HARVARD LONGWOOD CAMPUS

HARVARD MEDICAL SCHOOL | HARVARD School of Dental Medicine | HARVARD SCHOOL OF PUBLIC HEALTH

Regulatory Binder: Instructions and Guidance

Instructions

A Regulatory Binder helps 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 (QIP Tips), 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:
  - These Regulatory Binder tabs serve as a template. Include only sections pertinent to your protocol. Omit unused sections and add sections as needed. If unsure what sections to include/exclude, contact the ORARC's QA/QI Program (QIP) at qip@hsph.harvard.edu for assistance.
  - 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 for easy access).
  - Add additional tabs and/or documents to each section as needed.
- ✓ Keep the Regulatory Binder current and up-to-date.
- ✓ Identify the individual(s) responsible for maintaining the binder. Ensure that this person is on file with the IRB as a Primary Contact or PI Proxy in ESTR to ensure that all IRB correspondence and documents are received and can be filed in a timely manner.
- ✓ Store the Regulatory Binder in a safe and secure location, but accessible to study staff at all times.
- ✓ Participant-specific documentation and information such as signed consent forms, test results, and completed case report forms should be maintained separately in participant-specific binder/file.

Documentation

QIP Tips

- ✓ Documentation should be completed on the day that the activity occurred.
- ✓ Completely fill out the study materials.
- ✓ Write enough information to document the activity or data, but do not go overboard.
  - Checklist/Progress Notes should reconstruct the visit, but be as brief and to-the-point as possible.
  - Avoid using names in the progress notes (e.g., refer to "participant" rather than Mr. Jones).
  - If you need to refer to another person, refer to them by relationship rather than by name (e.g., "participant's girlfriend," not "Betty Smith").
- ✓ Be sure to complete all required sections on the forms, not leaving questions blank.
  - Fill in all of the spaces on CRFs, unless instructed to skip. This ensures completeness of information and keeps quality assurance monitors from thinking you forgot to ask a question.
  - Do not leave blank lines between notes. If you do leave a blank line for some reason, draw a line through. This prevents the appearance that space is being left in case you need to add information later. Also fill in the last line of the note with a line to the end of the page.
- ✓ Documentation mistakes may occur. The important thing is to know what to do about errors so that they do not create questions about the integrity of the data.
  - If you make a mistake and don't know what to do, consult with someone. Trying to guess your way through a mistake may make it look like you are trying to cover something up. Almost all mistakes can be addressed, but it is important to deal with them immediately.
  - Never backdate. Backdating is putting any date other than today's date on a form or note (e.g., putting yesterday's date on a note because that is the day that the data collection occurred). This is a form of data falsification. If you were unable to complete documentation on the date that a research or treatment activity occurred, write a late note.
  - If you make a mistake while writing something down, put a single line through it, initial and date beside that line, and then put in the correct information. Never cover up your mistakes by: scribbling over the mistake, using White-Out or similar product, or re-writing the note.

Protocol

Requirements

- ☐ Current IRB–approved Research Protocol and all previously IRB-approved versions
- ☐ Each version should contain a version date and/or number

QIP Tips

- ✓ Documentation is electronically maintained:
  - ☐ In ESTR
  - ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 8.2.2; 8.3.2

CVs

Requirements

- ☐ CVs for all study staff
  - ○ PI
  - ○ IRB-approved study staff
  - ○ Other staff performing significant study-related duties

QIP Tips

- ✓ If a CV is unavailable, a biosketch, resume, or similar documentation verifying the qualifications and expertise of study staff to perform delegated study tasks is an acceptable alternative.
- ✓ CVs should be signed, dated, and updated every two (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 a copy of the note-to-file behind this tab).
- ✓ If CVs are maintained electronically, write a signed and dated note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 4.1.1; 8.2.10; 8.3.5

Training

Requirements

- ☐ Human subjects training certification for all personnel required to complete human subjects training
- ☐ Good Clinical Practice (GCP) training certification as required for NIH-funded Clinical Trials
- ☐ Responsible Conduct of Research certification as required for NIH training grants or National Science Foundation funded research
- ☐ Additional training certification for study staff, e.g., phlebotomy, vital signs, etc.
- ☐ Any study-specific training documentation for point-of-care testing (pregnancy testing) or study-specific instruments or scales

QIP Tips

- ✓ If documents are maintained electronically, write a signed and dated note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).
- ✓ Any PI, Co-Investigator or study staff working directly with participants and/or identifiable data must fulfill human subjects research training requirements every three (3) years.
- ✓ Any study staff covered by an IRB other than an HLC IRB must fulfill the human subjects training requirements of that IRB. The PI should maintain that certification with all other human subjects training certifications.
- ✓ The Collaborative Institutional Training Initiative (CITI) Program is Harvard University's online human research training curriculum and can be accessed at www.citiprogram.org.
- ✓ Anyone (regardless of role) working on a project determined to be "Not Human Subjects Research" is not required to complete training.

Federal Regulations/Good Clinical Practice

GCP: 8.2.10; 4.1.1

NIH Clinical Trials (GCP Training):
https://support.citiprogram.org/customer/en/portal/articles/2578484-nih-new-policy-on-gcp-training

NIH and NSF RCR Requirements:
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-019.html

https://www.gpo.gov/fdsys/pkg/FR-2009-08-20/pdf/E9-19930.pdf

IRB Documentation

Requirements

- ☐ Materials submitted to the IRB
  - ○ Initial Application or Human Research
  - ○ Continuing Review(s)
  - ○ Modification(s)
  - ○ Reportable New Information form(s)
- ☐ IRB Notification Letters
- ☐ Investigator response to IRB notification (if applicable)
- ☐ Approved/validated recruitment and consent materials
- ☐ Approved/validated additional study information distributed to participants
- ☐ Foreign language materials (if applicable)
- ☐ IRB Membership Roster* containing HLC school FWA information
- ☐ Additional (significant) correspondence related to the study (e.g., emails)

*** Required for FDA-regulated protocols**

QIP Tips

- ✓ Copies of IRB applications submitted prior to ESTR go-live date (HSPH: 11/15/12; HMS/HSDM: 3/15/13) should be signed and dated.
- ✓ Approved/validated recruitment materials and additional study information distributed to participants should include version dates and/or numbers.
- ✓ File documents in reverse chronological order (e.g., most recent on top).
- ✓ For missing documents submitted prior to ESTR, request a copy from QIP.
- ✓ Documentation is electronically maintained:
  - ☐ In ESTR
  - ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 8.2.7; 8.2.9; 8.3.2; 8.3.3; 8.3.4

Logs

Recommended

- ☐ IRB submission Log
- ☐ Enrollment Log
- ☐ Staff Signature and Delegation of Responsibility Log
- ☐ Participant ID Log
- ☐ Study Monitoring / Visit Log*
- ☐ Adverse Event Tracking Log
- ☐ Participant Payment Log
- ☐ Human Research Training Log
- ☐ Other: _____

*** Required for FDA-regulated protocols**

QIP Tips

- ✓ Refer to http://www.hsph.harvard.edu/orarc under the "QIP Study Management Tools" tab for template logs and recordkeeping tools.
- ✓ Update logs in a timely manner. To ensure accuracy, logs should be updated as soon as possible after a recordable event occurs, preferably on the same day.
- ✓ Master enrollment logs that contain identifiable information which can be linked to individual/participant codes should be stored in a secure location with restricted access to only appropriate study staff.
- ✓ If documents are maintained electronically, write a signed and dated note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Consent / Recruitment

Requirements

- ☐ Original blank (unsigned) copies of all IRB approved version of consent and recruitment materials (evident by the IRB approval/validation watermark), with version date and/or number
- ☐ Copies of foreign language consent and recruitment materials, if applicable

QIP Tips

- ✓ For available consent and assent templates, refer to "Consent Forms" on the "Forms/Instructions" page of the ORARC website for available templates (www.hsph.harvard.edu/orarc)
- ✓ QIP is available to assist with drafting or reviewing consent/assent materials to ensure that they are regulatory compliant and appropriately written in plain language. Contact qip@hsph.harvard.edu for more information.
- ✓ Original signed and dated (executed) consent forms should be maintained separately, e.g., with participant files.
- ✓ The informed consent process should be documented with a log or a note-to-file that confirms:
  - The consent/assent process took place
  - The participant had sufficient time to consider participation
  - The participant's questions were adequately answered
  - The participant voluntarily signed the consent or assent form
  - The participant was provided with a copy of the signed consent form
- ✓ Documentation is electronically maintained:
  - ☐ In ESTR
  - ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 8.2.2; 8.3.2
HHS: 45 CFR §46
FDA: 21 CFR §50; 21 CFR §56

Data Collection

Requirement

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

QIP Tips

✓ Documentation is electronically maintained:
- ☐ In ESTR
- ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

✓ 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 data collection sheets. An industry sponsor usually provides CRFs; all protocol-required information is transferred to CRFs from data collection sheets. All studies should use some type of data collection sheet.

✓ Completed data collection sheets should include the participant number and date, and may additionally require the signature of the assessor if data includes a clinical measurement.

Federal Regulations/Good Clinical Practice

GCP: 8.3.14; 8.3.15; 4.9.3

FDA: 21 CFR §312.53; 21 CFR §312.62

Data Protection

Recommended

- ☐ Data Collection/Use Plan (if not in IRB approved protocol)
- ☐ Data Storage Plan (if not in IRB approved protocol)
- ☐ Data Transfer/Sharing Plan (if not in IRB approved protocol)
- ☐ Data Management Plan (if not in IRB approved protocol)
  - ○ Protection and security of research data
  - ○ Risk Management, which includes data breach and response
- ☐ Data Retention/Return and/or Destruction Plan (if not in IRB approved protocol)
- ☐ Data Use Agreement(s) or other agreement(s)/contract(s) 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)
- ☐ Signed Harvard Data Security worksheet/documentation of approval from HUIT (when appropriate)

QIP Tips

- ✓ If documents are maintained electronically, write a signed and dated note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).
- ✓ Investigators must follow the data protection policies and procedures of their home institution. Contact your institution for additional guidance.

Federal and State Regulations/Institutional Policies and Other Resources

HHS: 45 CFR §160; 45 CFR §162, 45 CFR §164 (Subparts A and C)

FDA: 21 CFR §11

OCR (Office of Civil Rights): HIPAA Privacy Rule and Security Rule (as amended): https://www.hhs.gov/hipaa/index.html

Massachusetts HITECH:
Standards for the Protection of Personal Information of Residents of the Commonwealth: http://www.mass.gov/ocabr/docs/idtheft/201cmr1700reg.pdf

Other Resources:
Harvard Research Data Security Policy: (http://vpr.harvard.edu/pages/harvard-research-data-security-policy)

Harvard Catalyst Regulatory Foundations, Ethics and Law Program - Data Protection: http://catalyst.harvard.edu/programs/regulatory/data-protection.html

Sponsor

Requirements

- ☐ Copy of all versions of the Sponsor's Protocol (with version dates)
- ☐ 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)

QIP Tips

- ✓ Documentation is electronically maintained:
  - ☐ In ESTR
  - ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 8.3.11

NIH

Requirements

- ☐ NIH grant application and progress report(s)
- ☐ Additional study correspondence (e.g., emails with the NIH and collaborators)

QIP Tips

- ✓ Submit the most recent progress report to the IRB at the time of continuing review
- ✓ Documentation is electronically maintained:
  - ☐ In ESTR
  - ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 8.3.11

FDA

Requirement

Sponsor-Investigator:

- ☐ All Form FDA 1571 submitted to the FDA, initial IND or Application
- ☐ Amendments to the Application
- ☐ Adverse Events Reports
- ☐ Annual Progress Reports
- ☐ Form 3674, certification of registration to ClinicalTrials.gov

Clinical Investigator:

- ☐ All versions of Form FDA 1572 (for investigational drugs)
- ☐ All versions of Investigator Agreement (for investigational devices)
- ☐ All Safety Reports submitted to the FDA
- ☐ Annual Progress Reports
- ☐ Form 3674, certification of registration to ClinicalTrials.gov
- ☐ Copy of local ethical approval notices (e.g., external IRB, Ethical Review Board, or Community Advisory Board (CAB))

Financial Disclosure:

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

QIP Tips

- ✓ Form FDA 1571 should be used as the cover sheet for all correspondence sent to the FDA.
- ✓ Form FDA 1572 should be updated each time there is a change to any of the information originally provided. Notify the sponsor of any updates.
- ✓ FDA Forms and instructions can be accessed at https://www.fda.gov/aboutfda/reportsmanualsforms/forms/default.htm

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

Federal Regulations/Good Clinical Practice

FDA: 21 CFR §54; 21 CFR §312.30; 21 CFR §312.32; 21 CFR §312.33; 21 CFR §812.150(b)(1); 21 CFR §812.150(b)(5); 21 CFR §812.35; 21 CFR §812.43(c)

GCP: 4.11; 5.16.2; 5.17.1; 8.3.16; 8.3.17; 8.3.18; 8.3.19

External / Local Ethical Review

Requirement

☐ Copy of local ethical approval notices (e.g., external IRB, Ethical Review Board, or Community Advisory Board (CAB))

QIP Tips

✓ It is insufficient for a U.S.-based institution to approve non-exempt human research conducted abroad if applicable law requires local review.
- ○ Local IRB/ethical review documents and correspondence should be on file and accessible to the PI, even if they are not maintained within a regulatory binder.

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

✓ For HHS-funded protocols:
- ○ Review should be done by the IRB of the collaborating institution or that of another institution in the same geographical area.
- ○ The local IRB must be registered with OHRP and have an FWA (check online at http://ohrp.cit.nih.gov/search/).

✓ For non HHS-funded protocols:
- ○ Review should be done by a local IRB/ethical review board or
- ○ Community Advisory Board

DSMB

Requirement

- ☐ Copy of DSMB Charter
- ☐ Copy of all DSMB reports
- ☐ Additional correspondence (e.g., emails, letters, meeting minutes) with the DSMB and its members

QIP Tips

- ✓ Documentation is electronically maintained:
  - ☐ In ESTR
  - ☐ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).
- ✓ Submit the most recent DSMB report to the IRB at the time of continuing review.

Federal Regulations/Good Clinical Practice

GCP: 5.19.3; 8.3.10

Licensure

Requirements

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

QIP Tips

✓ Licensure required only for study staff utilizing their professional license for study purposes (i.e., if the PI is and MD, there is no need to include license unless s/he is conducting medical testing, procedures, or exams).

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

✓ In Massachusetts, medical and nursing licenses must be renewed every two (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 updated/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

Laboratory Documents

Requirements

- ☐ Lab certification (e.g., CLIA, CAP) and updates for clinical labs that are used for diagnosis, treatment, prevention, and/or assessment
- ☐ Lab Director's current CV for research labs that will not be reporting any participant-specific results for diagnosis, treatment, prevention, and/or assessment
- ☐ Handling instructions (if not specified in the Investigator's Brochure, Device Manual, or Package Insert)
- ☐ Normal lab/reference values and updates for clinical labs

QIP Tips

- ✓ Keep updated documents to verify the competency of all lab facilities being utilized, and to support the reliability of test results.
- ✓ If documentation is maintained electronically, or a hard copy is filed in a location other than the regulatory binder, write a signed and dated note-to-file indicating the location and who maintains documentation (include a copy of the note-to-file behind this tab).
- ✓ Research labs typically do not have lab certification (e.g., CLIA, CAP) and may not have "normal lab values. If a research lab is used, ensure that the Lab Director's CV and research lab reference values are on file.

Federal Regulations/Good Clinical Practice

GCP: 8.2.11; 8.2.12; 8.22.14; 8.3.6; 8.3.7

Drug / Device

Requirements

- ☐ Drug/Device shipment, receipt, return, and destruction records
- ☐ Drug/Device Accountability Log
- ☐ Drug/Device dispensing Log

QIP Tips

- ✓ If documentation is maintained electronically, or a hard copy is filed in a location other than the regulatory binder, write a signed and dated note-to-file indicating the location and who maintains documentation (e.g., Research Pharmacy) (include a copy of the note-to-file behind this tab).

- ✓ The PI is responsible for following with respect to investigational drugs/devices:
  - Maintaining records for investigational product delivery to the study site, including dates, quantities received, batch/serial numbers, and expiration dates.
  - Maintaining an inventory of the investigational product at any site. Inventory control records should be updated, signed, and dates by the PI in a timely manner.
  - Recording/tracking 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 participants received the drug/device and the specific dosage/device that each received.
  - Storing 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.
  - Returning/disposing of unused investigational product as specified by the sponsor. Maintain documentation of return/disposal.

Federal Regulations/Good Clinical Practice

FDA: 21 CFR §312.57; 21 CFR §312.62; 21 CFR §812.140

Investigator Brochure / Device Manual / Package Insert

Requirements

- ☐ Most recent version of the 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)

QIP Tips

- ✓ Send updated versions to the IRB at the time of Continuing Review, unless the update requires a change to the protocol.
- ✓ If the investigational product is marketed and its pharmacology is widely understood, a basic product information brochure or package insert is appropriate.
- ✓ If documents are maintained electronically outside of ESTR, write a note-to-file indicating the location and who maintains them (include a copy of the note-to-file behind this tab).

Federal Regulations/Good Clinical Practice

GCP: 8.2.1; 8.3.1

FDA: 21 CFR §312.55