Regulatory Binder Instructions

25 April 2016

Instructions

This Regulatory Binder is available to help study sites achieve and maintain regulatory compliance and adhere to high standards of practice in the conduct of research involving human subjects.

Each section outlines the regulatory documentation requirements, general guidance for organization and record keeping, and, when applicable, references to federal regulations and Good Clinical Practice guidelines.

General Guidance for using the Regulatory Binder

- Tailor the binder to meet the needs of your specific protocol:
    - This Regulatory Binder is a template. Include only sections pertinent to your protocol. Omit unused sections and add sections as needed. See "Applicable sections" below for more information. If unsure what sections to include/exclude, contact your institutional representative or the Harvard Catalyst Regulatory program.
    - Organize and order the sections to facilitate easy use and reference, e.g., file most used and referenced sections in the front of the binder.
    - Add additional tabs and/or documents to each section as needed.

- Keep the Regulatory Binder current and up-to-date.

- Identify an individual(s) responsible for maintaining the binder. Ensure that this person is on file with the IRB as an Additional Person to Contact to ensure that all IRB correspondence and documents are received/filed in a timely manner.

- Store binder in a safe and secure location, but accessible to study staff at all times.

- Participant-specific documentation and information, e.g., signed consent forms, test results, and completed case report forms, should be maintained separately in participant-specific binder/file.

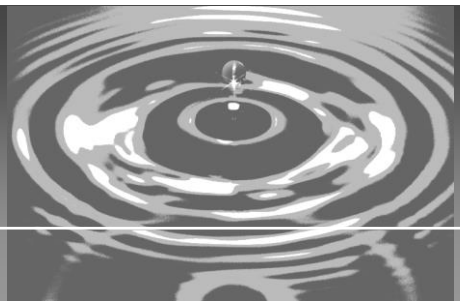
What sections apply to your research protocol

Depending on the nature of the research, some tabs may or may not be required. Use the below list to ensure that the applicable sections are maintained. For questions, contact your institution's or QA/QI program or the IRB.

1. **Human Research**
    a. Protocol
    b. IRB
    c. Consent Forms
    d. Data Collection

e. NIH
f. Sponsor
g. DSMB
h. Training
i. External IRB Documentation
j. Ethics Committee/Community Advisory Board Documentation
k. Scientific Review
l. Data Protection
m. Other

2. **FDA-regulated Human Research (e.g., IND, IDE)**. In addition to #1 above (Human Research), maintain the below tabs:
    a. Logs
    b. Investigator's Brochure/Device Manual/Package Insert
    c. Drug/Device
    d. FDA
3. **Good Clinical Practice.** In addition to #1 above (Human Research), maintain the below tabs:
    a. CVs
    b. Licensure
    c. Investigator's Brochure/Device Manual/Package Insert
    d. Laboratory Documents
    e. FDA



Protocol

Requirements

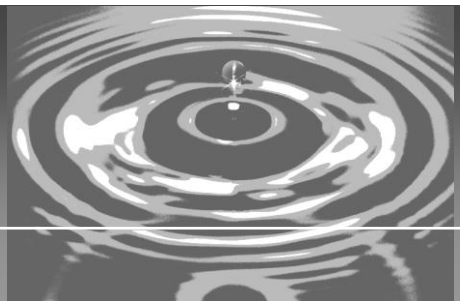
- ☐ Original Protocol and all amended versions
- ☐ All versions should contain a version date and/or number

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

GCP: 8.2.2; 8.3.2



CVs

Requirements

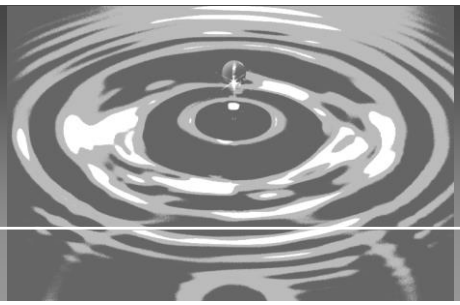
- ☐ CVs for all study staff

Guidance

- ✓ CVs should be signed, dated, and updated every 2 years to verify that the information is accurate and current.
- ✓ If CVs are filed collectively for the department, write a signed and dated note-to file indicating the location (include copy of note-to-file here).
- ✓ If CVs are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

GCP: 4.1.1; 8.2.10; 8.3.5



Licensure

Requirements

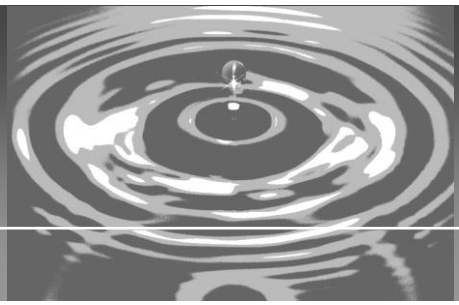
- ☐ Valid licenses/certification for all professional study staff (e.g., medical or nursing license)
- ☐ Current professional certification, as indicated

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ In MA, medical and nursing licenses must be renewed every 2 years. Licensure renewal dates coincide with birth dates. It is important to monitor licensure expiration dates so that those nearing expiration can be promptly replaced.
- ✓ Professional certification information should be included in individual CVs. The frequency with which certification must be renewed varies widely, depending on the requirements of the certifying body.

Federal Regulations/Good Clinical Practice

GCP: 4.1.1



Logs

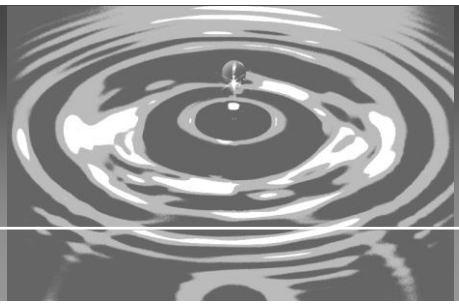
Check all that are included:

- ☐ Pre-Screening Log
- ☐ Enrollment Log
- ☐ Staff Signature Log
- ☐ Delegation of Responsibility Log
- ☐ Monitoring Log*
- ☐ Adverse Event Tracking Log
- ☐ Protocol Deviation/Exception Tracking Log
- ☐ Retained Tissue Log
- ☐ Training Log

***Required for FDA-regulated protocols**

Guidance

- ✓ Refer to the following links for available template logs:
  - ✓ Boston Children's Hospital http://www.childrenshospital.org/research-and-innovation/research/research-administration/equip/study-tools-and-templates
  - ✓ Harvard Longwood Medical Area Schools (Harvard T.H. Chan School of Public Health, Harvard Medical School, Harvard School of Dental Medicine) http://www.hsph.harvard.edu/ohra/qip/study-management-tools/
  - ✓ Partners HealthCare https://partnershealthcare-public.sharepoint.com/Pages/study-management-tools.aspx
- ✓ Update logs in a timely manner. To ensure accuracy, logs should be updated as soon as possible after a recordable event occurs, preferable on the same day.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).



IRB

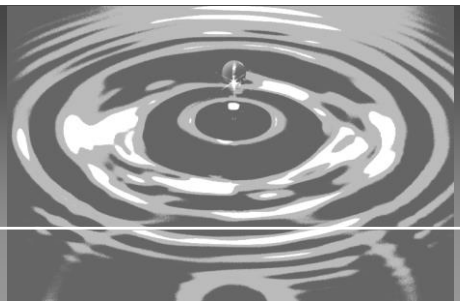
Requirements

- ☐ Copies of signed and dated submissions:
  - Initial Application for Human Research
  - Continuing Review(s)
  - Modifications/Amendments
  - Reportable New Information
  - Adverse Events
  - Protocol Violations
  - Unanticipated Problems
- ☐ Original Approval letters and/or notification of IRB decisions
- ☐ Copy of investigator response to IRB notification (if applicable)
- ☐ Approved/validated recruitment materials
- ☐ Approved/validated additional study information distributed to participants
- ☐ Any foreign language materials (if applicable)
- ☐ Print out of Institution's FWA Information from OHRP website
- ☐ IRB Membership Roster*
- ☐ Any additional correspondence related to the study (e.g. e-mails)

***Required for FDA-regulated protocols**

Guidance

- ✓ Submissions should be signed and dated as applicable. If your institution uses an electronic system for submitting and storing IRB documents, ensure that the electronic file contains all required documents and write a note-to-file indicating the location (include copy of note-to-file here).
- ✓ Approved/validated recruitment materials and additional study information distributed to participants should include version dates and/or numbers.
- ✓ File documents in reverse chronological order.
- ✓ Request a copy of missing documentation from your institutional representative



Consent Forms

Requirements

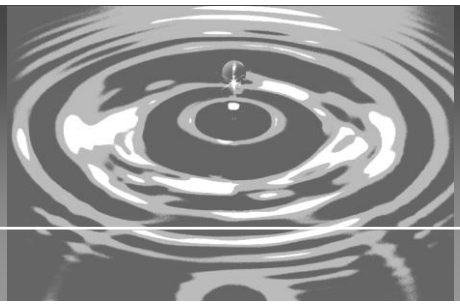
- ☐ Original copies of all IRB approved versions (evident by the IRB approval/validation stamp) with version dates or numbers
- ☐ Copies of foreign language consent materials, if applicable

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

HHS: 45 CFR 46
FDA: 21 CFR 50; 21 CFR 56
GCP: 8.2.3; 8.3.2; 8.3.12



Investigator's Brochure/Device Manual/Package Insert

Requirements

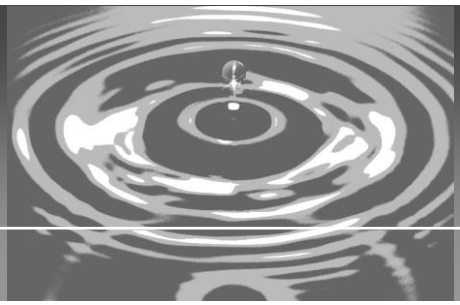
- ☐ Most recent version of investigator brochure or product information, e.g., package insert or sample label (for investigational drugs)
- ☐ Device Manual or Report of Prior Investigations, ROPI, (for investigational devices)

Guidance

- ✓ Send updated versions to the IRB.
- ✓ If the investigational product is marketed and its pharmacology is widely understood, a basic product information brochure or package insert may be an appropriate alternative.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.55
GCP: 8.2.1; 8.3.1



Laboratory Documents

Requirements

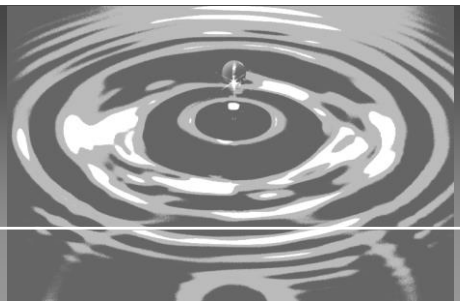
- ☐ Lab certification (e.g. CLIA, CAP) and updates
- ☐ Lab Director's CV
- ☐ Handling Instructions (if not specified in Investigator's Brochure, Device Manual, or Package Insert)
- ☐ Normal lab/reference values and updates

Guidance

- ✓ Keep updated documents to exhibit the competency of all lab facilities being utilized, and to support the reliability of test results.
- ✓ If lab documentation is filed separately, write a signed and dated note to file indicating the location (include note to file here).
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ Research labs typically do not have lab certifications, e.g., CLIA, CAP, and may not have "normal" lab values. If research labs are used, ensure that the lab director's CV and research lab references values are on file.

Federal Regulations/Good Clinical Practice

GCP: 8.2.11; 8.2.12; 8.2.14; 8.3.6; 8.3.7



Drug/Device

Requirements

- ☐ Drug/device shipment and receipt records
- ☐ Drug/device Accountability Log
- ☐ Drug/Device Dispensing Log

Guidance

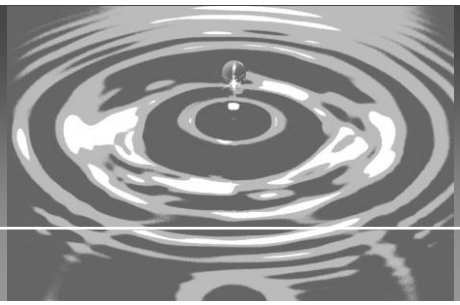
- ✓ The PI is responsible for the following with respect to investigational drugs/devices:
  - Maintain records of investigational product delivery to the study site. Include dates, quantities received, batch/serial numbers, and expiration dates.
  - Maintain an inventory of the investigational product at any site. Inventory control records should be updated, signed, and dated by the PI in a timely manner.
  - Record/track use of the investigational product by each participant. Documentation should verify that dosing/device use was in accordance with the approved protocol. Maintain an accountability log that records when the participant(s) received the drugs/device and the specific dosage/device the participant(s) received.
  - Return/dispose of unused investigational product as specified by the sponsor. Maintain documentation of return/disposal.
  - Store the investigational product. The storage area should be locked/secure with access limited to approved study staff only. Drugs/devices should not be stored with standard clinical inventory.

- ✓ If applicable, write a signed and dated note-to-file indicating where documentation is kept (e.g. Research Pharmacy). Include the note-to-file here.

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file behind tab).

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.57; 312.62; 812.140



Data Collection

Requirements

- ☐ Blank set of case report forms (CRFs), data collection sheets, and/or study questionnaires

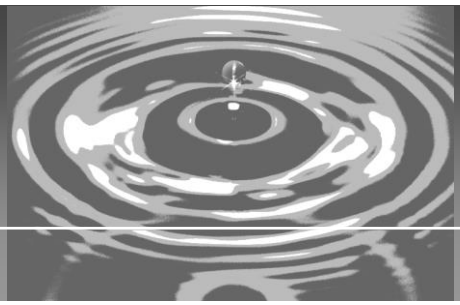
Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

- ✓ The difference between data collection sheets and case report forms is that data collection sheets typically act as source documentation. That is, during study visits, information is written directly onto the worksheets. An industry sponsor usually provides CRFs; all protocol-required information is transferred to CRFs from data collection sheets. Some studies do not use CRFs. All studies should use some type of data collection sheet.

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.53; 312.62
GCP: 8.3.14; 8.3.15; 4.9.3



FDA

Requirements

Clinical Investigator:

- ☐ Copy of all versions of the Form FDA 1572 (for investigational drugs)
- ☐ Copy of all versions of Investigator Agreement (for investigational devices)
- ☐ Copy of all Safety Reports submitted to the FDA

Financial Disclosure:

- ☐ Signed and dated copy of all Form FDA 3455 (Disclosure: Financial Interests and arrangements of Clinical Investigators)

Sponsor-Investigator:

- ☐ Copy of all Form FDA 1571 submitted to the FDA (for investigational drugs only), Initial IND/IDE or Application
- ☐ Amendments/Supplements to the application
- ☐ Safety Reports
- ☐ Annual Progress Reports
- ☐ Form 3674, certification of registration to ClinicalTrials.gov (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf)

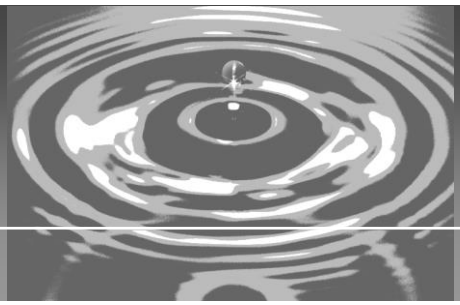
Guidance

- ✓ The Form FDA 1571 should be used as the cover sheet for all correspondence sent to the FDA.
- ✓ Instructions for completing The Form FDA 1572 can be found at: http://www.fda.gov/cder/forms/1571-1572-help.html
- ✓ Update the 1572 each time there is a change to any of the information originally provided. Notify the Sponsor of updates.

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 54; 312.30; 312.32; 312.33; 812.150(b)(1); 812.150(b)(5); 812.35; 812.43(c)
GCP: 4.11; 5.16.2; 5.17.1; 8.3.16; 8.3.17; 8.3.18; 8.3.19



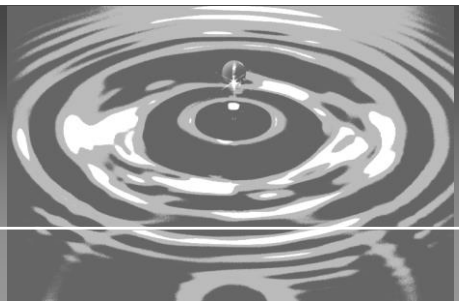
NIH

Requirements

- ☐ Copy of the NIH grant application and progress reports

Guidance

- ✓ Submit a copy of the most recent progress report as specified by your IRB.
- ✓ Any additional study correspondence (e.g. e-mails) with the NIH and Collaborators.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).



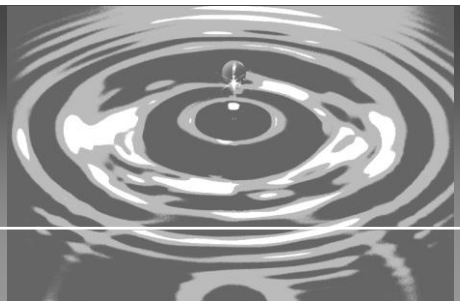
Sponsor

Requirements

- ☐ All correspondence to and from the sponsor (e.g. letters, meeting notes, and notes of telephone calls)
- ☐ Signed Agreements, including Financial Agreements
- ☐ Insurance Statement (when required)

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).



DSMB

Requirements

☐ Copy of all documentation for data safety monitoring plan as outlined in the IRB approved protocol

☐ Copy of all DSMB reports

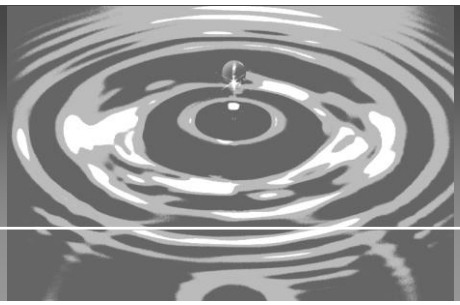
☐ Copy of all audit reports (internal and external)

Guidance

- ✓ If your study has a DSMB, submit a copy of the most recent DSMB report to the IRB at the time of continuing review
- ✓ Any additional correspondence (e.g. e-mails, letters, meeting minutes) with the DSMB and its members
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ More information can be found here: http://catalyst.harvard.edu/programs/regulatory/data-safety-monitoring.html

Federal Regulations/Good Clinical Practice

GCP: 8.3.10; 5.19.3



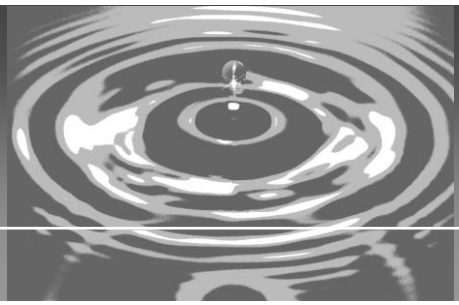
Training

Requirements

- ☐ Human research training
- ☐ Additional training certification of study staff, e.g., phlebotomy, vital signs, etc.)
- ☐ Sponsor training (e.g., EDC trainings, study initiation visits, use of device, GCP)
- ☐ Institution specific training

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).



External IRB Documentation

Instructions: Use this binder tab to maintain documentation from external, U.S.-based, institutions (e.g., Veteran's Affairs, additional site conducting concurrent IRB review).

Requirements

- External IRB documentation, including IRB submissions, IRB notifications, and significant correspondence between the IRB and investigator.
- Documentation of an institution's agreement to rely on another for IRB review, e.g., protocol-specific IRB Authorization Agreement, acknowledgement letter demonstrating cede review.

Documentation Tips

- If documentation is maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here)
- If helpful, maintain links to applicable local, regional, and/or national regulation/guidance on file
- To reduce the administrative burden of concurrent IRB review, consider an IRB Authorization Agreement whereby one institution relies on another for IRB review
  - Investigators must follow their institution's policies and procedures. Contact your institution for additional guidance.
  - Visit this link and use your eCommons or Harvard ID and pin, to request cede review between Harvard Catalyst affiliates.

EC/CAB Documentation

Instructions: Use this binder tab when conducting international research to maintain local host-country Ethics Committee (EC) and/or Community Advisory Board (CAB) documentation, including applicable local, regional, and/or national reviewing bodies in host country site(s).

Requirements

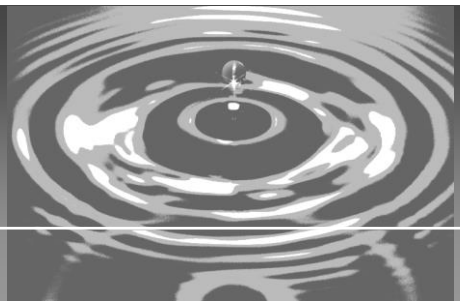
- EC or CAB documentation, including complete submissions, notifications, and significant correspondence.

Documentation Tips

- It is insufficient for a U.S.-based institution to approve non-exempt human research conducted abroad. Local ethical review is required.
- For Health and Human Service-funded protocols:
  - The review is recommended by the EC of an engaged organization or that of another organization in the same geographic area
  - The local EC should be registered with the Office for Human Research Protections and have a federal wide assurance (check online here)
- For non-Health and Human Service-funded protocols:
  - Review is recommended by a local EC or CAB
- When documentation is maintained locally in the host country and/or electronically, use a note-to-file to document their location and who is responsible
- If helpful, maintain links to applicable local, regional, and/or national regulation/guidance on file

Additional Resources

- Health Research Web
- National Institute of Allergy and Infectious Diseases ClinRegs
- Office for Human Research Administration's International Compilation of Health Research Standards:
- Additional information about Community Advisory Boards
  - Strauss, R. P.; Sengupta, S.; Quinn, S. C.; Goeppinger, J.; Spaulding, C.; Kegeles, S. M.; Millett, G. (2001). "The Role of Community Advisory Boards: Involving Communities in the Informed Consent Process". *American Journal of Public Health* **91** (12): 1938–1943.
  - Quinn, S. C. (2004). "Ethics in public health research: Protecting human subjects: The role of community advisory boards". *American journal of public health* **94** (6): 918–922.
  - National Institute of General Medical Sciences (September 2000). *Report of the First Community Consultation on the Responsible Collection and Use of Samples for Genetic Research*.



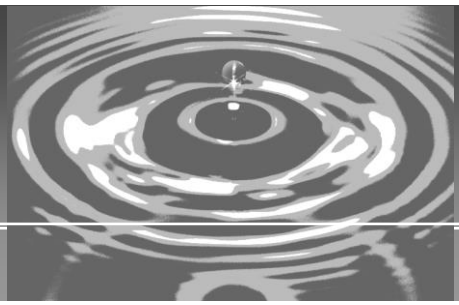
Scientific Review

Requirements

- ☐ Copy of materials submitted for scientific review
- ☐ Original, signed notification letters (when applicable)

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).



Data Protection

Recommended contents:

- ☐ Data Collection/Use Plan (if not in the IRB approved protocol)
- ☐ Data Storage Plan (if not in the IRB approved protocol)
- ☐ Data Transfer/Sharing Plan (if not in the IRB approved protocol)
- ☐ Data Management Plan (if not in the IRB approved protocol)
  - Protection and security of research data
  - Risk Management, which includes data breach and response
- ☐ Data Retention/Return and/or Destruction Plan
- ☐ Data Use Agreements or other agreements/contracts pertaining to data sharing with external collaborators, vendors, and/or 3rd party business associates (signed and dated by all parties)
- ☐ Documentation of Authorization to use protected health information for research purposes (in informed consent form or stand alone authorization)
- ☐ Waiver of HIPAA Authorization (if applicable)

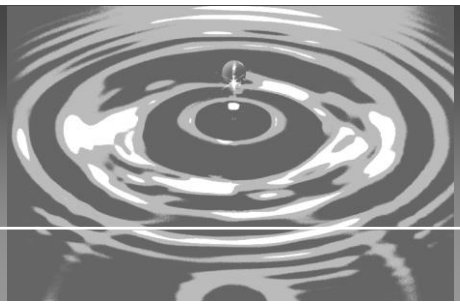
Federal and State Regulations

OCR:	HIPAA Privacy Rule and Security Rule (as amended):
HHS:	45 CFR 160, 162 and 164 (Subparts A and C)
FDA:	FDA: 21 CFR, Part 11
Massachusetts HITECH:	201 CMR 17.00: Standards for the Protection of Personal Information of Residents of the Commonwealth

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ Investigators must follow their institution's policies and procedures. Refer to the following links for institution-specific research data security policies, or contact your institution for additional guidance.

Other Resources:
Regulatory Atlas
Request the Harvard Catalyst Data Privacy and Security Matrix



Other