive the device.

The best strategy for reducing the risk that an investigational device could be improperly dispensed, whether purposely or inadvertently, is for the investigator to closely monitor devices. Investigators are required to maintain complete, current and accurate records of the receipt, use, and disposition of investigational devices. Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

Upon completion or termination of a clinical investigation or the investigator’s part of an investigation, or at the sponsor’s request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

1. Endpoints

For study defined clinical or laboratory-based endpoints, subject research records must document the specifics of the events or test results as required by the protocol. The results of all diagnostic evaluations needed to substantiate a diagnosis must be included in the research record.

1. Protocol Deviations

All protocol deviations must be recorded in the research record and if pertinent, the reasons for the deviations and/or attempts to prevent or correct the deviations are to be included in the documentation. For example, a missed visit needs a note stating it is a missed visit and the research staff’s attempts to locate the subject to request that he/she come in to make up that visit. A log of protocol deviations should be maintained as specified by the reviewing IRB and study sponsor.

1. **OTHER ESSENTIAL DOCUMENTS**

In addition to the requirements for research subject records, there are other documents essential to the conduct of a clinical trial. The ICH GCP Guideline outlines in detail the documents required for maintenance by both the study sponsor and investigator. Sponsors and investigators should thoroughly review this information and determine which documents are applicable to their clinical trial.

Regulatory documents may be maintained in electronic and/or hard copy format. For hard copy documents it is recommended that each section of the regulatory binder is labeled (e.g., IRB correspondence, protocol training, etc.) and that documents are stored in reverse chronological order, which means the newest document within a section is filed in the front of the section.

For electronic documents a memorandum with the document name should be filed in the relevant section of the regulatory binder and should direct an individual to the electronic storage pathway, or a memorandum listing all electronically stored documents should be filed in one section of the regulatory binder and should direct an individual to the electronic storage pathway for each document. It is recommended that a standardized naming convention is developed for electronic folders and documents. For example:

* + IRB folder → Subfolder for each submission named according to IRB approval date (e.g., year-month-day\_Initial Approval)
	+ Name each document according to IRB approval date (e.g., year-month-day\_ProtocolABC\_v1)

For email correspondence a memorandum may be filed in the regulatory binder to describe that email will be archived to a permanent storage medium on a particular schedule, which should be specified in documentation, and the media will be stored in the binder or an easily accessible location.

Electronic-only documents should be limited to documents that are easily accessible by research staff and by a monitor, auditor or inspector during a site visit. The electronic storage location should be controlled and regularly backed up, and processes should be in place to avoid inadvertent deletions of or edits to documents.

The following is a list of documents typically found within a regulatory binder.

1. Clinical Protocol/Investigational Plan

This section should include a copy of the IRB approved clinical protocol or investigational plan (device). If the clinical protocol or investigational plan is modified during the course of the study, a copy of each IRB approved clinical protocol or investigational plan must be stored in this section. Each clinical protocol or investigational plan should, at a minimum, be dated for tracking purposes and to ensure the correct version is utilized.

If a version of the clinical protocol or investigational plan was not submitted to or approved by the IRB, a note needs to be generated to explain the surrounding circumstances, and the investigator needs to sign and date the document.

1. Informed Consent Form

This section should include a copy of the IRB approved consent form. If the consent form is modified during the course of the study, a copy of each IRB approved consent form must be stored in this section. For consenting purposes, it is recommended that the research staff obtain the most recently IRB approved consent form directly from the electronic system at the time of a subject’s visit.

1. IRB Correspondence

This section should include IRB letters of initial, modification and renewal/continuing review approvals as well as any email exchanges with the IRB.

1. IRB Documentation

This section should include the IRB’s Federalwide Assurance (FWA) number and an IRB roster. The University of Pittsburgh IRB maintains the FWA number along with a listing of the membership of each committee on the University of Pittsburgh HRP website.

1. Ancillary Reviews

This section should include reviews by ancillary committees such as Radioactive Drug Research Committee, Institutional Biosafety Committee and Human Stem Cell Research Oversight Committee.

1. Investigator’s Brochure

For studies that involve an investigational drug or product, this section should include a) a clinical investigator’s brochure (IB) or equivalent, or b) a package insert with labeling for approved medications. If the package insert or IB is amended or updated during the course of the study, a copy of each version of the package insert or IB should be stored in this section.

The purpose of this document is to provide information on the mechanism of action, possible risks and adverse reactions, and the expected adverse reactions associated with the previous use of the drug or product.

1. Report of Prior Investigations

For studies that involve an investigational device, this section should include a report of all prior clinical, animal and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigational plan.

1. Qualification Documentation

This section should include current a) curriculum vitae (CV) or other relevant dated documentation, such as a biosketch and b) clinical license, if applicable, for research staff involved in the treatment and/or evaluation of subjects and for those listed on the Form FDA 1572/Investigator Agreement. Expired clinical licenses and outdated CVs must be retained as these demonstrate qualification for the duration of the study.

1. Financial Interest Forms

This section should include a signed financial interest form certifying the absence or presence of certain financial interests for research staff involved in the treatment and/or evaluation of subjects and for those listed on the Form FDA 1572. If a financial interest is present, then a financial disclosure form will need to be completed.

1. Conflict of Interest Management Plan and Notifications of Significant Financial Interest

For studies with research staff that have a conflict of interest, this section should include the management plan and emails from the University of Pittsburgh Conflict of Interest (COI)Division notifying the research team of the conflict. The COI Division can provide guidance on the implementation of a management plan.

1. Signature and Delegation of Authority Log

This section should include an ongoing log that lists the research staff and their specific responsibilities, signatures, initials, and obligation (start/stop) dates. Any changes in research staff or staff responsibilities during the course of the study require an update to the log.

1. Training

This section should include documentation of study-specific training for all research staff, e.g., investigator, sub-investigators, research coordinators, nursing staff, pharmacy, etc. At a minimum, the training documentation should include the protocol title, training date, trainer’s name, signed attendance record and training agenda/summary.

1. Enrollment Log

This section should include a log, without identifying information, that lists subjects who were enrolled in the study, enrollment dates, visit status, etc.

1. Lab Certifications and Normal Ranges

For studies that use clinical laboratories for specimen testing, this section should include current a) laboratory reference ranges if the reference range is not on the laboratory report and b) laboratory certifications or accreditations, e.g., CAP, CLIA and PA DOH. Expired certifications and outdated reference ranges must be retained. Laboratory norms and certifications for UPMC can be found online at: <https://path.upmc.edu/links.htm>.

1. Accountability Records

This section should include the drug/device accountability records. If the task of accountability has been delegated to another entity, e.g., UPMC IDS the records may be stored with that entity. A memo should be filed documenting who is maintaining accountability and where the records are located. At the conclusion of the study, the accountability records should be retrieved from the entity and stored in this section.

1. Specimen Tracking Log

This section should include a log of research samples indicating a) type of specimen, b) purpose of storage, c) location of storage, e.g., freezer #, shelf #, box # and d) link to subject ID number. If applicable, the log should be modified to track if consent for future use was obtained, refused or withdrawn.

1. Adverse Event Log

This section should include a summary of all adverse events. Adverse event logs should be kept in accordance to the requirements of the reviewing IRB and study sponsor. The University of Pittsburgh HRP Division requires sponsor-investigators to maintain adverse event logs and recognizes it as a best practice for all clinical investigators (refer to HRP Policies and Procedures, Chapter 17).

1. Serious Adverse Events or Unanticipated Adverse Device Effects

This section should include copies of all correspondence related to the reporting of serious adverse events or unanticipated adverse device effects to the IRB, FDA and/or other regulatory agencies.

1. Reportable Events/Reportable New Information

This section should include copies of all reportable events submitted to the IRB.

1. Noncompliance/Deviation Log

This section should include a summary of all protocol deviations or incidences of noncompliance. Noncompliance/Deviation logs should be kept in accordance with the requirements of the reviewing IRB and study sponsor. The University of Pittsburgh IRB requires Noncompliance/Deviation logs for:

* Greater than minimal risk studies,
* Studies that meet the federal definition of a “clinical trial” and
* Studies for which reporting is required by the funding agencies.

Refer to the HRP Policies and Procedures, Chapter 17 for additional information.

1. Monitoring Visits

This section should include a copy of the:

* Visit log signed by the monitor(s) at each visit,
* Visit reports initialed and dated by the investigator and
* Visit correspondence, such as visit confirmation and follow-up letters.
1. Sponsor Correspondence

If the investigator and sponsor is not the same individual, this section should include records of correspondence with the sponsor, including approval of initial study documents, approval to initiate the study and approval of protocol amendments. There should be documentation of regular communication between the sponsor and investigator throughout the conduct of the study.

1. Data and Safety Monitoring Documents

This section should include the:

* Data and safety monitoring plan, if not incorporated into the FDA clinical protocol or investigational plan,
* Study reports generated for the safety monitors,
* Minutes from the safety monitor meetings and
* Recommendations and correspondence from the safety monitors.
1. Case Report Form Templates

This section should include a copy of the case report forms. If changes are made to these forms throughout the conduct of the study, all versions of the case report forms must be retained.

1. Memorandum

This section should include a memorandum regarding the location of documents that are stored centrally, e.g., study team qualifications, laboratory reference ranges,and any documents stored in a location other than the main regulatory binder.

1. Standard Operating Procedures (SOPs) / Manual of Procedures (MOPs)

This section should include SOPs and MOPs, as applicable.

1. Multi-Site Studies

For multi-site studies, each site Principal Investigator is responsible for maintaining a local site regulatory file. The study initiator/sponsor, who is responsible for overall study preparation, planning and control (e.g., FDA IND/IDE holder), must maintain a central master file that includes a copy of each local site file.

1. Form FDA 1572 or Investigator’s Agreement

This section should include the original, signed Form FDA 1572 (drug) or Investigator’s Agreement (device). If these documents need to be revised during the conduct of the study, all signed versions with original signatures must be retained.

1. IND and IDE Support (IIS) Correspondence

This section should include correspondence with IIS, such as emails, FDA submission tracking documentation, fee sheets, etc.

1. FDA Correspondence

This section should include a complete record of all correspondence to and from the FDA, such as changes in protocol, annual reports, response to FDA request for information, requests for meeting, etc. The sponsor is responsible for ensuring that all FDA correspondence is provided to IIS.

For studies that involve an investigational device, the sponsor is responsible for submitting to FDA, at six-month intervals, a current list of the names and addresses of all investigators participating in the study. This section should also contain a copy of these lists.

1. Form FDA 3674

This section should include a copy of the Form FDA 3674 submitted to the FDA to certify compliance with clinical trial registration requirements outlined in the Food and Drug Administration Amendment Act (FDAAA).

1. **RECORD STORAGE AND RETENTION**

Research records must be securely stored when not in use by the research staff, such as a locked file cabinet within a locked office, or locked office inside a clinic that is locked when not in use. If research records are transported between sites every effort should be made to maintain confidentiality during transport.

Research records should be retained according to the funding agency, federal regulations (21 CFR 312.62 or 812.140), institutional policy, protocol requirements, and/or standard operating procedures. The records should be retained under the policy with the longest retention timeframe.

1. The NIH defines a Clinical Trials as: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. [↑](#footnote-ref-1)