Drexel University Research Office

**FAQs on Regulatory Documentation for Clinical Research:**

# What is a regulatory binder/file and why do I need one?

The term “Regulatory binder/file” 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. If the research is not funded by a sponsor, the PI is responsible for everything related to the research.

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).

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

These tabs are set up in this document as one example of how to organize your regulatory files. Other examples with QA/QI tips are provided on QA/QI website under “Research Regulatory File Tabs”. 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 and location of files so that files may be retrieved in your absence, if needed.

# 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/file” 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.

# 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.” If you keep any materials outside of the binder, it is helpful to document where they are and how they can be accessed. 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).

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

As you create your research team’s role responsibilities, it will be helpful to assign one individual to regulatory binder/file management. Maintenance of the regulatory documents should address the following:

* + Creation/required documents
  + Location of various components when study is on-going
  + Management/storage of outdated documents
  + Archiving when study is over (reference IRB’s policy for record retention)

# 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 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.

# 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 are located on QA/QI website, section Resources.

# Table 1: Regulatory Binder Documentation and Investigator and Sponsor Responsibilities

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| **Investigator responsibilities** | **Selected References** | **Suggested tabs(below) bbelow** |
| 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 (when no sponsor, PI is responsible)** | |  |
| 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. | 21 CFR 312.52; ICH GCP 5.2 | 8, 9, 10,  14, 15 |
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**Tab 1: IRB Information/Protocol Review Correspondence**

**IRB membership**: The IRB roster documents that the IRB’s composition is in compliance with DHHS and FDA regulations and GCP guidelines.

**Federal wide assurance (FWA)**: Federal wide assurance (FWA) from Department of Health and Human Services (DHHS) through the Office for Human Research protections (OHRP) is documentation that the IRB complies with requirements set forth in 45 CFR part 46 and the terms of assurance of FWA. The PI is responsible for ensuring that the IRB’s Assurance is in effect.

**IRB correspondence**: Documents submission/approval of study and study-related documents and submissions to the IRB: initial submission, amendments, progress reports, deviations, exceptions.

* IRB-approved protocol/application; you will have a new version of the INSPIR protocol with each approved amendment and progress report.

Outdated versions are stored:

* All approval/acknowledgment letters from IRB
* Per Drexel University policy, deviations should be reported to the IRB as soon as the PI/study team becomes aware of the deviation. Deviation submissions should include a corresponding Corrective Action Plan (CAP) to prevent further similar deviations. Deviations should also be explained in the participant-specific source documents, as applicable.
* Internal AE/UP Report Tracking Log and correspondence regarding AE/UP submissions may be filed under Tab # 6: Adverse Events and Unanticipated Problems.
* Final/close-out report

**Documentation of date of review or sign-off/approval of various institutional entities**\* Document sign-off of protocol from various institutional entities as necessary.

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| **Optional Log for this section** | |
| IRB Submission Log Deviation/Exception Submission Log | Communications Log  Institutional Sign-off/Approval Log |

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| **References** | |
| * 21 CFR 312.66 *Assurance of IRB review* * 21 CFR 56.107 *IRB membership* * 21 CFR 56.109 *IRB review of research* * 45 CFR 46.101/46.103 *Federal wide Assurance* * 45 CFR 45.107 *IRB membership* * OHRP: *Registration of an IRB* * ICH GCP 3.0 *IRB* * ICH GCP 4.4 *Communication with IRB* | * ICH GCP 4.5.2 *Compliance with Protocol* * ICH GCP 4.10 *Progress Reports* * ICH GCP 5.11 *Confirmation of Review by IRB* * ICH GCP 8.3.2 *Essential documents, Revisions to protocol & consents* * ICH GCP 8.3.3 *Essential documents, Approval of IRB* * DREXEL UNIVERSITY HRP-212 Continuing Review Progress Report Form (doc) |

**Tab 2: Study Protocol and Supporting Documents**

**Sponsor Protocol & Protocol amendments\***: Documents approval of study and study-related documents.

* All approved versions of sponsor protocols Outdated versions are stored: \_
* Protocol Signature page\*: signatories sign to their approval/promise to comply with the protocol.
* Copy of NIH Grant Application\* Filed elsewhere:
* Participant recruitment/educational materials may be filed under “Tab #3: Informed Consent Forms & Supporting Documents.”

**Data Safety Monitoring Plan (DSMP)**. Keep all approved versions of your DSMP.

* A DSMP should include: overall risk assessment; a plan for safety review (what is monitored, who monitors it and how frequently); AE and Unanticipated Problem definitions; AE grading (severity) and attribution (relatedness); and a reporting plan (what gets reported, and to whom and in what timeframe it will be reported).
* Outside review committee (such as a DSMB) Charter document or SOP detailing membership, meeting frequency, what is reviewed, and plan for dissemination of recommendations.
  + File reports from outside review committee meetings under Tab #6: Adverse Events and Unanticipated Problems.

**Investigator Drug Brochure\* (IB) (or Package Insert if the drug is already marketed)**:

The IB provides information on everything that is known about the study drug based on previous laboratory, animal, and human testing and is an important reference for all members of the research team. The IB/package insert should be readily available to all study staff; it is the site’s reference regarding action of the drug and potential side effects.

* All approved versions of the IB or updated package inserts.

Current/Outdated versions are stored:

* Signed receipt form for IB\* and updates. This is not a regulatory requirement, but industry practice. It is one way the sponsor can document that new IBs were received by investigators. The sponsor should have copies of all sites’ receipt forms on file. Individual investigators may keep their copy as documentation of receipt of the IB.

**Optional Log for this section**

DSMP meeting log

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| **References** | |
| * ICH GCP 4.5 *Investigator compliance with protocol* * ICH GCP 5.1.2.2 *Updating the Investigator’s brochure* * ICH GCP 5.19.3 *Auditing procedures* * ICH GCP 7.0 *Investigator’s brochure* * ICH GCP 8.3.10 *Essential documents, monitor visit reports* | * NIH Policy for Data and Safety Monitoring, June 10, 1998 * FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March, 2006 |

**Tab 3: Informed Consent Forms and Supporting Documents**

**Study consent forms/HIPAA forms:** Documents which consent forms were approved and valid at various points during the study.

* All approved versions of any consent or assent form used in the study (including translations, short forms, assent forms, screening consents, tissue storage/banking, etc.)
* Keep copies of outdated approved versions as well.

Older versions filed elsewhere:

(Make sure that if you save hardcopy versions of outdated consent forms that you make clear on the file that these are not to be copied to use to consent current research participants.)

* File any new approved versions of the consent forms, including 1) amendments that include changes to the consent form and 2) consent forms approved in a progress report.
* Include all versions of HIPAA forms, current and outdated (such as Waiver of Authorization, HIPAA Preparatory to Research form, etc.) as applicable.

**Study participant recruitment and educational materials:** These materials may be considered part of the consent process. Keep all approved versions as documentation that all materials provided to participants have been IRB-approved as appropriate components of the consent process.

* All approved versions of recruitment and educational materials, including flyers, brochures, advertisements, websites, etc.
* Keep copies of outdated approved materials as well.

Older versions filed elsewhere:

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| **References** | |
| * 21 CFR part 50 *Protection of Human Subjects* * 21 CFR part 56 *IRBs* * 45 CFR part 46 subpart D *Additional Protections for Children* * FDA Information Sheet Guidance: FAQs: Informed Consent * FDA Information Sheet Guidance: A Guide to Informed Consent * FDA Information Sheet Guidance: Recruiting Study Subjects, *section a.: Media Advertising* * ICH GCP 3.0 *IRBs* * ICH GCP 4.5 *Compliance with protocol* * ICH GCP 4.8 *Informed Consent of Trial Subjects* | * ICH GCP 4.9 *Records and Reports* * ICH GCP 4.10 *Progress reports* * ICH GCP 5.11 *Review by IRB* * ICH GCP 5.17 *Adverse drug reaction reporting* * ICH GCP 8.3.2 *Essential documents, info given to trial participants* * ICH GCP 8.3.3 *Essential documents, IRB approval of ICFs* * DREXEL UNIVERSITY Advertisements and Flyer Templates * DREXEL UNIVERSITY HRP-502 Template Consent Document Medical/Clinical * Drexel University HRP-502 Template Consent Document Social/Behavioral/Educational * Drexel University HRP-506 Template Consent Document Emergency Use * Drexel University Assent Form * Drexel University Short Form Consent Guidance to Investigators * OHRP Policy Guidance: Informed Consent |

**Tab 4: Case Report Forms (CRFs)/Data Collection Tools**

**All past and present working (“final”) versions of CRFs and CRF completion guidelines\***

Contained in this binder

Elsewhere or stored electronically: Filed NA

**All past and present working versions of data collection tools:** Instead of or in addition to utilizing CRFs in your study, you may develop data collection tools. Typically, you would use a data collection tool to collect source data pertaining to your study. This information may then be transcribed onto the sponsor-provided or internally-developed CRFs.

For example, you may develop a source data collection tool to collect vital signs, weight, height, pregnancy testing results, etc. performed at a screening visit. You should file completed forms in participant-specific files, but it is useful to keep all versions of these tools so that you may look back to understand what data was collected and how it was collected at a certain point in time.

These tools should be updated as needed to reflect the protocol.

Contained in this binder

Filed elsewhere or stored electronically: NA

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| **References** | |
| * 21 CFR 312.62(b) *Case histories* * ICH GCP 1.11 *CRFs definition* | * ICH GCP 4.9 *Records and Reports* |

**Tab 5: Study Participants**

Information on all participants who are screened for the study should be maintained as part of the clinical study documents. However, information on individual study participants is typically maintained outside of the regulatory “binder” in participant specific files or charts. This information includes signed consent forms, participant-specific source documents, and CRFs, etc.

Ensure that participants are consented prior to any research procedures being performed (this includes collection/recording of identifiable health data from telephone or in-person screening). For those participants who were screened but did not enroll, maintain information on reasons why. For participants who were phone screened where consent was not necessary (i.e. there was no collection of identifiable data) you may maintain their reasons for not enrolling under initials. This information can be useful in assessing effectiveness of recruitment strategies.

For participants who enroll in an NIH-supported research study, information on race/ethnicity/sex is collected to document compliance to NIH policy on inclusion of women and minorities in clinical research. **Note: many studies conducted at an academic research center are at least indirectly supported by the NIH, even when not directly supported by a federal grant.**

**Screening/enrollment Log:** Filed elsewhere: A list of individuals screened and their eligibility and their enrollment status.

**Withdrawal/Termination Log:** Filed elsewhere: A list of participants who withdrew or were terminated and reasons.

**Participant ID Code List:** Filed elsewhere:

Per ICH GCP 8.3.21 a confidential list of all participants who are enrolled on a trial should be kept, including the names/contact information of the individuals linked to participant ID numbers. This list should be kept in a secure location with limited access.

**Optional Log for this section**

Screening/Enrollment Log Eligibility checklist: Inclusion/exclusion criteria

Study Withdrawal/Termination Log

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| **References** | |
| * ICH GCP 8.3.20 *Essential documents, subject screening log* * ICH GCP 8.3.21 *Essential documents, subject identification code list* | * FDA Information Sheet Guidances: Recruiting Study Subjects (as of April, 2007) * FDA Information Sheet Guidances: Screening tests prior to enrollment (as of April, 2007) * NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001 |

**Tab 6: Adverse Events & Unanticipated Problems: Reportable New Information**

The DREXEL UNIVERSITY IRB requires reporting of Reportable New information within five business days of the site learning of the event (and a summary of all AEs in the progress report). The sponsor and FDA will have additional requirements for AE/UP reporting. A UP is an event which meets all of the three following criteria:

* The event is unexpected in terms of nature or severity; *and*
* The event is related or possibly related to participation in the research; *and*
* The event suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, or meets the definition of a serious adverse event.

**Internal AE/UPs:**

* Internal AE/UP Report Tracking Log
  + Track that you have reported the AE/UP to all required entities as applicable per your DSMP (i.e. IRB, Sponsor, NIH, FDA, DSMB, etc.)
* Participant-specific AE reports and source documentation should be filed in participant-specific files.

**External AE/UPs: IND Safety Reports or IDE Unanticipated Adverse Device Effects Reports (from other sites), or other external AE reports (if not conducted under an IND/IDE)\***

Filed elsewhere:

* Safety Report Tracking Log\*
  + Tracks/organizes receipt of outside (from other sites) IND Safety Reports or IDE Unanticipated Device Effects Reports.

**Misc. Correspondence related to reporting of AEs and SAEs to the IRB, sponsor, etc.**

**Data Safety Monitoring Board (DSMB) reports (or other monitoring committee)\***

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| **Optional Log Templates for this section** | |
| Internal AE Report Tracking Log Safety Report Tracking Log | Communications Log |

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| **References** | |
| * 21 CFR 312.32 *IND Safety reports* * 21 CFR 812.50 *(b) (1) Unanticipated device effects reports* * ICH GCP 4.11 *Safety reporting* * ICH GCP 4.13 *Final reports* * ICH GCP 5.17 *Adverse Drug Reaction Reports* * ICH GCP 8.3.16, 8.3.17. 8.3.18 *Essential documents, AE reporting* * NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Trials, June 11, 1999 | * OHRP Guidance on Reviewing and Reporting UPs Involving Risks to Subjects or Others and AEs * FDA Information Sheet Guidances: Continuing Review After Study Approval (3.: Process for Dealing with Reports of Adverse Reactions and Unexpected Events) * FDA Guideline for Monitoring of Clinical Investigations, January, 1998 * DREXEL UNIVERSITY HRP-214 Reportable New Information Form |

**Tab 7: Monitoring/Auditing**

The following reports should be a part of the regulatory files in those studies that are monitored by the sponsor or CRO. It is useful to keep track of all monitor/auditor site visits and applicable correspondence regarding the site visits in the regulatory files. Use the Site Visit Log and the Communications Log for documentation of site visits and related correspondence.

**Monitoring reports and site response (as necessary)\*** Filed elsewhere:

* **Pre-trial monitoring report**: Documents that the site is suitable for the trial.
* **Study Initiation Report**: Documents that the protocol and procedures were reviewed with site by sponsor study monitor and the site was trained on the protocol.
* **Interim Monitoring Reports:** Documents site visits and findings of the sponsor study monitor and site response to findings (corrective actions, as necessary).
* **Close-out report:** Documents that the study is complete at this site and that all issues/queries have been resolved. The investigator is reminded at this visit of his/her responsibilities to maintain study documentation for the required time period per regulations and/or sponsor requirements.

**Drexel QA/QI reports and other Audit certificates\***

* Sponsor audit reports and corresponding corrective action plan (CAP) should be filed outside the regulatory binder. (Unlike the sponsor monitoring reports described above, sponsor audit reports are usually not supplied to investigators.) If and when it is supplied, keep the audit certificate in the binder as documentation that the audit was conducted.
* Drexel University QA/QI report cover sheet can be used as the audit certifcate

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| **Optional Log Templates for this section** | |
| Site Visit Log | Communications Log |

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| **References** | |
| * 21 CFR 312.54 (d) *Selecting monitors* * ICH GCP 8.3.10 *Essential documents, monitoring visit reports* | * ICH GCP 5.18 *Monitoring* * ICH GCP 5.19 *Auditing* * FDA Guideline for Monitoring of Clinical Investigations, January, 1998 |

**Tab 8: Correspondence and Minutes**

Correspondence related to study management and conduct should be documented. You may decide to keep all correspondence here, or you may decide to keep certain correspondence (such as IRB, pharmacy, laboratory, etc.) under tabs specific to those entities. Correspondence documentation may also be kept in separate binders or files. Below is a list of possible correspondence that may be maintained here. Communications about a specific participant should be filed with the source documents in that participant’s research record.

**Correspondence with Sponsor/CRO/Funding Source**: Filed elsewhere:

Documents agreements between sponsor/CRO and site regarding any relevant issue pertaining to conduct of the trial (may include letters, notes documenting phone calls, meeting notes, e-mails, faxes etc.).

* Documentation should include date, list of people/groups involved in the correspondence.

**Correspondence with Site team and/or other sites**: Filed elsewhere:

Documents agreements regarding study conduct and processes that occur among staff at local site or between sites (such as in PI and/or coordinator conference calls).

**IRB Correspondence** Filed elsewhere:

**Meeting/Conference call minutes** Filed elsewhere:

**Misc. Correspondence**: Filed elsewhere: Documents communications/agreements by the site and other entities involved in the trial.

**Agreements between investigator/institution and sponsor; investigator/institution and affiliated sites, investigator/institution and authorities**

Agreements filed elsewhere:

* Signed Confidentiality Disclosure Agreement (CDA)\*: This is an agreement that is signed by the PI (as an individual) prior to getting to view a sponsor’s protocol to determine whether s/he will participate in the study. CDAs help to ensure that the sponsor’s proprietary information is protected.

Filed elsewhere:

* Signed Clinical Trial Agreement (CTA)\*: This is a legally binding agreement between the sponsor and the investigator/institution in regards to conduct of the clinical trial.

Filed elsewhere:

* Insurance statement: documents that compensation for trial-related injury will be available.\* Filed elsewhere:

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| **Optional Log for this section** | |
| Phone Call Summary Report | Communications Log |

**References**

* ICH GCP 4.96 *Agreements between sponsor and investigator/institution*
* ICH GCP 8.3.11 *Essential documents, communications*

**Tab 9: Study-related SOPs/MOPs**

**SOP List:** File study-specific standard operating procedures (SOPs). These may also be known as Manual of Procedures (MOP), Study Operations Manual (SOM) or some other similar name. They include procedures for various aspects of the study, such as handling of study test article, lab processing procedures, screening, consenting, randomization and unblinding procedures, etc. and are often supplied by the sponsor. Sites may also develop their own site-specific SOPs in addition to sponsor-provided ones.

Keep all final versions (even if they are updated), so that procedures guiding research at a certain point in time can be used to validate study conduct during that time.

Check here if SOPs (MOPs, SOMs, etc.) are filed elsewhere:

**Optional Log Templates for this section**

SOP Table of Contents

**References**

* ICH GCP 4.7 *Randomization Procedures and Unblinding*
* ICH GCP 8.2.17 *Essential documents, decoding for blinded trials*

**Tab 10: Study Staff**

Investigators may authorize others to perform certain study-related tasks. The investigator is responsible for providing and documenting adequate training and supervision of those to whom tasks are assigned. Even if tasks are assigned, the overall responsibility for study conduct cannot be delegated. This section contains documentation regarding appropriate authorization of study- related tasks by the PI, and the adequate training of those staff regarding the tasks to which they have been assigned. Documentation in this section helps validate that the PI adhered to his/her responsibilities to personally conduct or supervise the conduct of the research and to protect the rights, safety, and welfare of study participants.

**CVs and clinical licenses for PI, sub-I’s and site staff**: Provides evidence of qualifications to oversee trial (PI) and to assign trial tasks to Sub-Is and staff.

* There is no federal requirement for CVs to be updated every X years, but it is industry standard that they are updated if there are significant changes in affiliation, education, responsibilities, etc.
* To ensure that CVs are valid and to enable assessment of currency, ask each staff member to sign and date the CV they provide (authenticated electronic PDF signatures are acceptable.
* Clinical license information should be kept current.
  + Recommend obtaining a photocopy of the license and keep a log of license expiration dates for all licensed staff.
  + Keep copy of current license in chronological order with copies of expired licenses.
* CVs/licenses may be filed centrally, b/c the same documents may be collected for multiple studies within one study group. If so, write a note-to-file for this binder section stating where CVs/licenses are maintained.

CVs and/or clinical licenses maintained elsewhere:

* File FDA 1572 form for the site under “Tab #13: Regulatory Submissions: 1572 Forms.”

**Signature and delegation of responsibility log**: The PI may assign certain responsibilities to other qualified (by education, training, experience, license, etc.) members of the research team. Many clinical tasks require formal medical training and licensing requirements. This delegation of responsibilities should be clearly documented. Even though certain tasks may be assigned to others on the study team, the PI retains full responsibility for the study, including procedures performed by other staff members.

This log is an important piece of documentation and has multiple purposes. It shows “who is authorized to do what” so “who did what” may be verified. This documentation supports the validity of source data collected during the trial.

The log should include:

* Name, signature, initials, responsibilities, and dates responsibilities began and ended.

**Training log:** Document training (and updates as necessary) for site staff. Per FDA guidance, adequate training includes: general familiarity with the study and the protocol; specific understanding of the details of the protocol and the investigational product, relevant to the

*Continued on back*

assigned tasks; awareness of regulatory requirements and standards for study conduct; are competent to perform delegated tasks; are informed of any pertinent changes during the conduct of the trial and provided with education/training as appropriate.

Examples include: Human Subjects Protection training, Safety and Infection Control training, Shipping Biologicals training, phlebotomy training, training on point-of-care testing (for example urine pregnancy tests), investigator meetings, clinical research courses or seminars if related to conduct of the study.

* At the very least, for any study at DREXEL UNIVERSITY, training documentation must include Human Subjects Protection training and basic training on the protocol.
* Document all protocol-related training, including prior to trial, at regular meetings, when new safety information is obtained, etc.
* Include documentation of site initiation visit training and attendance.
* Include copies of study-related training certificates, if applicable.
* Include copies of individual training certificates such as NIH Human Subjects Protection Training certificates.

**Financial COI disclosure forms for PI and Sub-I’s** Filed elsewhere:

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| **Optional Log Templates for this section** | |
| Signature/Task Delegation Log Staff Training Log | Staff Training Log for Groups Staff License/Certification Log |

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| **References** | |
| * 21 CFR 312.23 (a) (6) (iii) (b) *Qualifications of investigators under an IND* * 21 CFR 312.23(a)(6)(iii)(b) *IND Content and Format: Investigator information [1572]* * 21 CFR 312.53 (c) (1) *Investigator statement/1572 form* * 21 CFR 312.60 *General responsibilities of investigators* * 21 CFR 312.62 (d) *Investigator financial disclosure reports* * 21 CFR 54 *Financial disclosure by clinical investigators* * FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects, October, 2009 * FDA Guidance: Financial Disclosure by Clinical Investigators | * ICH GCP 4.1 *Investigator’s qualifications and agreements* * ICH GCP 4.2.2 *Adequate staff and facilities* * ICH GCP 4.3 *Medical Care of trial subjects* * ICH GCP 4.5 *Compliance with protocol* * ICH GCP 5.6 *Investigator selection* * ICH GCP 8.2.10 *Essential documents, CVs* * ICH GCP 8.3.5 *Essential documents, CVs for new investigators* * DREXEL UNIVERSITY certificates of training * Evidence of Drexel University required CITI training |

**Tab 11: Laboratory\***

**Laboratory accreditation/certification and updates:** This section provides documentation as to the competence of laboratories performing protocol required tests with human samples. Such documentation supports the reliability of test results. CLIA stands for Clinical Laboratory Improvement Amendments of 1988. This law sets standards for lab testing of human samples to ensure that the test results are accurate, timely and reliable.

**For tests that are used for diagnosis, treatment, prevention, assessment:**

CLIA requires all facilities that perform tests on “materials derived from the human body for purpose of providing information for the diagnosis, prevention, or treatment of any disease… or assessment of health of human beings” to meet certain requirements. Any facility performing such tests is considered a laboratory under CLIA and must obtain CLIA certification. Include documentation of CLIA certification as applicable to your study:

CLIA Certification of Compliance

*or*

CLIA Certification of Accreditation AND certificate from a lab accreditation organization (i.e. College of American Pathologists – CAP or Joint Commission on Accreditation of Healthcare Organizations – JCAHO).

Other CLIA certificates may be applicable to your study: Certificate of Waiver; Certificate for Provider Performed Microscopy procedures; Certificate of Registration. Please see CLIA-specific references listed below for more information.

**For research labs that test protocol specimens but do NOT report any subject-specific results for the diagnosis, treatment, prevention or assessment of the health of subjects:**

CLIA certification is not relevant. In this case, provide documentation that the lab director and/or personnel performing the tests have training and qualifications to assure ability to perform the tests as required by the protocol.

**Laboratory normal ranges, and updates for all study tests**: Per ICH GCP guidance.

**Optional Log Templates for this section**

Stored Biosample Log

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| **References** | |
| * ICH GCP 4.2.2 *Adequate staff and facilities* * ICH GCP 8.2.11 *Essential documents, normal values/ranges* * ICH GCP 8.2.12 *Essential documents, lab certification* * OHRP Policy Guidance, Repositories, Tissue Storage | * CLIA law: CFR Title 42, chapter IV, Part 42: Laboratory Requirements * CLIA: How to Obtain a CLIA Certificate (CMS, brochure   #5, March, 2006) available at: [http://www.cms.hhs.gov/CLIA/downloads/](http://www.cms.hhs.gov/CLIA/downloads/%20HowObtainCLIACertificate.pdf)  [HowObtainCLIACertificate.pdf](http://www.cms.hhs.gov/CLIA/downloads/%20HowObtainCLIACertificate.pdf) |

**Drug/device accountability:** Helps to assess participant compliance with the use of the study test article(s). Also helps to validate sponsor and investigator compliance with FDA requirements regarding control of investigational drugs/devices. Your documentation should clearly show the trail from the sponsor/manufacturer to the investigator and/or pharmacy, to the participant, back to the investigator and/or pharmacy (if applicable) and then destruction or return to the sponsor/manufacturer. Some of the documentation listed below may be maintained in pharmacy.

* Correspondence/communications with supplier
* Correspondence/communication/agreements with pharmacy
* Copy of test article sample label: documents compliance with applicable labeling regulations
* Study agent order forms Filed elsewhere:
* Shipping receipts/records Filed elsewhere:
* Study agent dispensing and return documentation Filed elsewhere:
* Study agent disposition and/or return of unused

or damaged study agent Filed elsewhere:

* + Do not destroy or dispose of study drug without authorization from the sponsor.

**For Sponsors of drug studies: Certificate of Analysis\***: If you are the sponsor or sponsor- investigator of the study (i.e. you have initiated the research as well as conduct it) you must maintain documentation that the investigational product has been manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). Per ICH GCP 8.2.16, a Certificate of Analysis of the investigational product that documents identity, purity and strength of the product should be included in the files of the study Sponsor.

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| **Optional Log**  **for this section** | |
| Test Article Accountability  Test Article Shipping Receipt Log | Test Article disposition and/or return |

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| **References** | |
| * 21 CFR 312.23 (a) (7) Chemistry, Manufacturing, and Control * 21 CFR312.57(a) *Sponsor records on investigational drugs* * 21 CFR 312.59 *Sponsor disposition of unused drug* * 21 CFR 312.61 *Control of the investigational drug* * 21 CFR 312.62 (a) *Investigator disposition of unused drug* * 21 CFR 210 and 211 *Good Manufacturing Practice (GMP): Manufacturing, processing, packing or holding of drugs and finished pharmaceuticals* | * ICH GCP 2.12 *Manufacture and handling of investigational products* * ICH GCP 4.6 *Investigator Responsibilities regarding Investigational Product(s)* * ICH GCP 5.13 *Manufacturing, labeling, coding of investigational products* * ICH GCP 5.14 *Supplying and handling investigational products* * ICH GCP 8.2.13 *Essential documents, sample labels* * ICH GCP 8.2.16 *Essential Documents, Certificates of Analysis of investigational products shipped* |

**Tab 13: Regulatory Submissions: FDA 1572 Forms\***

**Selection of Qualified Investigators – FDA 1572 forms\***: Filed elsewhere:

* 1572 forms: completed and signed by each site investigator:
  + Investigators should maintain copies of the site’s 1572 form (and updates). Sponsor- investigators should maintain copies of all sites’ 1572 forms (and updates).
  + This form is required by the sponsor for any drug study being conducted under an Investigational New Drug (IND) application. The form provides an agreement of the commitments made by the site PIs: compliance to regulations; compliance to protocol; commitment to personally conduct or supervise the trial, etc. The overall purpose is to ensure that the rights, safety, and welfare of study participants are being protected.
  + Link to 1572 form: <http://www.fda.gov/opacom/morechoices/fdaforms/cder/html>
  + When should a new form be signed?
    - A sponsor must obtain a new signed form as each new site Principle Investigator joins the study (such as a new site or replacement of a PI at a current site), when drug is shipped to a new location, or for a new protocol (under the same IND) for an existing PI.
    - It is not necessary (per regulations) for sites to complete a new 1572 as sub- investigators begin or leave a site; however, it is industry practice for sponsors to use the form as a way to document these changes.
    - Sites SHOULD notify the sponsor (who updates the IND) of changes to the 1572 (such as new sub-I) and sites should document by updating the Site Signature log with start dates, responsibilities, and departure dates. Sponsors may require completion of an updated 1572 form.
* CVs for all PIs and sub-investigators listed on the 1572 forms.
* Sponsors should keep all CVs for those individuals listed on 1572 forms.
* Investigators should keep CVs for all site staff (see “Tab #10: Study Staff”).
* Financial disclosure forms (form FDA 3455) for all PIs and sub-investigators listed on the 1572 forms (see “Tab #10: Study Staff”).

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| **References** | |
| 21 CFR 312.53 (c) (1) *FDA form 1572* | * FDA Draft Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572), July, 2008 |

**Tab 14: Regulatory Submissions: IND Maintenance for Investigator IND Holders (Investigators who are also Sponsors)\***

A sponsor-investigator is an individual who *initiates and conducts* an investigation and under whose immediate direction the investigational drug is administered or dispensed.

Sponsor-investigators must follow regulations pertaining to both sponsors and investigators.

***Sponsor*** responsibilities include:

* Maintain an effective IND (protocol and information amendments, safety reports, annual reports)
* Select qualified investigators (1572 form/investigator agreement from each site PI).
* Provide investigators with information they need to conduct study.
* Ensure protocol compliance.
* Ensure ongoing monitoring of all sites and selection of qualified monitors.
* Ensure ongoing review of investigation: monitoring progress, investigator compliance to protocol, review and evaluate evidence relating to the safety and effectiveness of the drug, discontinue an investigation that poses unreasonable and significant risks.
* Ensure prompt reporting to FDA and participating investigators of significant new adverse affects or risks.
* Ensure control of investigational drug.
* Ensure recordkeeping of the investigational drug control (receipt, shipment, disposition, etc.), financial interests of the study investigators, and adequate retention of study records.
* If any sponsor responsibilities are transferred to a contract research organization, this transfer should be described in writing.

Tab 14 provides documentation pertaining to the original IND submission, the requirement to maintain an effective IND, and selection of qualified investigators. See other tabs in this binder for documentation on the other sponsor requirements listed above.

**General Correspondence/communication with FDA**

**Original IND information**: Note: the initial submission is serial number “0000” and following submissions/amendments, etc. are numbered sequentially.

* + IND cover sheet (form 1571)
  + IND application Filed elsewhere:
  + IND letter of acknowledgement: This is a letter generated by the FDA after receipt of your IND submission. It includes the receipt date and IND number. The clinical investigation may not start until after 30 days after the IND was received by the FDA.
  + IND letter of “no objections”: This is a letter that *may* be generated by the FDA after review of your IND submission and signifies that the proposed clinical investigation may begin.

**Maintenance of the IND**:

* + **Protocol amendments** Filed elsewhere:
    - New protocol (conducted under the same IND)
    - Changes to an existing protocol
    - Addition of new investigator (site PI) to protocol (notify FDA within 30 days)

*Continued on back*

* + **Information amendments** Filed elsewhere:
    - Examples: new toxicology, chemistry, or other technical information; report regarding discontinuation of a clinical investigation, etc.
  + **IND Safety Reports** Filed elsewhere:
    - Sponsor must notify FDA and all participating investigators of the following via an IND Safety Report (Form 3500A) no later than 15 calendar days after sponsor’s initial receipt of the information*.*
      * Any unexpected fatal or life-threatening experience associated with the use of the drug. Notify FDA asap but no later than 7 days by phone/fax after initial receipt of the information. Follow up with IND Safety Report within 15 days.
      * An adverse experience associated with the use of the drug that is both serious and unexpected or any finding from tests in laboratory animals that suggests a significant risk for human subjects.
  + **Annual reports** Filed elsewhere:
    - Within 60 days of the IND anniversary date a report of the progress of the investigation must be submitted to the FDA.

**Selection of Qualified Investigators – 1572 forms**: Filed elsewhere:

* + See Tab #13: Regulatory Submissions: FDA 1572 Forms.

**Optional Log Templates for this section**

Communications Log

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| **References** | |
| * 21 CFR 312 *Drugs*   21 CFR 312.23 (a) (1) *1571 cover sheet*   * 21 CFR 312.30 and 31 *IND amendments* * 21 CFR 312.32 *AE submissions to FDA* * 21 CFR 312.33 *IND annual reports* * 21 CFR 312.50 *General responsibilities of sponsors* * 21 CFR 312.52 *Transfer of obligations to a contract research organization* * 21 CFR 312.53 *Selecting investigators and monitors* * 21 CFR 312.55 *Informing investigators* * 21 CFR 312.56 *Review of ongoing investigations* * 21 CFR 312.57 *Sponsor recordkeeping* | * 21 CFR 312.57 (d) *Reserving samples of test articles* * 21 CFR 312.58 *Permitting inspection of records* * 21 CFR 312.59 *disposition of unused supply of investigational drug* * 21 CFR 54 *Financial disclosure* * FDA Information Sheet Guidances: Sponsor- investigator-IRB relationship (as of April, 2007) * ICH GCP 4.11 *Safety reporting* * ICH GCP 5.17.1 *AE drug reaction, sponsor reporting* * ICH GCP 8.3.9 *Essential documents, certificate of analysis for new batches*   ICH GCP 8.3.16, 17, and 19 |

**Tab 15: Regulatory Submissions (Device studies): IDE Maintenance for Investigator IDE Holders (Investigators who are also Sponsors)\***

A sponsor-investigator is an individual who *initiates and conducts* an investigation and under whose immediate direction the investigational device is administered, dispensed, or used.

Sponsor-investigators must follow regulations pertaining to both sponsors and investigators.

***Sponsor*** responsibilities for studies conducted under an IDE include:

* Maintain an effective IDE (application and reports).
* Select qualified investigators (obtain signed investigator agreements, CVs, Investigator statements, and financial disclosure information from each site PI).
* Provide investigators with information they need to conduct study, including copies of the investigational plan and reports of prior investigations of the device.
* Ensure protocol compliance.
* Ensure proper monitoring of the investigation.
* Ensure that IRB review and approval are obtained.
* Ensure that any reviewing IRB and FDA are promptly informed of significant new information about the investigation.
* Ensure that investigational device is shipped only to qualified investigators.
* Selection of monitors that are qualified by training and experience.
* Ensure investigator compliance with the investigational plan, and if an investigator will not comply the sponsor should discontinue shipments of the device and terminate the investigator’s participation in the investigation.
* Ensure immediate evaluation of any unanticipated adverse device effect.
* Ensure recordkeeping of the investigational device control (receipt, shipment, disposition, etc.).

Tab 15 provides documentation pertaining to the original IDE submission, the requirement to maintain an effective IDE, and selection of qualified investigators. See other tabs in this binder for documentation on the other sponsor requirements listed above and investigator requirements.

**General Correspondence/communication with FDA**

**Original IDE information**:

* + IDE application Filed elsewhere:
  + FDA approval of the application

**Maintenance of the IDE – Sponsor Reports**:

* + **IDE Unanticipated adverse device effects** Filed elsewhere:
    - The sponsor must report the results of the evaluation of an unanticipated device effect to the FDA and all reviewing IRBs and participating investigators within 10 working days after first receiving notice of the effect.
  + **Withdrawal of FDA approval**
    - Notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval of the investigation within 5 working days after receipt of notice of withdrawal of approval.
  + **Current investigator list**
    - Submit to FDA at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation.
  + **Progress reports** Filed elsewhere:
    - At regular intervals, and at least yearly, submit progress reports to all reviewing IRB’s. If the device is significant risk device progress reports should be submitted to the FDA.

If it is a treatment IDE, submission of progress reports to reviewing IRBs and FDA should be done semi-annually.

* + **Recall and device disposition**
    - Notify FDA and all reviewing IRBs of any request that an investigator return, repair, or dispose of any units of a device within 30 days after request was made.
  + **Final report**
    - For significant risk device, the sponsor should notify the FDA within 30 working days of the completion or termination of the investigation and should submit a final report to the FDA and all reviewing IRBs and participating investigators within 6 months after completion or termination. If not a significant risk device, sponsor should submit report to all reviewing IRBs within 6 months after completion or termination.
  + **Informed consent**
    - Submit to FDA a copy of any report by an investigator of use of a device without obtaining informed consent within 5 working days of receipt of notice.
  + **Significant risk device determination**
    - If an IRB determines that a device is a significant risk device, and the sponsor has proposed that the IRB consider the device not to be a significant risk device, the sponsor should submit to the FDA a report of the IRBs determination within 5 working days of learning of it.
  + **Other**
    - Upon request by a reviewing IRB or the FDA the sponsor should provide accurate, complete and current information about any aspect of the investigation.

**Selection of Qualified Investigators – Investigator agreements, CVs, Investigator statements, and Financial disclosure forms**: Filed elsewhere:

**Optional Log Templates for this section**

Communications Log

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| **References** | |
| * 21 CFR 812 *Devices*   21 CFR 312.23 (a) (1) *1571 cover sheet*   * 21 CFR 812.40 *General responsibilities of sponsors* * 21 CFR 812.43 *Selecting investigators and monitors* | * 21 CFR 812.45 *Informing investigators* * 21 CFR 812.46 *Monitoring investigations* * 21 CFR 812.140 *Records* * 21 CFR 812.150 *Reports* |