GCP Essential Documents and the Regulatory Binder: A Toolkit

FDA regulated research is required to conform to standards of Good Clinical Practice (GCP). Section 8 of the GCP guidelines outlines the "Essential Documents" that investigators are responsible for creating and maintaining. The collection of these Essential Documents for a GCP-covered study are commonly referred to as the "Regulatory Binder." Although the name implies a physical binder with hard-copy documents, investigators are free to determine the most appropriate method and format for fulfilling these recordkeeping requirements. In the event of an FDA inspection or audit, the FDA will review the Regulatory Binder. In addition, the Regulatory Binder and all associated essential documents are to be reviewed during routine monitoring of the study in accordance with its prescribed monitoring plan.

To assist sponsor-investigators in complying with the GCP requirements for Essential Documents, the following process, tools, and templates are recommended:

Step 1: Review GCP's list of Essential Documents (starts page 45). They are broken down into 3 categories: "Before the Clinical Phase of the Trial Commences," "During the Clinical Conduct of the Trial," and "After Completion or Termination of the Trial." The Essential Documents should be maintained separately for each separate protocol/study.

Step 2: Evaluate and determine your preferred method for fulfilling each recordkeeping requirement. You may utilize hard copies or electronic format, or a combination of both. Please see the remaining pages of this toolkit document for a collection of recordkeeping templates and tools for your consideration.

Step 3: Determine responsibility for creation and maintenance of each Essential Document. Communicate this delegation of authority to each responsible person, and train them on your preferred methods. As Principal Investigator, you have ultimate responsibility over the proper maintenance of the Regulatory Binder.

Step 4: At each stage of the study, complete the "**Checklist of GCP Essential Documents"** to record each document, its location, format, and responsible person.

Step 5: Ensure that the Regulatory Binder is part of your routine self-monitoring, and that the records are made accessible to any internal or external monitor, University administrators, the IRB, and any applicable regulatory agency.

Step 6: Record Retention - study records and essential documents must be retained for the following time period (whichever is longest):

- 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or
- 3 years after completion/closure of the protocol, or
- Retention period required by specific funding agency.

Templates and Tools for Essential Documents / Regulatory Binder

1. Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts. Guidance: https://www.nidcr.nih.gov/research/toolkit/#startup

Title of Essential Document	Purpose	Guidance, Templates, & Tools
Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	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 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 this guidance. A basic product information brochure, package leaflet, or labeling may be an appropriate alternative. See pg. 42: https://www.fda.gov/media/93884/download
Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator agreement to the protocol/amendment(s) and CRF	Maintain copies of your current IRB protocol, any continuing reviews, any amendments, and any related IRB protocol documentation. Copies may be maintained in hard or electronic format, or accessed at any time on the IRB Electronic Submission System. CRF: 1. A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial subject. 2. A record of clinical study observations and other information that a study protocol designates must be completed for each subject. CRF templates and guidance: https://nccih.nih.gov/grants/toolbox#forms https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170533/
Information given to trial subject - Informed consent form (Including all applicable translations) - Any other written information - Advertisement for subject recruitment (if used)	To document the informed consent; to document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent; to document that recruitment measures are appropriate and not coercive	All information presented/given to subjects should be included in the IRB protocol, so the records may be maintained with the protocol (see row above).

Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	Maintain copies of any contracts, lease agreements, lab service agreements, etc.
Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	UTA maintains insurance as a state-entity; if additional insurance is obtained for a particular study, maintain records.
Signed agreement between involved parties, e.g.: - Investigator/institution and sponsor - Investigator/institution and CRO - Sponsor and CRO - Investigator/institution and authority(ies) (Where required)	To document agreements	Maintain copies of any contracts, MOUs, data use agreements, material transfer agreements, consulting agreements, etc.
Dated, documented approval/favorable opinion of IRB of the following: - Protocol and any amendments - CRF (if applicable) - Informed consent form(s) - Any other written information to be provided to the subject(s) - Advertisement for subject recruitment (if used) - Subject compensation (if any) - Any other documents given approval /favorable opinion	To document that the trial has been subject to IRB review and given approval/favorable opinion. To identify the version number and date of the document(s).	With the protocol file/documents, maintain a copy of the IRB approval letter for the original protocol, plus any subsequent modification approvals or continuing review approvals. Copies may be maintained in hard or electronic format, or accessed at any time on the IRB Electronic Submission System.
IRB composition	To document that the IRB is constituted in agreement with GCP	Maintained by Regulatory Services, Research Administration. https://resources.uta.edu/research/regulatory-services/human-subjects/irb-meeting-schedule.php

Regulatory authority(ies) authorization/approval/ notification of protocol (where required)	To document appropriate authorization/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	When related approvals are obtained from FDA or another regulatory agency for the trial, IND, or IDE: 1) Provide a copy to the IRB Staff to be uploaded with your protocol file in the IRB Electronic System 2) Maintain a copy in hard or electronic format, or access at any time on the IRB Electronic Submission System.
Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	Maintain a copy of each protocol personnel's cv OR Ensure that each person maintains their cv as up-to-date on the UTA Profiles System, and maintain links to each electronic cv Sample Training Log: https://www.nidcr.nih.gov/research/toolkit/Documents/TrainingLog_approved_v40_11202013.doc
Normal value(s)/range(s) for medical/laboratory/ technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	Maintain values with a copy of the protocol or elsewhere.
Medical/ laboratory/ technical procedures/ tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	Maintain copies of validation/quality control/certification records for related tests, laboratory facilities, instrumentation, etc.
Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects	Maintain copy of investigational product label.

Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	Maintain instructions in hard-copy or electronic format. Ensure process for communicating instructions to (and understanding by) study personnel. The Principal Investigator is responsible for proper storage, packaging, and disposition of investigational products, even if authority is delegated to other personnel. Study Product Guidelines and Considerations [37KB Word file] Sample SOP: https://www.hsa.gov.sg/clinical-trials/conducting/template-forms Investigational Product Accountability Log: Stock Record [1MB Word file] Investigational Product Accountability Log: Subject Record [1MB Word file]
Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	Maintain log in hard-copy or electronic format. Sample SOPs: https://www.hsa.gov.sg/clinical-trials/conducting/template-forms
Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial	Obtain a certificate of analysis from the manufacturer and/or dispensing pharmacy. Guidance – description of certificate of analysis: http://firstclinical.com/fda-gcp/?show=Re+Certificate+of+Analysis&search=pharmacy&type=&page=1 FDA Guidance – GMP of phase I investigational products: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf
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	Maintain a hard or electronic copy of the SOP for decoding/blinding studies. Ensure process for communicating instructions to (and understanding by) study personnel.
Master randomization list	To document method for randomization of trial population	Maintain a hard or electronic copy. Ensure process for communicating instructions to (and understanding by) study personnel.
Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with trial initiation monitoring report)	If working with a sponsor, maintain documentation of site start-up and monitoring reports conducted by sponsor.

Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with pretrial monitoring report)	If working with a sponsor, maintain documentation of site start-up and monitoring reports conducted by sponsor. If investigator-initiated, maintain records of personnel training.

2. During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available. Guidance: https://www.nidcr.nih.gov/research/toolkit/#during

Title of Essential Document	Purpose	Guidance, Templates, Tools
Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	If investigator's brochure is available, maintain copies and any subsequent versions/updates.
Any revisions to: - Protocol/amendment(s) and CRF - Informed consent form - Any other written information provided to subjects - Advertisement for subject recruitment	To document revisions of these trial-related documents that take effect during trial	Maintain copies (and copies of each amended version) of your IRB protocol, any amendments, and any related IRB protocol documentation. Copies may be maintained in hard or electronic format, or accessed at any time on the IRB Electronic Submission System.
Dated, documented approval/favorable opinion of IRB of the following: - Protocol amendment(s) - Revision(s) of: Informed consent form; Any other written information to be provided to the subject; Advertisement for subject recruitment (if used); Any other documents given approval/favorable opinion; Continuing review of trial	To document that the amendment(s) and/or revision(s) have been subject to IRB review and were given approval/favorable opinion. To identify the version number and date of the document(s)	Maintain a copy of the IRB approval letter for the original protocol, plus any subsequent modification approvals or continuing review approvals. Copies may be maintained in hard or electronic format, or accessed at any time on the IRB Electronic Submission System.

Regulatory authority(ies) authorizations/ approvals/notifications where required for: - Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	When related approvals are obtained from FDA or another regulatory agency for the trial, IND, or IDE: 1) Provide a copy to the IRB Staff to be uploaded with your protocol file in the IRB Electronic System, and 2) Maintain a copy in hard or electronic format, or access at any time on the IRB Electronic Submission System.
Curriculum vitae for new investigator(s) and/or subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	Maintain a copy of each protocol personnel's cv OR Ensure that each person maintains their cv as up-to-date on the UTA Profiles System, and maintain links to each electronic cv
Updates to normal value(s)/range(s) for medical laboratory/ technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial	Maintain any updated/changed values with a copy of the protocol or elsewhere.
Updates of medical/ laboratory/ technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document that tests remain adequate throughout the trial period	Maintain copies of validation/quality control/certification records for related tests, laboratory facilities, instrumentation, etc.
Documentation of investigational product(s) and trial-related materials shipment	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	Maintain log in hard-copy or electronic format. Sample SOPs: Investigational Product Accountability Log: Stock Record [1MB Word file] Investigational Product Accountability Log: Subject Record [1MB Word file] Study Product Guidelines and Considerations [37KB Word file]
Certificate(s) of analysis for new batches of investigational products	To document identity, purity, and strength of investigational products to be used in the trial	Obtain a certificate of analysis from the manufacturer and/or dispensing pharmacy. Guidance – description of certificate of analysis: http://firstclinical.com/fda-gcp/?show=Re+Certificate+of+Analysis&search=pharmacy&type=&page=1 FDA Guidance – GMP of phase I investigational products: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf

Monitoring visit reports	To document site visits by, and findings of, the monitor	Maintain a hard or electronic copy of any monitoring reports received from the IRB, regulatory agency, sponsor, etc. It is also helpful to keep a monitoring log: http://www.nidcr.nih.gov/research/toolkit/Documents/Monitoring_Visit_Log.doc
Relevant communications other than site visits - Letters - Meeting notes - Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	Maintain copies of trial-related correspondence received from the IRB, regulatory agency, sponsor, etc. Template telephone log: https://www.nidcr.nih.gov/sites/default/files/2017-12/extramural-essential-documents-binder-file-tabs.pdf
Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	Informed consent documents signed by subjects must be maintained in a secure location (hard copy or can be uploaded to a secure electronic location).
Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	Templates/Examples: Source Document Template Source Document Template with Medication Administration Source Document Completion Guidelines Source Document Example Physician Orders Template
Signed, dated, and completed case report forms (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	CRF templates and guidance: https://nccih.nih.gov/grants/toolbox#forms https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170533/
Documentation of CRF corrections	To document all changes/ additions or corrections made to CRF after initial data were recorded	CRF templates and guidance: https://nccih.nih.gov/grants/toolbox#forms https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170533/

Notification to sponsor and IRB of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with FDA and GCP requirements	Unanticipated Problem (UP) Form [1MB Word file] Adverse Event Forms [24KB Word file]
Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s) of unexpected serious adverse drug reactions and of other safety information	Notification by investigator, where applicable, to regulatory authorities and IRB(s) of 1) unexpected serious adverse drug reactions and 2) other safety information, in accordance with FDA and GCP requirements	FDA requirements for adverse events and safety reporting: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362555.htm
Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with FDA and GCP requirements	If working with an external sponsor, maintain copies of all correspondence, reports, and safety information.
Interim or annual reports to IRB and authority(ies)	Interim or annual reports provided to IRB and to authority(ies) in accordance with FDA and GCP requirements	Maintain a copy of the IRB approval letter for the original protocol, plus any subsequent modification approvals or continuing review approvals. Copies may be maintained in hard or electronic format, or accessed at any time on the IRB Electronic Submission System.
Subject screening log	To document identification of subjects who entered pretrial screening	Template: http://www.nidcr.nih.gov/research/toolkit/Documents/Screening_and_Enrollment_Log.doc
Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	Template: Subject Identification Code List
Subject enrollment log	To document chronological enrollment of subjects by trial number	Template: http://www.nidcr.nih.gov/research/toolkit/Documents/Screening_and_Enrollment_Log.doc

Investigational product(s) accountability at the site	To document that investigational products(s) have been used according to the protocol	Sample SOPs: Investigational Product Accountability Log: Stock Record [1MB Word file] Investigational Product Accountability Log: Subject Record [1MB Word file] Study Product Guidelines and Considerations [37KB Word file]
Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	Templates: http://www.nidcr.nih.gov/research/toolkit/Documents/Delegation_Responsibilities.doc
Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	Templates: Specimen Tracking Log [1MB Word file]

3. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 1 and 2 (listed above) should be in the file together with the following documents. Guidance: https://www.nidcr.nih.gov/research/toolkit/#completion

Title of Essential Document	Purpose	Guidance, Templates, Tools
Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	Templates: https://nccih.nih.gov/sites/nccam.nih.gov/files/CR-Toolbox/Investigational_Product_Accountability_Log_Stock_Record_ver1_07-17-2015.docx https://nccih.nih.gov/sites/nccam.nih.gov/files/CR-Toolbox/Investigational_Product_Accountability_Log_Subject_Record_ver1_07-17-2015.docx
Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	Sample SOPs: Investigational Product Accountability Log: Stock Record [1MB Word file] Investigational Product Accountability Log: Subject Record [1MB Word file] Study Product Guidelines and Considerations [37KB Word file]

Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	
Audit certificate (if required)	To document that audit was performed (if required)	
Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	Closeout Site Visit Checklist [20KB Word file]
Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred	Maintain records of communication with sponsor.
Final report by investigator/institution to IRB where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial	Submit a Final Report to the IRB and maintain a copy of the IRB letter/correspondence for the protocol close-out. Copies may be maintained in hard or electronic format, or accessed at any time on the IRB Electronic Submission System.
Clinical study report	To document results and interpretation of trial	If applicable/received, maintain copy of any interim or final clinical trial results or interpretation.

Additional Resources:

1. NIH Toolkit #1: https://www.nidcr.nih.gov/research/toolkit/
2. NIH Toolkit #2: https://nccih.nih.gov/grants/toolbox
3. NIH Regulatory Binder Template with Printable Binder Tabs/Divider Sheets: https://nccih.nih.gov/sites/nccam.nih.gov/files/CR-Toolbox/Regulatory_Binder_Guidance_and_Tabs_ver2_07-17-2015.docx
4. NIH Template for Manual of Procedures for a lab/study: https://www.nidcr.nih.gov/research/toolkit/Documents/mop_template_v6_22DEC2014.dotx
5. NIH Template for Standard Operating Procedures for a lab/study: https://www.nidcr.nih.gov/research/toolkit/Documents/SOPTemplate_Approved20101001.doc