CRRO Clinical Research Resources Office

FAQs on Regulatory Documentation for Clinical Research:

1) **What is a regulatory binder and why do I need one?**

The term "Regulatory binder" refers to the place (and it's not necessarily one place or even organized in a "binder"!) where regulatory documentation related to your research study is stored and updated.

Your data is the ultimate product of your study, as it enables you to answer the study question and support or reject your hypothesis. Quality documentation supports quality data and provides assurance that the data is reliable and valid to answer the study question. Your regulatory documentation tells the story that validates your data. From this documentation, one can assess many aspects of investigator and sponsor responsibilities (see Table 1) and the conduct of the study, including training and qualifications of study staff, appropriate delegation of study-related tasks, appropriate assessment and management of conflicts of interest of the investigators, appropriate recruitment and enrollment of study participants, adequate accountability of the test article, adequate study oversight by PI, etc. A well-known saying regarding clinical documentation is: "If it's not documented, it didn't happen." This extends to clinical research documentation, with an important addition: "… *and* the resulting data cannot be validated." Data that cannot be validated is not reliable and cannot be used to answer the study question. The only way for an outside person (such as a monitor, auditor, or FDA inspector) to assess the quality of your study and its results is through your documentation.

A complete regulatory binder provides documentation to support that the investigator adhered to his or her responsibilities under federal laws and guidance for conduct of human subjects research. Table 1 lists investigator and sponsor responsibilities, along with the suggested tabs in the binder where documentation supporting the fulfillment of these responsibilities is located.

The tabs and templates are provided here to help you in organizing your regulatory files to ensure that your documentation tells the story of your study.

2) **Do I have to have everything in a binder and in exactly the order of the tabs provided?**

There is no requirement to have all of your regulatory information in a particular order, or all organized in a physical binder, for that matter. In addition, it's likely that not all of the supplied tabs will apply to your study. These tabs are set up as one example of how to organize your regulatory files. However, the study sponsor may have specific requirements for how this documentation is organized and those requirements must be followed.

Your regulatory documentation can be organized as files and/or one or multiple binders in specific locations. You may also store some files electronically. The requirement is that you maintain and update the appropriate documentation for your study and that you and others on your study team are able to locate and retrieve this information as needed. Therefore, you should organize files in a way that makes sense to you and your team and the type of study

you are conducting. It is a good idea to document the organization of files so that files may be retrieved in your absence, if needed. Use the Essential Documents Location Log documentation template to document where files are located so that they are easy to retrieve when needed.

3) If my study is not a drug/device study, or if my study is not conducted under an IND or IDE, do I need to have a regulatory binder?

Clinical research is expected to be conducted to the highest ethical and clinical standards. Your documentation provides assurance that the study is being conducted to these standards.

As noted above, a physical "binder" containing regulatory information is not required. The documentation demonstrating appropriate study conduct IS required for any study. There are additional requirements that are specific to studies conducted under FDA regulations. For example, IND Safety Reports and 1572 forms only pertain to those studies conducted under an FDA IND.

That said, industry or government sponsors of clinical studies may have their own requirements that regulatory information maintained by the site be maintained in specific ways. Many sponsors supply sites with binders and organization strategies. It is important to follow sponsor instructions regarding organization of such files.

Documentation requirements in clinical research are specified in regulations such as DHHS OHRP, FDA, and guidance documents such as ICH Good Clinical Practice Guidelines (GCP).The tabs provided here have drawn directly from these references. Even if your study is not conducted under an IND or IDE, the standards for study conduct and documentation provided in these references are very useful.

You should pick and choose those components of the regulatory files that do pertain to your study. Much of the documentation specifically required by FDA and/or ICH GCP guidance is common to studies that are not regulated by the FDA (such as staff training records, delegation logs, informed consent versions; data collection form versions; protocol versions; enrollment logs, etc.).

Regarding GCP guidance: This guidance was developed by an expert working group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (This group is now called International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.) The guidance was published in the US Federal Register in May 1997, and, per FDA, "represents the FDA's current thinking on conduct of clinical research." There is a reason this is called "Good Clinical Practice"… it is an international standard for the conduct of clinical research. Compliance with ICH GCP helps ensure compliance with OHRP and FDA regulations and also ethical standards guiding clinical research.

4) Do I have to keep documentation of all the outdated/expired sponsor protocols, IRB protocols, investigator brochures, etc.? This binder could get to be pretty large!

Yes, you should maintain these outdated materials; they are a document of how the study should have been conducted at a certain point in time. However, you may decide to file certain outdated documents outside of the *main* regulatory "binder." For example, if your study protocol is attached to your IRB electronic submission system, you may decide only to keep the hard copy of the current protocol because the outdated ones are archived and accessible in the

IRB electronic submission system. (Be sure this process is acceptable to the study sponsor.) You may also store outdated materials in a separate binder or file. If you keep any materials outside of the binder, it is helpful to document where they are and how they can be accessed. You can use the Essential Documents Location Log template to do this. Likewise, some information, such as training certificates, investigator/staff CVs, and clinical license information may be maintained centrally, especially in centers that have multiple studies and staff working on more than one study (as above, be sure this process is acceptable to the sponsor).

5) How do I go about updating the regulatory binder/files?

As you create your site's Standard Operating Procedures (SOPs), it will be helpful to develop an SOP on regulatory binder/file management that is specific to this question. An SOP on regulatory binder/file maintenance should address the following:

- Required documents
- Location of various components of the regulatory documentation when study is on-going
- Frequency and responsibility for updating the regulatory documentation
- Management/storage of outdated regulatory documents
- Archiving when study is over (including where and for how long records will be stored)

6) Is there a place where I can go to look for a listing of all the required documentation for a research study?

FDA regulations often state generalities regarding documentation, such as "assure," "provide qualification," etc. Section 8 of the ICH GCP guidelines provides a more specific listing of 'essential' documents which will assist you in meeting FDA requirements. The list is titled "Essential Documents for the Conduct of a Clinical Trial." This section of ICH GCP provides a listing of essential study documents, along with the purpose of each and who is responsible for maintaining the documentation (sponsor, investigator, or both). Also, each of the Regulatory binder divider tabs provided here lists regulatory references to help you navigate the requirements for your study.

7) Should any documentation be maintained outside of the regulatory "binder?"

Yes. Per ICH GCP 8.3.21, you should keep a confidential list of all participants who are enrolled on a trial that includes the names of the individuals linked to participant ID numbers. This type of document should not be kept in the regulatory binder and should be separate from participant-specific files but in another secure location, such as in a locked file in a locked office.

Participant-specific source documents, completed data collection forms and Case Report Forms (CRFs), and signed informed consent forms are typically kept in participant files. Financial documents such as contracts, Letters of Indemnity, budgets, etc. are often kept in a separate confidential file.

Though not considered study documentation, staff should have easy access to references such as regulations and guidelines guiding the research. These may include but are not limited to: FDA regulations (21 CFR 312 for drugs and 21 CFR 812 for devices), applicable FDA guidance, DHHS OHRP regulations (45 CFR 46; Subpart A is also known as "The Common Rule"), ICH GCP guidelines, ethical guidelines such as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report, and local (institutional) policies. A list of selected regulations and guidelines is included in the pages that follow.

Table 1: Regulatory Binder Documentation and Investigator and Sponsor Responsibilities

Investigator responsibilities	Selected References	Relevant binder tabs
Personally conduct or supervise the investigation.	21 CFR 312.53 (c) (1) (vi) (a), 812.100; Investigator agreement (1572)	8, 10, 13
Ensure that an investigation is conducted according to the approved protocol and applicable regulations.	21 CFR 312.60, 812.110 (b); Investigator agreement (1572); ICH GCP 4.5	1, 2, 9, 10, 11
Protect the rights, safety, and welfare of subjects under the investigator's care.	21 CFR 312.60, 812.100; Investigator agreement (1572); ICH GCP 4.2, 4.3	5, 7, 10, 11
Control and adequate record-keeping of product under investigation.	21 CFR 312.60, 61, 62 (a), 812.110 (e); ICH GCP 4.6	12
Obtain informed consent from each study participant.	21 CFR 312.60, 62 (b), 812.140 (a) (3) (i); Investigator agreement (1572); ICH GCP 4.8; 45 CFR 46.116; 45 CFR 46.117	3
Maintain adequate and accurate documentation for each study participant.	21 CFR 312.62 (b), 812.140 (a); Investigator agreement (1572); ICH GCP 4.9	4
Ensure record retention per applicable regulations.	21 CFR 312.62 (c), 812.140 (d)	9
Investigator reports, i.e. progress reports, safety reports, final report, financial disclosure report.	21 CFR 312.64, 812.150; ICH GCP 4.10, 4.13	1, 6
Assurance of IRB review.	21 CFR 312.66, 56, 812.110 (a), 812.60; Investigator agreement (1572); ICH GCP 4.4; 45 CFR 46.103; 45 CFR 46.108	1, 16, 17
Promptly report to the IRB all unanticipated problems involving risk to human subjects or others.	21 CFR 312.66, 812.150 (1) and (4); Investigator agreement (1572); ICH GCP 4.11; 45 CFR 46.108	1, 6, 16, 17
Ensure appropriate training for staff and others working on the protocol.	21 CFR 312.53 (c) (1) (vi) (g); Investigator agreement (1572); ICH GCP 4.1.5, 4.2.4	10
Sponsor Responsibilities		
Selection of qualified investigators; obtain agreements from investigators regarding study conduct.	21 CFR 312.50, 312.53 (a) and (c); 21 CFR 812.43 (a) and (c); ICH GCP 5.3, 5.6	10, 11, 13, 14, 15
Provide investigators with information they need to conduct the investigation.	21 CFR 312.50, 312.55, 812.45; ICH GCP 5.6.2	2, 4, 13
Ensure proper monitoring of the investigation (quality assurance and quality control).	21 CFR 312.50, 312.56, 812.46; ICH GCP 5.1, 5.18, 5.19	7
Ensure protocol compliance.	21 CFR 312.50; ICH GCP 5.1, 5.23	7, 13, 14, 15
Maintain an effective IND or IDE	21 CFR 312.50, 312.30, 31, 32, 33, 812.1; ICH GCP 5.22	2, 6, 8, 10, 14, 15
Ensure that FDA and all participating investigators are promptly informed of significant new AEs or risks.	21 CFR 312.50, 812.46 (b); ICH GCP 5.17	6, 8, 14, 15
Ensure review by IRB for all sites	ICH GCP 5.11	1, 16, 17
Control of investigational drug/device, including records of shipment, receipt, and disposition.	21 CFR 312.53 (b), 312.57 (a), 312.59, 812.43 (b); ICH GCP 5.12, 5.13, 5.14	12, 14, 15
Ensure ongoing review of investigation: monitoring progress, investigator compliance, review/evaluate evidence relating to the safety and effectiveness of the intervention, and d/c an investigation that poses unreasonable/significant risks.	21 CFR 312.56; ICH GCP 4.12, 5.1, 5.16, 5.17, 5.18	1, 6, 7, 14, 15
If any sponsor responsibilities are transferred to a CRO, this should be described in writing.	21 CFR 312.52; ICH GCP 5.2	8, 9, 10, 14, 15
Ensure record access for trial-related monitoring	ICH GCP 5.15	7, 9

Selected Website Links to Regulations, Guidance, and Ethical Codes

US Regulations:

Code of Federal Regulations, Title 21, Part 312 (Investigational New Drug Application):
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312

Code of Federal Regulations, Title 21, Part 812 (Investigational Device Exemptions):
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812

Code of Federal Regulations, Title 45, Part 46 (Protection of Human Subjects):
https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML

Guidance:

FDA Information Sheet Guidance (for IRBs, Clinical Investigators, Sponsors):
https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm

ICH Good Clinical Practice (GCP) guidelines (E6):
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

Ethics:

Belmont Report:
https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Declaration of Helsinki:
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

The Nuremberg Code: https://history.nih.gov/research/downloads/nuremberg.pdf

Misc. FDA and DHHS links:

Department of Health and Human Services:
http://www.hhs.gov/

US Food and Drug Administration (FDA):
http://www.fda.gov/

Office of Human Research Protections (OHRP):
http://www.hhs.gov/ohrp/

NIH and Clinical Research:
https://osp.od.nih.gov/clinical-research/clinical-research-policy/

NIH: Institutes, Centers and Offices:
http://www.nih.gov/icd/index.html

FDA: The Investigational New Drug (IND) Application Process:
https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

FDA: Investigational Device Exemption (IDE) Application Process:
https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-approval-process