

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 a “binder”!) where regulatory documentation related to your study is stored and updated.

Just as your data validates and or invalidates your study hypothesis, your documentation validates or invalidates your data. Your regulatory documentation tells part of 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 the non-bias of the investigators, training and qualifications of study staff, appropriate recruitment and enrollment of study participants, adequate accountability of the test article, adequate 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 cannot be used to answer the study question. The only way for an outside person (such as a sponsor 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 (that it happened according to the approved protocol and the resulting data can be validated).

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

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

Your regulatory documentation can be organized as files and/or one or multiple binders in specific locations. 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 when you need to. 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’s a good idea to also document the organization of files so that files may be retrieved in your absence, if needed. A template log listing the documents is provided here for this purpose: Essential Documents Location Log.

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 validation that the study is being conducted to these standards.

As above, a physical “binder” containing regulatory information is not required. The documentation demonstrating appropriate study conduct IS required for any study, though there may be additional requirements that are specific to studies conducted under FDA regulations. For example, IND Safety Reports 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 and these binders should be used and sponsor instructions regarding organization of such files should be followed.

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) and 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.

If your study is not a drug or device study, it will still be useful to 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 informed consent versions; CRF versions; protocol versions; study staff logs; 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). It 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 documentation of how the study was 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 is in INSPIR, you may decide only to keep the hard copy of the current INSPIR protocol because the outdated ones are archived and accessible in INSPIR. (Be sure this process is acceptable to the study sponsor.) 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 to do this. Likewise, some information, such as 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:

- Creation/required documents
- Location of various components when study is on-going
- Updating frequency and responsibility
- Management/storage of outdated 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. The ICH GCP guidelines provide a more specific listing of documents which will assist you in meeting FDA requirements.

You can go to the ICH GCP guideline, section 8 titled “Essential Documents for the Conduct of a Clinical Trial.” This can be located on the FDA website at:

<http://www.fda.gov/cder/guidance/959fnl.pdf>. This section provides a listing of essential study documents, along with the purpose of each and suggestions on where the document should be located (i.e. whether it will be in the sponsor files, investigator files, or both). Also, each of the divider tabs provided here lists regulatory references.

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 and Case Report Forms are typically kept in participant files. Signed consent forms are typically kept in the participant files or in a separate location. Financial documents should be stored separately.

Though not considered study documentation, staff should have easy access to references such as regulations and guidelines guiding your 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, 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 including website links is attached to these FAQs.

Table 1: Regulatory Binder Documentation and Investigator and Sponsor Responsibilities

Investigator responsibilities	Selected References	Suggested 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, 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	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; assure that IRB complies with requirements of 21 CFR 56.	21 CFR 312.66, 56, 812.110 (a), 812.60; Investigator agreement (1572); ICH GCP 4.4	1
Promptly report to the IRB all changes in the research activity and 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	1, 6
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 and 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.	21 CFR 312.50, 312.56, 812.46; ICH GCP 5.1, 5.18, 5.19	7, 13, 14, 15
Ensure protocol compliance.	21 CFR 312.50; ICH GCP 5.1, 5.23	7, 13, 14, 15
Maintain an effective IND (protocol amendments, information amendments, IND safety reports, annual reports) or IDE	21 CFR 312.50, 312.30, 31, 32, and 33, 812.1; ICH GCP 5.22	2, 6, 8, 13, 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, 13, 14, 15
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, 13, 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 and significant risks.	21 CFR 312.56; ICH GCP 4.12, 5.1, 5.17, 5.18	1, 6, 7, 13, 14, 15
If any sponsor responsibilities are transferred to a CRO, this should be described in writing. (Ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor).	21 CFR 312.52; ICH GCP 5.2	8, 9, 10, 14, 15

Selected Website Links to Regulations, Guidance, and Ethical Codes Related to Conduct of Human Subjects Research

US Regulations:

Code of Federal Regulations, Title 21, Part 312 (Investigational New Drug Application):

<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=419a84cc3b1bacdb634ff3039fea6869&rqn=div5&view=text&node=21:5.0.1.1.3&idno=21>

Code of Federal Regulations, Title 21, Part 812 (Investigational Device Exemptions):

<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=419a84cc3b1bacdb634ff3039fea6869&rqn=div5&view=text&node=21:8.0.1.1.9&idno=21>

Code of Federal Regulations, Title 45, Part 46 (Protection of Human Subjects):

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

Guidance:

FDA Information Sheet Guidances (for IRBs, Clinical Investigators, Sponsors):

<http://www.fda.gov/oc/ohrt/irbs/>

ICH Good Clinical Practice guidelines (E6):

<http://www.ich.org/LOB/media/MEDIA482.pdf>

Ethics:

Belmont Report:

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

Declaration of Helsinki:

<http://www.fda.gov/oc/health/helsinki89.html>

The Nuremberg Code:

<http://www.hhs.gov/ohrp/references/nurcode.htm>

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:

<http://clinicalresearch.nih.gov/index.html>

NIH: Institutes, Centers and Offices:

<http://www.nih.gov/icd/index.html>

FDA: The Investigational New Drug (IND) Application Process:

http://www.fda.gov/cder/Regulatory/applications/ind_page_1.htm

