CRRO Clinical Research Resources Office

REGULATORY BINDER TABS FOR BMC/BU MEDICAL CAMPUS CLINICAL RESEARCH STUDIES

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* Denotes documentation that is required only for certain types of studies.

REGULATORY BINDER TABS

Tab 1: IRB Review Documentation

Tab 2: Study Protocol and Supporting Documents

Tab 3: Informed Consent Forms and Supporting Documents

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

Tab 5: Study Participants

Tab 6: Adverse Event (AE) Monitoring and Reporting

Tab 7: Monitoring/Auditing/Site Initiation

Tab 8: Correspondence and Meeting Minutes

Tab 9: Study-related SOPs/MOPs

Tab 10: Study Staff

Tab 11: Laboratory

Tab 12: Drug/Device Accountability

Tab 13: FDA 1572 Forms and Financial Disclosure Forms (FDFs)

Tab 14: IND Maintenance for Investigator IND Holders (Investigators who are also Sponsors)

Tab 15: IDE Maintenance for Investigator IDE Holders (Investigators who are also Sponsors)

Tab 16: Single IRB – Relying Institution Site

Tab 17: Single IRB – Lead Study Team Site

Tab 18: Miscellaneous (Agreements, CoC, Equipment calibration, etc.)

Tab 19: Notes-to-File/Deviation Reports/CAPAs

Tab 20:

Tab 1: IRB Review Documentation

IRB membership: The IRB roster documents that the IRB's composition is in compliance with Department of Health and Human Services (DHHS) and FDA regulations and Good Clinical Practice (GCP) guidelines, as applicable.

Federalwide assurance (FWA): Federalwide assurance (FWA) from DHHS through the Office for Human Research Protections (OHRP) is documentation that the institution commits to complying with requirements set forth in Protection of Human Subjects regulations at 45 CFR part 46.

An institution must have an FWA in order to receive HHS support for research involving human subjects. Each FWA must designate at least one IRB registered with OHRP. Before obtaining an FWA, an institution must either register its own IRB (an "internal" IRB) or designate an already registered IRB operated by another organization.

IRB documentation of approvals: Documents initial and continuing approval of the research and applicable changes to the research (including initial application, amendments, progress reports, reportable events, exceptions, final close out report, etc.).

☐ Check here if IRB review documentation is maintained in an electronic IRB submission system that is accessible by study staff.

If your study has multiple sites, and you are using a single IRB as the IRB of record (i.e. a reviewing IRB that is different from the local institution), use Tabs 16 and 17:

- Tab 16: Single IRB – Relying Institution Site
- Tab 17: Single IRB – Lead Study Team Site

Optional Customizable Documentation Templates for this section	
IRB Submission Tracking Log Exception Submission Log	Communications Log

References	
• 21 CFR 312.66 Assurance of IRB review • 21 CFR 56.107 IRB membership • 21 CFR 56.109 IRB review of research • 45 CFR 46.103 IRB assurance • 45 CFR 46.107 IRB membership • 45 CFR 46.109 IRB review of research • 45 CFR 46.114(b)(1) Cooperative research • ICH GCP 3.0 IRB • ICH GCP 4.4 Communication with IRB • ICH GCP 4.5.2 Compliance with Protocol • ICH GCP 4.10 Progress Reports • ICH GCP 5.11 Confirmation of Review by IRB	• ICH GCP 8.3.2 Essential documents, Revisions to protocol & consents • ICH GCP 8.3.3 Essential documents, Approval of IRB • FDA Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review After Clinical Investigation Approval, February 2012 • BU/BMC HRPP Policies & Procedures – 11.2 • NIH Single IRB Policy for Multi-site Research: http://www.bumc.bu.edu/ohra/required-training/good-clinical-practice-gcp-certification/

Tab 2: Study Protocol and Supporting Documents

Study Protocol & Protocol amendments: Protocol and protocol-related documents.

- All approved versions of study protocol ☐ Outdated versions are stored: _____
- Protocol Signature page: signatories sign their approval/promise to comply with the protocol.
- Copy of NIH Grant Application ☐ Filed elsewhere: _____
- Participant recruitment/educational materials may be filed under Tab #3: Informed Consent Forms & Supporting Documents.
- Data Safety Monitoring Plan (DSMP): Your DSMP may be part of your study protocol; it might also be a separate document. Keep all versions of the DSMP.
    - If you have a Data Safety Monitoring Board (DSMB) or other independent outside monitoring group you should have a "Charter" document that describes the processes to be followed by the group. ☐ Filed elsewhere: _____
- Some NIH Institutes/Centers require a Study Accrual and Retention Plan (SARP) for new grants. This plan can be saved here. ☐ Filed elsewhere: _____

Investigator Drug Brochure (IB) (or Package Insert if the drug is already marketed):
The IB provides information on everything that is known about the study drug based on previous laboratory, animal, and human. The package insert can be used if the drug is already FDA-approved.

These documents (IB and/or package insert) should be readily available to all study staff; it is the site's reference regarding action of the drug and potential side effects.

- All approved versions of the IB or updated package inserts.
  ☐ Current/Outdated versions are stored: _____
- Signed receipt form for IB and updates. This is industry best practice, not a regulatory requirement. It is one way the sponsor can document that new IBs were received by investigators. The sponsor should have copies of all sites' receipt forms on file. Individual investigators may keep their copy as documentation of receipt of the IB.

References	
• ICH GCP 4.5 Investigator compliance with protocol • ICH GCP 5.1.2.2 Updating the Investigator's brochure • ICH GCP 7.0 Investigator's brochure • NIH Policy for Data and Safety Monitoring, June 10, 1998	• Further Guidance on a Data and Safety Monitoring for Phase 1 and Phase 2 Trials, June 5, 2000 • FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March, 2006

Tab 3: Informed Consent Forms and Supporting Documents

Study consent forms: Documents which consent form versions were approved and valid at various points during the study.

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

  ☐ Older versions filed elsewhere: _____

  (If you save hardcopy versions of outdated consent forms, make it clear on the file that these versions are out of date, and should not be used to consent current research participants.)

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

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

  ☐ Older versions filed elsewhere: _____

References	
• 21 CFR part 50 Protection of Human Subjects • 21 CFR part 56 IRBs • 45 CFR 46.116 General requirements for informed consent • 45 CFR part 46 subpart D Additional Protections for Children • FDA Informed Consent Information Sheet – Guidance for IRBs, Clinical Investigators, and Sponsors (Draft), July 2014 • FDA Information Sheet Guidance: A Guide to Informed Consent • FDA Information Sheet Guidance: Recruiting Study Subjects • FDA Information Sheet Guidance: Payment to Research Subjects	• FDA Guidance: Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers, December 2016 • ICH GCP 3.0 IRBs • ICH GCP 4.5 Compliance with protocol • ICH GCP 4.8 Informed Consent of Trial Subjects • ICH GCP 4.9 Records and Reports • ICH GCP 4.10 Progress reports • ICH GCP 5.11 Review by IRB • ICH GCP 8.3.2 Essential documents, Info given to trial participants • ICH GCP 8.3.3 Essential documents, IRB approval of ICFs • OHRP Policy Guidance: Informed Consent

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

All past and present working versions of CRFs and CRF documentation completion guidelines

☐ Contained in this binder

☐ Filed elsewhere or stored electronically: _____

☐ N/A

All past and present working versions of source data collection tools: Typically, you would develop and use a data collection tool to collect source data pertaining to your study. The data may then be transcribed onto the sponsor-provided or internally-developed CRFs (which may be in electronic or hardcopy form).

For example, you may develop a source data collection tool to collect vital signs, weight, height, pregnancy testing results, etc. performed at a screening visit. You should file completed forms in participant-specific files (not in the Regulatory Binder), but it is useful to keep all versions of your data collection tools so that it is clear what data was collected at what timepoints. These tools should be updated as needed to reflect changes to the protocol. Data collection tools include questionnaires, surveys, subject diaries, and tools you use to record data from the medical record.

Your data collection tools should be identified by a version number and date.

☐ Contained in this binder

☐ Filed elsewhere or stored electronically: _____

☐ N/A

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

Tab 5: Study Participants

Information on individual study participants is typically maintained in participant specific files or charts (not in the regulatory documentation or "binder"). Participant-specific files should include signed consent forms, participant-specific source documents, and completed CRFs, etc.

- Ensure that participants are consented prior to any research procedures being performed (this includes collection/recording of identifiable health data from telephone or in-person screening).
- For those participants who were screened but did not enroll, maintain information on reasons why. This information can be useful in assessing effectiveness of recruitment strategies.

For NIH-supported research, information on race/ethnicity/sex should be collected to document compliance to NIH policy on inclusion of women and minorities in clinical research.

Screening/Enrollment Log: ☐ Filed elsewhere: _____

A list of individuals screened and their eligibility and enrollment status.

Withdrawal/Termination Log: ☐ Filed elsewhere: _____

A list of participants who withdrew or were terminated and reasons why.

Participant Identification Log: ☐ Filed elsewhere: _____

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

This list should be kept in a secure location with limited access.

Optional Customizable Documentation Templates for this section	
Screening/Enrollment Log Study Withdrawal/Termination Log	Participant Identification Log

References	
• ICH GCP 8.3.20 Essential documents, subject screening log • ICH GCP 8.3.21 Essential documents, subject identification code list • FDA Guidance for Sponsors, Clinical Investigators, and IRBs – Data Retention When Subjects Withdraw from FDA-regulated Clinical Trials, Oct 2008 • OHRP Guidance on Withdrawal of Subjects from Research: Data Retention and other Related Issues, Sept. 21, 2010	• FDA Information Sheet Guidance for IRBs and Clinical Investigators: Recruiting Study Subjects • FDA Information Sheet Guidance for IRBs and Clinical Investigators: Screening tests prior to enrollment • NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001

Tab 6: Adverse Event (AE) Monitoring and Reporting

The BMC/BU Medical Campus IRB requires reporting of Unanticipated Problems (UPs) associated with fatal or life-threatening events within 7 days of the site learning of the event. Adverse Events (AEs) that are not UPs should be reported to the IRB at the time of continuing review.

Note that for studies where the BMC/BU Medical Campus IRB has ceded review to another IRB, you must follow the reporting requirements of the Reviewing IRB in addition to reporting the UP to the BMC/BU Medical Campus IRB.

Internal AE/UP Reporting Tracking Log

- Track that you have reported the AE/UP occurring at your site to all required entities as applicable per your protocol and DSMP.
- AE reports and AE source documentation should be filed in participant-specific files.

Safety Report Tracking Log

Tracks/organizes receipt of IND Safety Reports or IDE Unanticipated Device Effects Reports (or other reports if not under an IND or IDE) that occur at external sites.

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

Communications Log

Correspondence related to reporting of AEs and SAEs, deviations and other reportable events to the IRB, sponsor, etc.

Optional Customizable Documentation Templates for this section	
Internal AE Report Tracking Log	Communications Log
Safety Report Tracking Log	Protocol Deviation Log

References	
• Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies, FDA, December, 2012 • OHRP Guidance on Reviewing and Reporting UPs Involving Risks to Subjects or Others and AEs, Jan. 15, 2007 • 21 CFR 312.32 IND Safety reports • 21 CFR 812.50 (b) (1) Unanticipated device effects reports	• ICH GCP 4.11 *Safety reporting* • ICH GCP 5.17 *Adverse Drug Reaction Reports* • ICH GCP 8.3.16, 8.3.17, 8.3.18 *Essential documents, AE reporting* • FDA Guidance for Clinical Investigators, Sponsors, and IRBs: AE Reporting to IRBs…., Jan. 2009 • NIH Guidance on Reporting Adverse Events to IRBs for NIH-Supported Multicenter Trials, June 11, 1999

Tab 7: Monitoring/Auditing/Site Initiation

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

Monitoring reports and site response (as necessary) ☐ Filed elsewhere: _____

- **Pre-trial monitoring report**: Documents that the site is suitable for the trial.
- **Study site Initiation Report**: Documents that the protocol and procedures were reviewed with site by sponsor study monitor and the site was trained on the protocol. File the agenda, attendance, minutes for the meeting. File training materials in the Study Staff tab (10).
- **Interim Monitoring Reports:** Documents site visits and findings of the sponsor study monitor and site response to findings (corrective actions, as necessary).
- **Close-out report:** Documents that the study is complete at this site and that all issues/queries have been resolved. The investigator is reminded at this visit of his/her responsibilities to maintain study documentation for the required time period per regulations and/or sponsor requirements.

Optional Customizable Documentation Templates for this section	
Site Visit Log	Communications Log

References	
• 21 CFR 312.54 (d) Selecting monitors • ICH GCP 5.18 Monitoring • ICH GCP 5.19 Auditing • ICH GCP 8.3.10 Essential documents, monitor visit reports • FDA Guidance for Industry: Oversight of Clinical Investigations – A Risk-based Approach to Monitoring, August, 2013	• FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects, October, 2009 • CRRO Tools for Self-assessments (CRRO website: www.bumc.bu.edu/crro)

Tab 8: Correspondence and Meeting Minutes

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

Correspondence with Sponsor/CRO/Funding Source: ☐ Filed elsewhere: _____

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

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

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

IRB Correspondence: ☐ Filed elsewhere: _____

Meeting/Conference call minutes: ☐ Filed elsewhere: _____

Misc. Correspondence: ☐ Filed elsewhere: _____

Optional Customizable Documentation Templates for this section	
Phone Call Summary Report	Communications Log

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

Tab 9: Study-related SOPs/MOPs

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

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

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

Optional Customizable Documentation Templates for this section
SOP Table of Contents

References
• ICH GCP 1.55 Standard Operating Procedures • ICH GCP 4.7 Randomization Procedures and Unblinding • ICH GCP 8.2.17 Essential documents, decoding for blinded trials

Tab 10: Study Staff

This section contains documentation regarding appropriate delegation of study-related tasks by the PI, and the adequate qualifications and training of those staff regarding the tasks to which they have been assigned. Documentation in this section helps validate that the PI adhered to his/her responsibilities to personally conduct or supervise the conduct of the research and to protect the rights, safety, and welfare of study participants.

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

- It is industry standard to update these when there are changes in affiliation, education, responsibilities, etc. To ensure that CVs are valid and to enable assessment of currency, you may ask each staff member to sign and date the CV they provide.
- Clinical license information should be filed if proof of medical licensure is needed *for the individual's role in the study*. Keep copy of current license in chronological order with copies of expired licenses for the individual's time on the study.
- CVs/licenses may be filed centrally, because the same documents may be collected for multiple studies within one study group. If so, write a note-to-file for this binder section stating where CVs/licenses are maintained.

  ☐ CVs and/or clinical licenses maintained elsewhere: _____

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

Training log: Document training (and updates as necessary) for site staff.

Examples include: Human Subjects Protection training, Good Clinical Practice (GCP) training, training on conduct of the consent discussion, training on the protocol, Safety and Infection Control training, Shipping Biologicals training, phlebotomy training, training on point-of-care testing (for example urine pregnancy tests), investigator meetings, site initiation visit training. Anytime new responsibilities are delegated to staff the training to fulfill those responsibilities should be provided and documented.

Optional Customizable Documentation Templates for this section	
Signature/Task Delegation Log	Staff Training Log for Groups
Staff Training Log	Staff License/Certification Log

References	
• 21 CFR 312.23 (a) (6) (iii) (b) Qualifications of investigators under an IND • 21 CFR 312.23(a)(6)(iii)(b) IND Content and Format: Investigator information [1572] • 21 CFR 312.53 (c) (1) Investigator statement/1572 form • 21 CFR 312.60 General responsibilities of investigators • FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects, October, 2009	• ICH GCP 4.1 Investigator's qualifications and agreements • ICH GCP 4.2.2 Adequate staff and facilities • ICH GCP 4.3 Medical Care of trial subjects • ICH GCP 4.5 Compliance with protocol • ICH GCP 5.6 Investigator selection • ICH GCP 8.2.10 Essential documents, CVs • ICH GCP 8.3.5 Essential documents, CVs for new investigators

Tab 11: Laboratory

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

Tests performed by the BMC Laboratory, as well as point of care tests being performed at specific BMC locations, fall under the Lab's CLIA certificate and CAP accreditation.

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

- CLIA Certification of Compliance, *or*
- CLIA Certification of Accreditation AND certificate from a lab accreditation organization
  (i.e. College of American Pathologists – CAP or Joint Commission on Accreditation of Healthcare Organizations – JCAHO).
- Other CLIA certificates may be applicable to your study: Certificate of Waiver; Certificate for Provider Performed Microscopy procedures; Certificate of Registration.

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

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

Point of Care testing: All point of care testing must be approved prior to start of testing by the Point of Care section within the BMC Department of Pathology and Laboratory Medicine. The Point of Care section has oversight of point of care testing being performed at BMC and specific licensed BMC satellite locations. *(Information is accurate as of 4/15/19.)*

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

Optional Customizable Documentation Templates for this section
Stored Biosample Log

References	
• ICH GCP 4.2.2 Adequate staff and facilities • ICH GCP 8.2.11 Essential documents, normal values/ranges • ICH GCP 8.2.12 Essential documents, lab certification • OHRP Policy Guidance, Repositories, Tissue Storage • CLIA law: CFR Title 42, chapter IV, Part 42: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/CLIA	• CLIA: How to Obtain a CLIA Certificate: http://www.cms.hhs.gov/CLIA/downloads/HowObtainCLIACertificate.pdf • For BMC lab (& CLIA certification) info see: https://internal.bmc.org/departments/pathology-and-laboratory-medicine/laboratory-medicine • BMC Point-of-Care Testing (POCT): https://internal.bmc.org/departments/pathology-and-laboratory-medicine/laboratory-medicine/point-care-testing-poct

Tab 12: Drug/Device Accountability

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

- Correspondence/communications with supplier
- Correspondence/communication/agreements with pharmacy (i.e. written authorization is required if investigational drugs are stored outside of IPS)
- Copy of test article sample label: documents compliance with applicable labeling regulations
- Study agent order forms ☐ Filed elsewhere: _____
- Shipping receipts/records ☐ Filed elsewhere: _____
- Study agent dispensing and return documentation ☐ Filed elsewhere: _____
- Study agent disposition and/or return of unused or damaged study agent ☐ Filed elsewhere: _____
    - Do not destroy or dispose of study drug without documented authorization from the sponsor.

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

Optional Customizable Documentation Templates for this section	
Test Article Accountability Log	Test Article disposition and/or return
Test Article Shipping Receipt Log	Device Accountability Log

References	
• 21 CFR 312.23 (a) (7) Chemistry, Manufacturing, and Control • 21 CFR312.57(a) Sponsor records on investigational drugs • 21 CFR 312.59 Sponsor disposition of unused drug • 21 CFR 312.61 Control of the investigational drug • 21 CFR 312.62 (a) Investigator disposition of unused drug • 21 CFR 210 and 211 Good Manufacturing Practice (GMP): Manufacturing, processing, packing or holding of drugs and finished pharmaceuticals • ICH GCP 2.12 Manufacture and handling of investigational products	• ICH GCP 4.6 Investigator Responsibilities regarding Investigational Product(s) • ICH GCP 5.13 Manufacturing, labeling, coding of investigational products • ICH GCP 5.14 Supplying and handling investigational products • ICH GCP 8.2.11 Normal Value(s)/ranges for medical/laboratory/technical procedure(s) and/or test(s) • ICH GCP 8.2.12 Medical/laboratory/Technical Procedures/Tests • ICH GCP 8.2.13 Essential documents, sample labels • ICH GCP 8.2.16 Essential Documents, Certificates of Analysis of investigational products shipped

Tab 13: FDA 1572 Forms and Financial Disclosure Forms (FDFs)

- 1572 forms: completed and signed by each site Principal Investigator:
  - This form is required by the sponsor for any drug study being conducted under an Investigational New Drug (IND) application. The form provides an agreement of the commitments made by the site PIs: compliance to regulations; compliance to protocol; commitment to personally conduct or supervise the trial, etc. The overall purpose is to ensure that the rights, safety, and welfare of study participants are being protected.
  - Investigators should maintain copies of the site's 1572 form (and updates).

    Sponsor-investigators should maintain copies of all sites' 1572 forms (and updates).
  - Link to FDA 1572 form guidance: https://www.fda.gov/media/78830/download
  - When should a new 1572 form be signed?
    - A sponsor must obtain a new signed form as each new site Principal Investigator joins the study (such as a new site or replacement of a PI at a current site), when drug is shipped to a new location, or for a new protocol (under the same IND) for an existing PI.
    - It is not necessary (per regulations) for sites to complete a new 1572 as sub-investigators begin or leave a site; however, it is industry practice for sponsors to use the form as a way to document these changes.
      - Sites should notify the sponsor (who updates the IND) of changes to the 1572 (such as new sub-I) and changes should be documented by updating the Site Signature/Delegation log with start dates, responsibilities, and departure dates.
- CVs for all PIs and sub-investigators listed on the 1572 forms.
  - Sponsors (including Sponsor-Investigators) should keep all CVs for those individuals listed on 1572 forms. This includes investigators from other institutions (sites) involved in the study under the Sponsor. See Tab 10 Study Staff.
- Financial disclosure forms (form FDA 3455) for all PIs and sub-investigators listed on the 1572 forms.

References	
• 21 CFR 312.53 (c) (1) *FDA form 1572* • Information Sheet Guidance: Frequently Asked Questions – Statement of Investigator (Form FDA 1572), May, 2010	• 21 CFR Part 54: Financial Disclosure by Clinical Investigators • FDA Guidance: Financial Disclosure by Clinical Investigators, February 2013

Tab 14: IND Maintenance for Investigator IND Holders (Investigators who are also Sponsors)

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

Sponsor-Investigators must follow regulations pertaining to both sponsors and investigators. ***Sponsor*** responsibilities include:

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

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

General Correspondence/communication with FDA

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

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

Maintenance of the IND:

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

Continued on back

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

Optional Customizable Documentation Templates for this section	
Communications Log	Safety Report Tracking Log

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

Tab 15: IDE Maintenance for Investigator IDE Holders (Investigators who are also Sponsors)

A sponsor-investigator is an individual who *initiates and conducts* an investigation and under whose immediate direction the investigational device is administered, dispensed, or used. Sponsor-investigators must follow regulations pertaining to both sponsors and investigators.

Sponsor responsibilities for studies conducted under an IDE include:

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

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

General Correspondence/communication with FDA

Original IDE information:

- IDE application ☐ Filed elsewhere: _____
- FDA approval of the application

Maintenance of the IDE – Sponsor Reports:

- **IDE Unanticipated adverse device effects** ☐ Filed elsewhere: _____
  - The sponsor must report the results of the evaluation of an unanticipated device effect to the FDA and all reviewing IRBs and participating investigators within 10 working days after first receiving notice of the effect.
- **Withdrawal of FDA approval**
  - Notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval of the investigation within 5 working days after receipt of notice of withdrawal of approval.

Continued on back

- **Current investigator list**
  - Submit to FDA at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation.
- **Progress reports** ☐ Filed elsewhere: _____
  - At regular intervals, and at least yearly, submit progress reports to all reviewing IRB's. If the device is a significant risk device, progress reports should be submitted to the FDA. If it is a treatment IDE, submission of progress reports to reviewing IRBs and FDA should be done semi-annually.
- **Recall and device disposition**
  - Notify FDA and all reviewing IRBs of any request that an investigator return, repair, or dispose of any units of a device within 30 days after request was made.
- **Final report**
  - For a significant risk device, the sponsor should notify the FDA within 30 working days of the completion or termination of the investigation and should submit a final report to the FDA and all reviewing IRBs and participating investigators within 6 months after completion or termination. If not a significant risk device, sponsor should submit report to all reviewing IRBs within 6 months after completion or termination.
- **Informed consent**
  - Submit to FDA a copy of any report by an investigator of use of a device without obtaining informed consent within 5 working days of receipt of notice.
- **Significant risk device determination**
  - If an IRB determines that a device is a significant risk device, and the sponsor has proposed that the IRB consider the device not to be a significant risk device, the sponsor should submit to the FDA a report of the IRBs determination within 5 working days of learning of it.
- **Other**
  - Upon request by a reviewing IRB or the FDA, the sponsor should provide accurate, complete and current information about any aspect of the investigation.

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

Optional Customizable Documentation Templates for this section
Communications Log

References	
• 21 CFR 812 *Devices* • 21 CFR 312.23 (a) (1) *1571 cover sheet* • 21 CFR 812.40 *General responsibilities of sponsors* • 21 CFR 812.43 *Selecting investigators and monitors* • 21 CFR 812.43 (c)(4) *Investigator Agreements*	• 21 CFR 812.45 *Informing investigators* • 21 CFR 812.46 *Monitoring investigations* • 21 CFR 812.140 *Sponsor Records* • 21 CFR 812.150 *Reports*

Tab 16: Single IRB – Relying Institution Site

Use this tab if your site is ceding review to an outside IRB. Documentation on the following should be maintained by the Relying Institution Site:

- Copy of Executed Reliance Agreement between Relying Institution and the Reviewing IRB: Provides confirmation of agreement between both IRBs, and spells out the responsibilities of the institution providing IRB review as well as the institution relying on the external IRB.

- Departmental approval documents

- Documentation that the following information was provided to the Relying Institution Site Point of Contact (POC); copies of these items should be maintained in the regulatory binder:
  - Changes in Relying Institution investigator or study team.
  - Relying Institution changes in COI disclosures and COI management plans.

- Reviewing IRB Policies and Procedures Documents/Manual: The Relying Institution investigator must adhere to the reviewing IRB's policies and procedures for reporting unanticipated problems, noncompliance, and other important items.

- Copies of communication from the lead site investigator regarding all reviewing IRB determinations.
  - Initial approval letter
  - Continuing review/progress approval letters
  - Amendments, approval letters
  - Final close-out acknowledgment letter

- Reviewing IRB Approved Study Documents: Copies of communication from the lead investigator regarding all approved IRB documents.
  - Informed consent forms
  - Authorization forms (if applicable)
  - Recruitment materials
  - Participant hand-outs, flyers, surveys, etc.
  - Case Report Forms
  - Amendments (including funding changes)

- Documentation of communication of local considerations ("local context") through the Point of Contact.

- Documentation of communication to the Reviewing IRB of communications to and from the Relying Institution and FDA, OHRP, and/or other regulatory agencies.

- Documentation showing "prompt reporting" to lead study team of any unanticipated problems (see Tab 6) suspension of the study or noncompliance at the local site.

- Documentation that the Relying Institution Sponsored Programs Office has Received Relying IRB Approval Documentation.

- Relying Institution IRB Materials/Documents Submitted to Lead Investigator.
  - Initial IRB approval materials
  - Relying Institution approved IRB Informed Consent Form (if applicable)
  - Study Staff Lists and Training Documents
  - Continuing Review information

References	
• NIH Single IRB Policy for Multi-site Research: https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm • NIH FAQs on Single IRB Policy for Multi-site Research: https://grants.nih.gov/grants/policy/faq_single_IRB_policy_research.htm	• CTTI Considerations to Support Communication Between Institutions and Outside IRBs for Multicenter Protocols: https://www.ctti-clinicaltrials.org/files/recommendations/considerations_document_-_use_of_central_irbs_for_multicenter_clinical_trials_nb2web.pdf

Tab 17: Single IRB – Lead Study Team Site

Use this tab only if your site is the Lead site of a multi-center study. Documentation on the following should be maintained by the Lead Study Team Site about the Relying Sites.

- Copy of Executed Reliance Agreement between Relying Institutions and the Reviewing IRB: The Lead Investigator should maintain executed reliance agreements for each participating Relying Institution. These documents provide confirmation of agreement between the reviewing and Relying IRBs, and spells out the responsibilities of the institution providing IRB review as well as the institution relying on the external IRB.

- COI documents received from Relying Institutions:
  - COI disclosures and, if applicable, COI management plans.

- Documentation that the reviewing IRB Policies and Procedures documents were provided to each Relying Institution investigator.

- Documentation of the reviewing IRB's determinations regarding the research.

- Documentation of notifying relevant PoCs from Relying Institutions of findings and actions with respect to Unanticipated Problems or research related subject complaints or injuries or serious and/or continuing non-compliance.

- Documentation on Relying Sites local context.

- The Lead Investigator should ensure (and document) that each Relying Institution investigator was provided with a copy of IRB approval letters and IRB-approved study documents:
  - Reviewing IRB initial approval letter
  - Reviewing IRB continuing review/progress approval letters
  - Reviewing IRB amendments, approval letters
  - Reviewing IRB final close-out acknowledgment letter
  - Reviewing IRB Informed Consent Form
  - Reviewing IRB authorization forms
  - Reviewing IRB recruitment materials
  - Reviewing IRB participant hand-outs, flyers, surveys, etc.

- Documentation of communications with Relying Sites including responses to questions or requests from site investigators/staff at Relying Institutions.

- The Lead Investigator should maintain all copies of all Relying Institution IRB documents provided by the Relying Institution investigator:
  - Initial IRB approval materials
  - Relying Institution approved IRB Informed Consent Form (if applicable)
  - Study staff Lists and Training Documents
  - AE/UP information
  - Other Items

Tab 18: Miscellaneous

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

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

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

  ☐ Filed elsewhere: _____
- Budget documentation: These documents serve to document the financial agreement between the investigator/institution and the sponsor of the trial.

  (Note that financial documents such as contracts, Letters of Indemnity, budgets, etc. are often kept in a separate confidential file.)

  ☐ Filed elsewhere: _____

Certificate of Confidentiality (CoC): CoCs allow researchers to refuse to disclose names or other identifying characteristics of research subjects in response to legal demands. CoCs are issued automatically for any NIH-funded projects using identifiable, sensitive information. Research that is not NIH-funded can apply online to obtain a CoC.

- CoC application
- CoC approval

☐ Filed elsewhere: _____

Equipment calibration/maintenance logs: Demonstrates that measurements from study equipment are reliable.

☐ Filed elsewhere: _____

Documentation on NIH or Foundation/other grant maintenance

References	
• Certificate of Confidentiality: https://humansubjects.nih.gov/coc/index	

Tab 19: Notes-to-File/Deviation Reports/CAPAs

Notes-to-File

A note-to-file is a way to explain errors/omissions/discrepancies. They can be generated on a case-by-case basis or used to explain when errors/omissions/discrepancies occur in multiple instances. If appropriate, a note-to-file should include the corrective or follow-up action taken to address the issue (or reference a detailed CAPA).

Protocol Deviation Tracking

Track deviations from the protocol. You can use the Protocol Deviation Tracking log. Make sure to refer to the policies of the reviewing IRB for what constitutes a "reportable event" and in what timeframe reporting should be done.

At BMC/BU Medical Campus IRB, major deviations should be reported within 7 days of the study team being aware of the deviation and minor deviations should be logged and then submitted at the time of continuing review/check-in. Deviations should also be explained in the participant-specific source documents, and corrective actions put in place and documented, as applicable.

Corrective and Preventative Action Plans (CAPAs)

CAPAs should include a description of the issue, the reasons why it occurred, what was put in place to correct the problem, what is put in place to prevent the problem from occurring in the future, and how these corrections will be assessed to have sufficiently addressed the problems.

Note that CAPAs almost always include training of staff as a part of the plan to prevent future occurrences of the deviation as well as a check to make sure that the CAPA worked to resolve the problem. Make sure to maintain documentation related to your CAPA such as a self-audit and study staff training (Tab 10).

Optional Log Templates for this section	
Note-to-File template	Protocol Deviation Tracking Log

Tab 20: