

Regulatory File Document Guidelines

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Introduction:

The regulatory files serve as comprehensive documentation of your human subjects research activities including but not limited to: identification of the study protocol(s); assurance of IRB approval of the study as originally proposed as well as of any amendments that may have been enacted during the course of the trial; all correspondence and information exchange with the Sponsor/Funder, IRB, and regulatory Agencies; identification of each of the members of the research team and their role in conducting the study; support from ancillary services (e.g. clinical laboratory); and the history of the subject's participation in the research. Complete regulatory files that reflect adherence to Good Clinical Practice (GCP) will demonstrate knowledge of and compliance with applicable regulatory requirements and allow for evaluation of the conduct of the trial, as well as the quality of the data that is generated.

What follows is a guide to assist in identifying the documents that comprise your regulatory files. Depending upon your research, all items may not apply. You should recognize that development of complete files is a process that is ongoing throughout the course of your study, and that there is no single accepted manner in which files are organized. In fact, one approach you may consider is to establish one file for your regulatory documents and study logs, another specific to correspondence (IRB, sponsor), and to create an individual file for each research participant. In addition, you may find that there are common documents among a number of studies you are conducting, in which case it is reasonable to create centralized files with the location referenced in a note to file placed in your study specific records.

Basic documents to be maintained for all studies in accordance with GCP standards:

- Study protocol - original, dated version; amended versions with version number and date indicated. All protocols should include signature and date of investigator, study sponsor. (GCP 8.2.2, 8.3.2)
- Study-specific procedures/ procedure manual - original, dated version; amended versions with version number and date indicated.
- IRB approval letter - including notation of protocol version approved, version of approved informed consent document, approval of any written information that will be provided to subjects and any subject recruitment advertisements that will be utilized. Approval letters for any amended versions of the protocol, informed consent document, written information provided to subjects or recruitment documents must be maintained. (GCP 8.2.7, 8.3.3)

- Copies of all IRB Approval stamped versions of the following: informed consent document, research authorization, any written information that will be provided to subjects and subject recruitment advertisements, as applicable. (GCP 8.2.3, 8.3.2)
- Assurances: FWA, IRB registration, IRB composition. (GCP 8.2.8)
- CVs of principal investigator, co-investigator, key research personnel documenting qualifications and eligibility to conduct the study. These should be signed and dated by the individual and updated every two years. (GCP 8.2.10, 8.3.5, 4.1.1)
- Valid licenses and certifications for all professional study personnel. (GCP 8.2.10, 4.1.1)
- Human subjects training certificates for all investigators/key research personnel. (UIC HSPP Policy - *Investigator and Research Personnel Education Program and Training Requirements*, <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0895.pdf>)
- Copies of all correspondence between the investigator and the IRB (e.g., continuing review, prompt reporting forms, amendments, protocol exception, final study report). (GCP 8.3.3, 8.4.7, 3.1.4, 4.13)
- Copies of all correspondence between the investigator and the sponsor (e.g., serious adverse event reporting, IND Safety reports, approval to deviate from protocol, monitoring visit reports, letters, notes of telephone calls, email, final/closeout report). (GCP 8.2.19, 8.2.20, 8.3.10, 8.3.11, 8.3.16)
- Copies of all correspondence between the investigator and the study monitor (if applicable).
- Study logs (as applicable):
Please note that samples of select logs are available at the OVCR QIP Toolbox, <http://tigger.uic.edu/depts/ovcr/research/QIP/toolbox.shtml>.
 - Screening log (GCP 8.3.20)
 - Subject identification code list (GCP 8.3.21, 8.4.3)
 - Enrollment/randomization log (GCP 8.3.22)
 - Delegation of Responsibility log (GCP 4.1.5)
 - Staff Signature log (GCP 8.3.24)
 - Internal adverse event log
 - Training log (GCP 4.2.4)
 - Monitoring log (GCP 5.18, 8.2.20, 8.3.11)
 - Retained tissues log (GCP 8.3.25)
 - Sample tracking and shipping log.
- Executed clinical trial agreement with description of financial aspects of the trial. (GCP 8.2.6, 8.2.4)
- Insurance statement (if applicable). (GCP 8.2.5)
- Master copies of all case report forms (CRFs), data collection sheets, subject surveys, questionnaires or diaries. (GCP 8.2.2, 8.3.2)
- Original and updated laboratory certifications. (CLIA, CAP) (GCP 8.2.12, 8.3.7)
- Laboratory director's CV. (GCP 8.2.12)
- Normal laboratory values/reference ranges with updates. (GCP 8.2.11, 8.3.6)

- Data safety monitoring board/data monitoring committee/monitoring committee reports. (GCP 8.3.10, 5.19.3)
- Signed, dated copies of all informed consent documents, research authorizations, and other appropriate documentation of informed consent (e.g. signed progress note by physician, capacity assessment by a psychiatrist, advanced directive, documentation of surrogate's relationship to the subject). (GCP 8.3.12 and UIC HSPP Policy - *Approval Criteria: Decisionally Impaired and Cognitively Impaired Subjects*, <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0854.pdf>)
- Source documents for each enrolled subject. (GCP 8.3.13)
- Completed, signed, dated CRFs/data collection sheets for each enrolled subject. (GCP 8.3.14)
- Documentation of corrections to CRFs/data collection sheets (single line through [being certain to not obliterate original entry], initial, date, and/or copies of data queries and their resolution). (GCP 8.3.15, 4.9.3)
- Notes to file clarifying protocol decisions and logistics.
- Site, protocol specific Standard Operating Procedures (SOP). (UIC HSPP policy - *Investigator Essential Documents*, <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0899.pdf>)
- Clinical Database validation. (21 CFR 11)
- Protocol violations (as applicable). Study sponsors may provide specific forms to capture documentation and ensure reporting of such occurrences. While it may be necessary to immediately communicate these occurrences to sponsors, the investigator must consider the actual event to determine whether it meets the threshold of an event requiring prompt reporting to the IRB. (UIC HSPP policy - *Unanticipated Problems and Other Events Requiring Prompt Reporting*, <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0279.pdf>)
- Adverse events (as applicable). Study sponsors may provide specific forms to capture documentation and ensure reporting of such occurrences. While it may be necessary to immediately communicate these occurrences to sponsors, the investigator must consider the actual event to determine whether it meets the threshold of an event requiring prompt reporting to the IRB per UIC HSPP policy or at the time of continuing review (internal serious adverse events). (UIC HSPP policy - *Unanticipated Problems and Other Events Requiring Prompt Reporting*, <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0279.pdf>)

In addition to the documents listed above, the following regulatory documents are required when conducting investigational drug or device studies:

- Original and any updated versions of signed Form FDA 1572 (Statement of Investigator - for investigational drugs), or Investigator Agreement (for investigational devices) 21 CFR 312 (drugs), 21 CFR 812.43 (c) (devices).
- Copy of all Safety Reports submitted to the FDA. (21 CFR 312.32 [drugs], 21 CFR 812.150 (b)(1) [devices], GCP 5.16.2, 8.3.18)

- Signed and dated copy of Financial Disclosure for all investigators participating in the research. (Form FDA 3455 [Disclosure: Financial Interests and Arrangements of Clinical Investigators], 21 CFR 54)
- Drug/device shipment/receipt records. (GCP 8.2.15, 8.3.8)
- Drug/device accountability log. (GCP 8.3.23, 8.4.1)
- Drug/device dispensing/destruction log. (GCP 8.3.23, 8.4.2)
- Original and updated version(s) of the Investigator Brochure/Device Manual/Package Insert. (GCP 8.2.1, 8.3.1)
- Instructions for handling of investigational product and/or trial-related materials (if not specified in the Investigator Brochure/Device Manual/Package Insert. (GCP 8.2.14)
- Decoding procedure (for blinded/masked trials). (GCP 8.2.17)

Additional documentation when conducting investigator-initiated studies (sponsor-investigator):

- Form FDA 1571 (Investigational New Drug Application). (21 CFR 312.20 [drugs], or IDE application (21 CFR 812.20 [devices])
- Investigational Plan. (21 CFR 312.22 [drugs], 21 CFR 812.25 [devices])
- FDA approval. (21 CFR 312.20, 21 CFR 812.30, 21 CFR 812.42 [devices])
- Copy of all amendments to the initial IND or IDE application. (21 CFR 312.30 [drugs], 21 CFR 812.35 [devices])
- Copy of all adverse event reports submitted to the FDA. (21 CFR 312.32 [drugs], 21 CFR 812.150(b)(1) [devices], GCP 4.11, 5.17.1, 8.3.16, 8.3.17)
- Copy of all annual progress reports submitted to the FDA. (21 CFR 312.33 [drugs], 21 CFR 812.150(b)(5) [devices], GCP 8.3.19)
- Public Registration of the Clinical Trial. (U.S. Public Law 110-85 Food and Drug Administration Amendments Act of 2007 or FDAAA, Title VIII, Section 801 and UIC HSP Policy - *Clinical Trial Registration*, <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0268.pdf>)

Records retention/destruction

The retention or destruction of research regulatory file/data must follow applicable federal regulations, UIC OVCR policy, sponsor requirements, and other applicable guidelines. All applicable sources above must be reviewed and the records must be kept for the longest period of time applicable.

Health and Human Services (HHS), including NIH regulations (45 CFR 74.53) requires that research records be maintained for at least three years after completion of the research and submission of the last expenditure report. FDA regulations (21 CFR 312.62(c), 21 CFR 812.140(d)) require that records of research subject to the IND or IDE regulations be maintained for two years following the approval/support of the marketing/pre-market approval application for a drug/device or for two years after the investigation is terminated/discontinued and the FDA is notified. Sponsors are

responsible for notifying the investigator/institution when documents no longer need to be retained (GCP 4.9.5). The HIPAA regulations (45 CFR 164.528) require that HIPAA-related records (authorizations, documentation of waiver approvals) be maintained for six years.

Plans for long-term storage may be needed to ensure the confidentiality and availability of the records should these documents be requested by regulatory agencies, outside parties with authority, publishers, University officials, and/or OPRS.