CHAPTER #10
Clinical Trial Regulatory Maintenance

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CHAPTER 10: Clinical Trial Regulatory Maintenance

10.1 Reporting to the IRB

Before starting, review:
- Form HRP-213 “Modification”
- Form HRP-213 “Reportable New Information”

*Forms are located within IRBNet under the “Forms and Templates” section


10.1.1 Reporting New Information

New Information is reported by completing the multipurpose IRB form “Reportable New Information” (HRP-214). This form is used to report a wide spectrum of information to the IRB, including serious harms and protocol deviations. The information that falls into one or more of the following two categories needs to be reported to the IRB within 5 business days:

1. Information that indicates a new or increased risk, or a new safety issue, for example:
   a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk;
   b. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm;
   c. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm;
   d. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude or a previously known risk, or describe a new risk;
   e. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol;
   f. Changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
2. **Serious harm experienced by a subject or other individual**, which in the opinion of the investigator is unexpected and probably related (>50% likely; “Don’t know” = <50%) to the research procedures.

   a. A harm is "**serious**" when it meets any of the following criteria:
      - results in death;
      - is life-threatening (place the subject at immediate risk of death from the event as it occurred);
      - results in inpatient hospitalization or prolongation of existing hospitalization;
      - results in a persistent or significant disability/incapacity;
      - results in a congenital anomaly/birth defect;
      - based upon appropriate medical/psychological judgment, may jeopardize the subject’s health and may require medical, counseling, or surgical intervention to prevent one of the other outcomes listed in this definition; or
      - results in criminal or civil liability or damaging of the subject’s financial standing, employability, or reputation

   b. A harm is “**unexpected**” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.

   c. A harm is “**probably related**” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.

The information that falls into one or more of the following ten categories below needs to be reported to the IRB within **10 business days**:

1. **Non-compliance with the federal regulations** governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.

2. **Failure to follow the protocol** due to the action or inaction of the investigator or research staff.

3. **Change to the protocol** done without prior IRB review to eliminate an apparent immediate hazard to a subject.

4. **Breach of confidentiality**.

5. **Complaint** of a subject that cannot be resolved by the research team.

6. **Premature suspension or termination** by the sponsor, investigator, or institution.

7. **Incarceration of a subject** in a study not approved by the IRB to involve prisoners.

8. **Audit**, inspection, or inquiry by a federal agency or other entity and any resulting reports (e.g., FDA Form 483).

9. **Ancillary approvals** (e.g., COI, SCRO) that do not result in a protocol revision, Data Safety Reports that include a recommendation to terminate or modify a study and written reports of study monitors with reportable events that have not yet been reported.

10. **Unanticipated adverse device effect** (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in
10.1.2 Reporting Serious Harms

When reporting any of the above, report the date the Investigator became aware of this information, the number of subjects currently enrolled at this organization, are any currently enrolled subjects receiving intervention(s) and/or interactions at this organization, and if the study is currently enrolling at this organization. Also indicate if the protocol and/or the consent document(s) require revision.

Investigators are required to report, with form “Reportable New Information (HRP-214)”, serious harms to the IRB within five business days of the investigator becoming aware of such harm, provided that all four of the following criteria are met:

- The event or problem:
  1. Occurred at UC Davis; and
  2. Is a serious harm; and
  3. Is unanticipated; and
  4. Is related or probably related to the research: a harm is “related to the research procedures” if, in the opinion of the principal investigator, it was more likely than not to be caused by the research procedure (>50% likely; “Don’t know” = <50%).

This information regarding serious harms may impact the risk/benefit ratio of the study. Based on such information, the IRB may need to reconsider its approval of the study, require a modification to the study, or revise the continuing review timetable. The IRB is also responsible for ensuring that harms that are determined to be unanticipated problems involving risks to research participants or others are reported to FDA. Such reporting may go through the investigator to the sponsor to the FDA, or in the case of investigator-initiated studies, from Sponsor-Investigator to FDA.

In the Report, the Investigator will either justify why no changes to the protocol or consent form are needed or attach proposed modifications to the report. The Investigator must respond to all requests from the IRB for further information within 10 working days of receipt of the request. Failure to respond may result in suspension of the study until the issue is resolved.

10.1.3 Reporting Protocol Deviations

Types of Deviations

A protocol deviation is any departure or discrepancy between the IRB approved protocol and the actual research activities being performed.

Minor protocol deviations are deviations with no substantive effect on the risks to research subjects and that have no substantive effect on the value of the data collected. Deviations that did not
result from willful or knowing misconduct on the part of the investigator(s) or research staff; and did not result in or require any substantive action to be taken or result in any change to the subject’s condition or status are considered minor.

**Major protocol deviations** are deviations that result in or require a substantive action to be taken or result in a change to the subject’s condition or status. Deviations that harmed or posed a significant risk of substantive harm to the research participants or damaged the scientific integrity of the data collected for the study, or are evidence of willful or knowing misconduct on the part of the investigator(s) or research staff, or involve serious or continuing noncompliance with federal, state, or local research regulations are considered major.

**All protocol deviations** from an IRB approved study must be avoided, including deviations to eliminate an immediate hazard to research subjects. Deviations must be reported to the UC Davis IRB in accordance with “Reportable New Information (HRP-214),” if they fall under the categories listed on the form. Investigators are required to report deviations in these categories to the IRB within 10 working days. Review SOP “New Information (HRP-024)” for how and when to report to the IRB.

### 10.1.4 Reporting Modifications

It is advisable to consult the UC Davis IRB Investigator Manual (HRP-103) prior to preparing your application:


Complete the IRB form “Modification” (HRP-213). This form is used to request a modification to previously approved study activity, such as:

- Study Protocol Amendments
- Changes in Research Personnel
- Responses to a Letter of Action (LOA) for requested modifications by the IRB in order to secure approval

Research must continue to be conducted without implementation of the modification until IRB approval is received.

### 10.1.5 Continuing Review Progress Reports

All studies are required to be reviewed by the IRB at least annually and perhaps more often if the IRB has determined that more frequent review is warranted. Documents reviewed by the IRB are given an expiration date. Using expired consent forms is a common error identified by the audits. The IRBNNet sends out a courtesy notice approximately 3 months prior to the approval expiration date, and it is the Principal Investigator’s responsibility to assure that the required updated information is submitted to the IRB by the administrative due date in order to meet the deadline for application to a meeting of the IRB so as to receive approval for the following period prior to the expiration date.
The following review criteria are the same for initial review and continuing review and include a determination by the IRB that:

- Risks to subjects are minimized by using procedures, which are consistent with sound research design and which do not unnecessarily expose subjects to risk.
- Risks to subjects are minimized by using procedures already being performed on the subjects for other purposes.
- Risks to subjects are reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Informed consent is adequate and appropriately documented.
- Were appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects.
- There are adequate provisions to protect the privacy of subjects and to maintain.

Complete the IRB form “Continuing Review Progress Report” (HRP-212). If the Investigator is requesting any protocol modifications at the time of renewal, complete form HRP-213 Modification Form for submission.

The following documents may be required with your Continuous Review:

- If any changes are being made to the protocol document, submit a Marked copy indicating changes being made (with new text underlined or highlighted; language being removed/changed with strike-through; or tracked changes shown – remember to update version date) Also submit a ‘clean copy’ of the protocol document (incorporating any changes being made at the time with new version date);
- The online initial review application cannot be marked, provide a detailed description of the changes within Form HRP 213: Modification;
- If any changes are being made to the consent document(s), submit a Marked copy indicating changes being made (with new text underlined or highlighted; language being removed/changed with strike-through; or tracked changes shown – remember to update version date) Also submit a ‘clean copy’ of consent document(s) (incorporating any changes being made at the time with new version date); If any changes are being made to the recruitment material(s), submit a ‘marked copy’ indicating changes being made (with new text underlined or highlighted; language being removed/changed with strike-through; or tracked changes shown). Also submit a ‘clean copy’ of all recruitment materials/flyers/scripts (incorporating any changes being made at the time with new version date);
- Foreign language translated versions of any of the above as applies to your study;
- Copy of Sponsor’s progress report(s) or annual report, if available;
10.2 Reporting to the FDA and the Sponsor

10.2.1 Reporting New Information to the FDA and the Sponsor

Reporting under IND (Protocol Amendments)

Submit an IND Protocol Amendment for the following changes during the course of your study:

- New Protocol
- Change in Protocol
- New Investigator (new site)

The study may begin after obtaining an IRB approval based on the new or amended protocol and after the FDA receives the amendment. FDA does not issue “permissions” or “approvals” for protocol amendments, your changes are effective immediately upon the receipt of your amendment by the FDA.

For changes in the Protocol, the IND Protocol Amendment consists of:

- Cover Letter identifying the submission as “Protocol Amendment: Change in Protocol” or “Protocol Amendment: New Protocol”
- Form 1571 - Check an appropriate box under Paragraph 11, “Protocol Amendments”
- A document outlining the differences between the new protocol and the original protocol

For changes in the Investigators, the IND Protocol Amendment consists of:

- Cover Letter identifying the submission as “Protocol Amendment: New Investigator”
- Form 1571 - Check an appropriate box under Paragraph 11, “Protocol Amendments”
- Form 1572 for the new investigator

If there are Manufacturing or other changes, the manufacturer (in many cases, industry sponsor) will notify the study team:

- Changes in Chemistry, Manufacturing and Control,
- Changes in Pharmacology/toxicology (new findings affecting safety and efficacy),
- Decides to discontinue a clinical study,

The Principal Investigator is responsible to notify the IRB and make a decision as to whether to proceed with your trial.

Reporting under IDE (IDE Supplements)

Any changes in the Investigational Plan should be approved by the FDA and, when appropriate, IRB, prior to implementing any change to a previously accepted Investigational Plan. The following types of protocol changes would require an approved IDE Supplement, because they are likely to have a significant effect on the scientific soundness of the trial design and/or validity of the data resulting from the trial:

- Change in indication
- Change in type or nature of study control
- Change in primary endpoint
- Change in method of statistical evaluation
• Early termination of the study (except for reasons related to patient safety)
• Change in the number of investigational sites
• Change in the number of study subjects

However, if the modifications meet certain criteria, the sponsor of an IDE may modify the device and/or clinical protocol without prior FDA approval. The sponsor still needs to provide notice to FDA within 5 working days of making the change. These notices must be identified as a “notice of IDE change.”

1. **Emergency use.** If PI deviates from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviations should be reported to the IRB promptly after its occurrence, and to the FDA within 5-working days after the sponsor becomes aware of it.

2. **Certain changes to the device.** Advanced IRB notification is not required if the changes do not constitute a significant change in design or basic operation and are made in response to information gathered during the course of an investigation. Examples include: creditable data generated under the device control procedures (21 CFR Sec. 820.30), preclinical/animal testing, peer reviewed published literature, and clinical information gathered during a clinical trial or marketing.

3. **Certain clinical protocol changes** that do not affect (i) the validity of the data or information resulting from the completion of the approved protocol, or the relationship of the likely patient risk to benefit ratio relied upon to approve the protocol; (ii) the scientific soundness of the investigational plan; or (iii) the rights, safety, or welfare of human subjects involved in the investigation.

4. **If changes will be submitted in the annual report.** A sponsor may make minor changes to an Investigational Plan without prior FDA approval; provided that the respective changes are reported in the annual progress report for the IDE (see Annual Reports).


### 10.2.2 Reporting Adverse Events to the FDA and Sponsor

**Adverse Event (AE):** An adverse event is an undesirable and unintended event occurring as a result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy). It also includes any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research.

**Serious Adverse Event (SAE):** Events are classified as serious if they meet any of the following criteria:

- Results in death or any life threatening event that places the subject at immediate risk of death from the event as it occurred.
- Any event that requires or prolongs in-patient hospitalization.
- Any event that results in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who participated in the study and received study drug.
- Other medically important events that in the opinion of the investigator may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.
**Unanticipated AE**: Any adverse experience, the frequency or severity of which is not consistent with the current consent form or investigator brochure.

**Unanticipated Problem Involving Risk to Participants or Others**: any unanticipated event involving any aspect of a research study involving anyone (participants, research staff, or others not directly involved in the research) that increases the risk to the person involved.

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**Adverse Events**

Under 45 CFR part 46: Do not report A, Do report (B+C)

An adverse event occurs in one or more subjects.

1. Is the adverse event unexpected in nature, severity, or frequency?
   - YES
   - NO

2. Is the adverse event related or possibly related to participation in the research?
   - YES
   - NO

3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? NOTE: If the adverse event is serious, the answer is always YES.
   - YES
   - NO

![Diagram](image-url)

**Report the adverse event as an unanticipated problem under 45 CFR part 46**

**The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46**

Adapted from DHHS Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

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Reporting SAEs to the Sponsor

Once an adverse event becomes serious, the site should inform the Sponsor by submitting an SAE report. Typically, the Sponsor will provide the report form to use and inform the study investigator/coordinator where and how (i.e., email, fax, etc.) to send the report. An SAE report should be submitted to the Sponsor no later than 24 hours after the site becomes aware of the event. As the site gains more information (i.e., admission records, hospital discharge summaries) updated SAE reports with the new information should be submitted to the Sponsor. In this case the Sponsor (Industry/cooperative group) holds the IND and is therefore responsible for deciding whether the SAE should be reported to the FDA.

Reporting SAEs to the FDA (for investigator-initiated studies under IND or IDE)

IND Safety Reports

In cases where the PI is both the Investigator and the Sponsor, the PI assumes the responsibility of reporting certain SAEs to the FDA. Once it is determined that an SAE must go to the FDA an IND Safety Report is prepared (usually the PI, in association with the medical monitor, will determine whether an IND Safety Report needs to be prepared). An IND Safety Report is an expedited, written notification to the FDA of an adverse experience associated with the use of a study drug that is both serious and unexpected.

For more on filing requirements and follow-up, see: http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/index.html

When to file:

1. For any unexpected fatal or life threatening SAE associated with the use of the drug, the IND Sponsor-Investigator notifies the FDA of the SAE by telephone or fax as soon as possible, but no later than seven calendar days after initial receipt of the SAE. The investigator follows with the written report no later than 15 days after the occurrence.

2. For serious and unexpected, but non-fatal adverse events, file as soon as possible and no later than 15 days after initial receipt of the SAE.

IDE Safety Reports

An unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

If the Investigator is a Sponsor-Investigator, he/she will notify the FDA and all participating investigators in a written IDE safety report of any unanticipated adverse device effects. The report is
also provided to the device manufacturer and to the reviewing IRB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect. Thereafter the sponsor (or Sponsor-Investigator) shall submit such additional reports concerning the effect as FDA requests.


10.2.3 Reporting Protocol Deviations

**Reporting Protocol Deviations to the Sponsor**

In many cases Sponsors will specify at the beginning of the study how they would like to handle protocol deviations. Minor deviations (as described above) are usually recorded in the case report forms and tabulated by site at the end of the study. Most Sponsors do not require that minor deviations be reported in any immediate fashion. For major deviations the site often reports to the Sponsor the same information that is reported to the IRB (see major protocol deviations above).

In the case where a site needs a deviation in order to enroll a patient that is not otherwise eligible per the protocol inclusion/exclusion criteria, a Sponsor will request that a planned protocol deviation be filed requesting permission from the Sponsor for the site to enroll the patient. Sponsors will respond to this request in writing and this form along with documentation of all communication between the site and Sponsor should be kept in the patient's source documentation.

**Reporting Protocol Deviations to the FDA (for investigator-initiated studies under IND and IDE)**

**Reporting Protocol Deviations under IND** (adapted from [www.firstclinical.com](http://www.firstclinical.com))

FDA's regulations have numerous references to “changes” or “amendments” to study protocols. For example, 21 CFR 312.30 addresses the responsibility of sponsors to submit amendments to their IND[s] to ensure that clinical investigations are conducted according to protocols included in the application. 21 CFR 312.30(b) specifically discusses changes in a protocol, and provides several examples of changes that would require sponsors to submit protocol amendments to the IND. However, the FDA regulations do not provide specific guidances on deviation reporting.

A protocol deviation directed at eliminating an apparent immediate hazard to a research subject or group of subjects may be implemented immediately provided that the reviewing IRB is so notified. The respective protocol deviation should be addressed in the next Annual Report to the IND application. If the protocol deviation will be incorporated as a permanent change (i.e., revision) to the protocol, a respective Protocol Amendment must be submitted prospectively to the IND application/FDA and the revision to the protocol must be approved prospectively by the responsible IRB [see below].

**Reporting Protocol Deviations under IDE**

FDA device regulations at 21 CFR 812.150(a)(4) discuss protocol deviations under IDE regulations. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB should be made aware in accordance with 812.35(a).
10.2.4 Submit Annual Reports to the FDA

Annual Reports to CDER

For clinical trials being conducted under an IND, FDA requires an annual report from the Sponsor or Sponsor-Investigator. The annual report is due within 60 days of the anniversary date that the IND went effect (i.e., the date that the FDA permitted the study to begin). Required content is listed in 21 CFR 312.33.

For more details, see: http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/index.html

Annual Reports to CDRH

For clinical trials being conducted under an IDE, FDA requires Sponsors to submit progress reports, at regular intervals, and at least yearly. Reports must be submitted to all reviewing IRBs and in the case of significant risk devices the sponsor must also submit the progress report to FDA (21 CFR 812.150).


10.3 Maintain Study Documentation

“Essential documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements”

ICH Guideline E6

There are many ways to organize essential documents, and there is no gold standard for how to do this. For example, the ICH GCP E6 guideline recommends that the documents be grouped according to the stage of the trial, i.e. documents relevant to the trial before it commences, documents relevant to the trial during the conduct of the trial, and those documents relevant to the trial after completion or termination of the trial. See http://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial for specific information.

The most important thing is that the documentation is organized and that all of the necessary documents are present. This chapter provides examples of a potential system to organize essential documents.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful
management of a trial. These documents are also the ones which are usually audited by the independent audits and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

Another way to organize the essential documents into study binders is by the content of the binder. For example, many sites have a “source document binder,” a “case report form binder,” a “financial binder,” and a “regulatory binder.”

### 10.3.1 Regulatory Binder

At UC Davis, the following list represents the required essential documents that must be filed in the regulatory binder. All essential documents must be available for audit/inspection by the sponsor and regulatory authorities.

The following Regulatory Binder Table of Content is adopted from Partners Healthcare.

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference to regulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>• Current protocol and all previously approved versions</td>
<td>ICH GCP E6 Sections 8.2.2 &amp; 8.3.2</td>
</tr>
<tr>
<td></td>
<td>• When applicable, a copy of the fully executed protocol signature page</td>
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<tr>
<td></td>
<td>for original protocol and all approved versions</td>
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<tr>
<td>CVs &amp; Licensure</td>
<td>• Signed and dated CVs for all study staff</td>
<td>ICH GCP E6 Sections 4.1.1, 8.2.10, 8.3.5</td>
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<tr>
<td></td>
<td>• Valid medical licenses/professional certifications for all study staff</td>
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<tr>
<td>Logs</td>
<td>• Pre-Screening Log: Captures subjects who have been pre-screened to</td>
<td>ICH GCP E6 Sections 8.3.20, 8.3.25</td>
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<td>determine initial eligibility for enrollment.</td>
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<td>• Enrollment Log: Captures all subjects who sign a consent form.</td>
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<td>• Delegation of Authority/Delegation of Responsibility Log*: Documents</td>
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<td></td>
<td>the study-related procedures delegated to staff. The PI should initial,</td>
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<td>sign and date this list, and update it as new staff or study procedures</td>
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<td>are added to the protocol.</td>
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<td>• Training Log**: documents training of all study staff on</td>
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<td>protocol-related procedures.</td>
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<td>• Adverse Event Tracking Log: Tracks and ensures timely reporting of all</td>
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<td>applicable adverse events to the IRB. This is often done electronicly.</td>
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<td>• Minor Deviation/Violation Tracking Log: Provides a record of all minor</td>
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<td>deviations from the approved protocol and facilitates reporting at</td>
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<td>continuing review. This is often done electronically.</td>
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<td>• Tissues and/or Blood Sample Log: Tracks tissue and/or blood samples</td>
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<td>collected during research.</td>
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<tr>
<td>Tab</td>
<td>Documents</td>
<td>Reference to regulations</td>
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<td>------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
</tbody>
</table>
| **IRB**                      | • Signed and dated submissions:  
  - Application  
  - Continuing Review(s)  
  - Amendments  
  - Adverse Events  
  - Violations/Deviations  
  - Close out Information  
  - Approval letters and/or notification of IRB decisions  
  - Investigator response(s) to IRB notification (if applicable).  
  - Approved recruitment materials.  
  - Approved educational materials/additional study information distributed to subjects (e.g., subject diary).  
  - Memo regarding FWA, IRB registration. Copy of IRB membership roster.  
  - Any additional correspondence relating to the study (e.g., e-mails). |
| **Consent/Assent Forms**     | • Current IRB-approved consent and/or assent form version(s) with the IRB approval stamp.                                                                                                                  | Code of Federal Regulations 45 CFR 46, 21 CFR 50, 21 CFR 56  
ICH GCP E6 Sections 8.2.3, 8.2.7, 8.3.2, 8.3.12 |
| **Financial Disclosure**     | • Signed and dated FDA Financial Disclosures for all clinical investigators listed on the form FDA 1572 (drug) or IRB application (device)  
• Internal Conflict of Interest documentation and management plan.                                                                                           | Code of Federal Regulations 21 CFR 54  
ICH GCP E6 Sections 8.2.11, 8.3.6 |
| **Laboratory Documents**     | • Current Lab Certification (e.g., CLIA, CAP)  
• Normal Lab/Reference Values                                                                                                                                                                              | ICH GCP E6 Sections 8.2.11, 8.3.6 |
| **Drug/Device Accountability** | • Drug/Device shipment and receipt records  
• Drug/Device Accountability Log  
• Most recent version of Investigator’s Brochure or Device Manual                                                                                                                                          | ICH GCP E6 Sections 8.2.14, 8.2.15 |
| **Data Collection**          | • Blank set of CRFs, data collection sheets, and IRB-approved study questionnaires  
• If data are being captured electronically a copy of the eCRF completion guidelines could be filed here.                                                                                         | 21CRF 312  
ICH GCP E6 Sections 8.3.14, 8.3.15, 4.9.3 |
<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference to regulations</th>
</tr>
</thead>
</table>
| DSMB (if applicable)         | • Copy of all Data and Safety Monitoring Board (DSMB) reports  
• Additional correspondences with DSMB (e.g., meeting minutes, information provided to the DSMB, emails) | Guidance for Clinical Trial Sponsors- Establishment and Operation of Clinical Trial Data Monitoring Committees, Section 4.4.3.2 |
| Correspondence               | • All relevant communications, other than site visits, to document any agreement or significant discussions regarding trial or administration, protocol violations, trial conduct, adverse event reporting, etc.  
• Includes communications to and from the Sponsor and/or the study team  
• Communications about a specific subject should be filed with source documents for that subject | ICH GCP E6 Sections 8.3.11                                                                 |
| Monitoring                   | • Monitoring Log: Documents any form of study oversight/monitoring. Both the monitor and clinical research coordinator should sign the log.  
• Pre-study Visit Report, Site Initiation Visit Reports, Monitoring Visit Reports, Close-Out visit reports or follow up letters if visit reports are not provided. | ICH GCP E6 Sections 8.2.19, 8.2.20, 8.3.10, 8.4.5                                        |
| Subject Identification Code List | • This is a document containing a unique identifier assigned by the investigator to each trial subject to protect the subject’s identity and used in lieu of the subject’s name when the investigator reports adverse events and/or other trial related data. | ICH GCP E6 Sections 1.58, 8.3.21, 8.4.3                                                   |
| Final Study Report           | • Final report by the Investigator to the IRB, and where applicable, to the regulatory authorities to document completion of the trial. | ICH GCP E6 Section 8.4.8                                                                   |

**Notes:**

*Delegation of Authority/Responsibilities Log*

It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). However, the Principal Investigator (PI) is ultimately responsible for the conduct of the study. When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. A Delegation of Authority log should be created documenting delegated tasks to delegated individuals. The same applies to staff/contract organizations not in direct employ of the investigator.
Example:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Task(s)</th>
<th>Start Date</th>
<th>End Date</th>
<th>Signature of the delegate</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Smith</td>
<td>CRC</td>
<td>Consent; Delivery of investigational drug from IDS to clinic</td>
<td>1/1/2011</td>
<td>1/31/2012</td>
<td></td>
</tr>
</tbody>
</table>

**Training Log**

The investigator has to assure that the staff has appropriate education, training, and experience to perform delegated tasks. The training log should also document that individuals have been trained on protocol-specific topics relevant to their job responsibilities. This training is documented in the training log.

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. Such a plan is outlined in the FDA Guidance on Investigator Responsibilities and may include routine meetings, procedures for reviewing staff performance, procedures for correction of protocol deviations, and procedures for ensuring quality control. [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf)

### 10.3.2 Source Document Binder

Per ICH GCP guideline E6 section 5.1 source data is identified as “all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.” This is the first recording of subject-related information. According to 21 CFR 312.62(b), and investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual. Source documents must be complete, accurate, and valid. The regulatory authorities consider source documents to be the basis for all trial data and the adjudication of the outcome of events.
The purpose of source documents/patient record binder is to:

- Document the existence of the participant and substantiate integrity of trial data collected.
- Include original documents related to the trial, medical treatment, history of participant, and participant’s condition while on-study or in follow-up.
- Provide an auditable link in the chain from the study database back to the original source (visit worksheet)
- Collect data for transfer to CRFs and then to the study database.
- Instruct study coordinators and other site personnel on what data to collect and information necessary to answer data queries.
- Can be electronic media, original documents or certified copies

The Source Binder is often organized according to the patient visit schedule and acts as a mechanism to plan for the next visit and ensures that all necessary data points are collected.

The following Source Document Binder Table of Content is adopted from Partners Healthcare.

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>• Written informed consent form to document that consent is:</td>
<td>OHRP Informed Consent Guidance Information</td>
</tr>
<tr>
<td></td>
<td>- Obtained in accordance with regulations, GCP, and protocol</td>
<td>ICH GCP E6 Section, 4.8</td>
</tr>
<tr>
<td></td>
<td>- Dated prior to participation of each subject in trial.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• HIPAA form</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Subject Bill of Rights</td>
<td></td>
</tr>
<tr>
<td>Records</td>
<td>• Includes but not limited to hospital, clinic and office records, progress notes, medical history, subject diaries, subject questionnaires unless accessible via EMR</td>
<td>ICH GCP E6 Section, 1.5.1, 1.5.2, 8.3.13</td>
</tr>
<tr>
<td>Inclusion/Exclusion Checklist</td>
<td>• Documentation of subject eligibility to be part of the study</td>
<td></td>
</tr>
<tr>
<td>Correspondence</td>
<td>• Notes to file, memos, correspondence, documentation of phone or email contact (all subject related)</td>
<td></td>
</tr>
<tr>
<td>Outside reports</td>
<td>• Laboratory, x-ray, CT, ECG, etc</td>
<td></td>
</tr>
<tr>
<td>Con Meds, AEs, SAEs</td>
<td>• Forms used to collect and document adverse events, concomitant medications, serious adverse events, etc.</td>
<td></td>
</tr>
</tbody>
</table>
When making a correction on a source document, draw a single line through the incorrect entry. Enter the correct data above or next to the incorrect entry. Date and initial the correction. Do not use white-out or eraser to correct an error and take care to ensure that the original entry is still legible. Blanks identified prior to the investigator’s review and sign-off on the source documents can simply be completed. Those identified after sign-off must be dated and initialed.

10.3.3 Case Report Form (CRF) Binder/ Electronic Case Report Form (eCRF)

According to ICH GCP EC 1.11, a case report form is a printed, optical, or electronic document designed to record all of the protocol required information to be reported on each trial subject. CRFs are designed by the sponsor or sponsor-investigator and maintained at the investigative site. Information documented on the CRF (or eCRF) must be supported by source documentation.

At a minimum the CRF should record:
- Inclusion/Exclusion criteria and assessment as to whether the subject met them
- Protocol-specific clinical laboratory testing (including EKGs, X-rays, eye exams, scans, etc) are documented by laboratory records
- All AEs, SAEs, concomitant therapies, and/or inter-current illnesses
- Assessment of severity of AEs, relationship to test article, and expectedness of the AE
- Report of all dropouts and the reasons
- Any other protocol-specific data points

One of the most essential tasks performed by the CRC is completing and/or ensuring the completion of the subject’s CRF. Most sponsors will provide instructions or a guide for CRF completion. Handwriting must be legible and should be completed in black ink. All data points must be addressed and for fields that cannot be completed, “not available,” “not done,” or “unknown” should be marked in accordance with the sponsor’s instructions.

The CRC will ensure that all required data are collected and entered on the CRF as soon as possible after, if not during, the visit. All CRFs should be checked for completeness and legibility. The CRFs should be reviewed and signed by the investigator prior to submission, if required. Only those physicians identified on the 1572 may sign CRFs.

10.3.4 Study Financial Binder

Per CTSC SOPs, UC Davis requires that a study financial binder be prepared and kept on file with all of the financial documentation for the trial. As of December 2010, the following documents are mandatory for each clinical trial, and should be kept in the Study Financial Binder (or in electronic format).
1. Coverage Analysis (consists of Qualifying Clinical Trial form and Billing Grid). The QCT form may be printed from the Bridge (CTSC SOP#4, #13)

2. For industry-sponsored studies:
   a. Internal Budget prepared in the Unified Budget Template (CTSC SOP #5)
   b. External Budget negotiated with the Sponsor (if applicable)
   c. Monthly accounts receivable and invoices to sponsor (CTSC SOP #7)

3. For Grant-or Department-sponsored studies:
   a. Budget estimate (CTSC SOP#6)

4. Feasibility assessment - optional (a document outlining the scientific value of the trial and assessing the feasibility of the performance)

5. Patient Financial Services (PFS) and Professional Billing Group (PBG) research account statements and any statements of billing corrections.

The following is an outline of the documents that should be kept in the financial binder:

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference</th>
</tr>
</thead>
</table>
| **Coverage Analysis**| • Coverage Analysis is a document that outlines what hospital procedures may be paid by Medicare/Insurance, and what procedures must be paid by the study budget. The coverage analysis consists of two parts: Qualifying Clinical Trial Form (QCT) and Billing Grid. QCT form can be printed from the BRIDGE | CTSC SOP #4 “Coverage Analysis”  
                         |                                                                                                                                                | CTSC SOP #13 “Create and manage research studies in EMR/Epic” |
| **Internal Budget**  | • Internal budgets for all clinical trials are based on the coverage analysis and on the contract (if applicable)                                | CTSC SOP #8 “Completing an internal industry-sponsored clinical trials budget” |
| **Feasibility Assessment (optional)** | • This document outlines the scientific importance of the study and balances it with the probability of accrual and financial solvency.             | CTSC SOP #5 “Budget approval for industry-initiated studies”  
                                                                                         |                                                                                     | CTSC SOP #6 “Development of Clinical Trials Budgets for grant proposals” |
| **Billing Statements** | • Monthly billing statements from the Reports2Web                                                                                               | ICH GCP E6 Sections 4.9.6, 5.6, 8.2.6                                       |
| **Signed Agreements with external budget** | • This is where agreements between involved parties, if any, are kept. These include Confidential Disclosure Agreements (CDA), Nondisclosure Agreements (NDA), Material Transfer Agreements (MTA), and Clinical Trial Agreements (CTA) | ICH GCP E6 Sections 4.9.6, 5.6, 8.2.6                                       |
### Monthly statements accounts receivables
- Accounting of completed procedures/visits by each patient on the study and rolled-in summary of all patients on the study
- Account of Receivables (money owed by a Sponsor based on the completed events)

**Reference:** CTSC SOP#7 “Financial Management of Clinical Trials”

### Invoices to Sponsors and granting agencies
- Invoices generated in Sponsor Format based on the Receivables

**Reference:** CTSC SOP#7 “Financial Management of Clinical Trials”

#### 10.3.5 IND/IDE Binder (if study conducted under an IND or IDE)

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference</th>
</tr>
</thead>
</table>
| **FDA (if study conducted under and IND or IDE)** | 1) Clinical Investigator [individual who conducts the study]  
- FDA 1572 [drug] (The form FDA 1572/ Investigator Agreement identifies the facilities where the research will take place, the reviewing/ approving IRB and sub-investigators participating in the study. The 1572 should be updated if changes are made during the course of the investigation)  
- Investigator Agreement [device]  
- Serious Adverse Event reports submitted to Sponsor  

2) Sponsor-Investigator [individual who initiates and conducts the study]  
- FDA 1572 [drug] (The form FDA 1572/ Investigator Agreement identifies the facilities where the research will take place, the reviewing/ approving IRB and sub-investigators participating in the study. The 1572 should be updated if changes are made during the course of the investigation)  
- Investigator Agreement [device]  
- Original application and all subsequent submissions to the FDA:  
  - IND Application [drug]  
  - IDE Application [device]  
  - Amendments to the Application  
  - Adverse Event Reports  
  - Annual Reports  
- Form 3674 (Certification of Registration to ClinicalTrials.gov) | 21 CRF 312 & 812  
ICH GCP E6 Section 4.1 |
10.4  Study Monitoring and Audits

10.4.1  Monitoring, Auditing and Inspecting

**Auditing** is a systematic and independent examination of trial-related activities and documents to evaluate whether the trial-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, Sponsor’s SOP, GCP, and other applicable regulatory requirements. Auditors collect evidence and compare against standards, review documents, assess deviations and non-compliance and recommend actions.

**Monitoring** is the act of overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirement(s). The purpose of monitoring is to ensure that:

- The rights and well-being of subjects are being protected
- The data are accurate, complete and verifiable
- The trial is being conducted in compliance with the protocol, SOPs, GCP, regulatory requirements

**Inspecting** is the act by a regulatory authorities of conducting an official review of all elements deemed by the authorities to be related to the clinical study. These may be located at the site of the study, at the sponsor’s and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authorities.

10.4.2  Monitoring by Industry Sponsors

Typically, in an industry-sponsored study, the pharmaceutical or medical device company will provide the monitor for the study. However, in the case of a study conducted by a Sponsor-Investigator, the Investigator takes on the responsibility of ensuring that the study is being monitored.

For industry-sponsored studies a monitoring plan will often be used to guide the frequency of monitoring visits to investigative sites whereas in an Investigator-initiated study the Investigator and/or study staff should develop a monitoring plan. The frequency of visits is affected by the complexity of the study and the rate of enrollment. Monitoring plans can be updated during the course of the study if, for example, enrollment is faster than expected.

When a monitor comes to a clinical site to conduct a monitoring visit, he/she will need access to all source documents, including the Electronic Medical Record (EMR). At UCDHS, **PhysicianConnect** is the system that provides monitors access to the selected electronic medical records in a read-only format. The monitors will only have access to the records of those patients who are enrolled in their study. To request EMR access for a study monitor use the IT Service Catalog. Once the request is entered into the system the researcher will be sent a link to complete their registration. Once the registration portion is completed Physician Connect access will be provided.

The monitor’s driver’s license should be visually verified by the department manager/ sponsor (or designees), who approved the access request. These individuals attest to UCDHS process that the federal issues ID has been verified and this user is truly who they say they are.
At the time of writing of this Guidebook, monitors are required to submit 4 last digits of SSN. This is done to eliminate duplicate EMR accounts.

For more information and directions on how this process works please see CT Newsletter V.19, March 2014 [http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/](http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/).

### 10.4.3 FDA Inspections

The Bioresearch Monitoring Unit of the FDA may conduct inspections of medical research and testing facilities in order to ensure studies avoid bias and follow proper testing procedures. The FDA inspector will review all case study data and may interview subjects and doctors. In all types of inspections, an FDA inspector checks the study for errors that affect the outcome.

At UC Davis, we may expect the following types of inspections:

- **Routine Inspection** may be conducted at random. It is sometimes triggered by abnormally high enrollment rate as well as large studies to promote a pivotal drug.
- **For Cause Inspections** FDA investigator has a reason to check out a research facility i.e., subject complaint, a highly publicized drug, unqualified investigators, large AE clustering.

Upon the receipt of notification of the FDA audit, notify the UCDHS Compliance Office at 916-734-8808. Specific procedures to follow when preparing for an inspection and on the day of the inspection are outlined in P&P 1506 [http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/consents_legal_documents_continued_/1506.shtml](http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/consents_legal_documents_continued_/1506.shtml).


### 10.4.4 Audits by the Office of Research Compliance and Integrity

Office of Research Compliance and Integrity (RCI) fulfills the auditor role for investigator-initiated studies. RCI conducts for-cause reviews (requested by the IRB), random/routine reviews and self-evaluation questionnaires. The purpose of routine/random reviews is to assist investigators with achieving high quality of regulatory compliance. The reviews are meant to be more educational rather than punitive in nature. RCI summarizes and reports the findings directly to the investigators. The investigators are required to provide the notification of findings or modifications to the IRB within 5 business days; then the reviewer monitors the IRB records for completion.

### 10.4.5 CTSC Clinical Trials Group – Monitoring and QA program

If there is a concern about the study preparedness for an audit, contact the Clinical Trials Resource Group to request an audit readiness assessment for both industry and investigator-initiated studies. This program helps ensure compliance with FDA, GCP, and IRB regulations, and UC Davis Health System SOPs and P&Ps as related to clinical research. The results of the pre-audit assessment will be provided for investigators and teams. For further information see [http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html).