Regulatory File Guidelines

Version 6.0, 18 October 2024

Division of Microbiology and Infectious Diseases (DMID)

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1.0 Introduction

1.1 Background

These guidelines support National Institute of Allergy and Infectious Diseases (NIAID) Division of Microbiology and Infectious Diseases (DMID) Staff and Clinical sites in order to achieve and maintain compliance with the collection of essential regulatory documents, as defined by U.S. Federal Regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) E6, and DMID policies and procedures. ICH guidelines Section 8 define essential regulatory documents as "…documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements…". These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and integrity of the data collected."

1.2 Principles

It is the responsibility of the investigator to ensure compliance with GCP, institutional review board (IRB), and other applicable regulatory agencies.

A site regulatory file (synonyms: Site File, Investigator Binder, Investigational Site File (ISF), Regulatory Binder, Study Binder, and Trial Master File (TMF)) must be established at the beginning of each study and updated throughout the life of the study. Study files must be maintained for a minimum of 2 years after the last approval is received for a marketing application of the drug for the indication for which it is being investigated in the US. If no application is to be filed or if the application is not approved for such indication, study files must be maintained for a minimum of 2 years after the formal discontinuation of the clinical development of the drug. The site must contact DMID for authorization prior to the destruction

of any study records. The retention requirements vary from 3 to 25 years or more for other federal and international regulatory bodies (e.g. EMA). By maintaining a current and complete regulatory file for each study, clinical sites are better prepared, and in a state of readiness for inspection and oversight by authorized agents of the U.S. Food and Drug Administration (FDA) and DMID, respectively.

1.3 Essential Regulatory Document Submission

NIAID Clinical Research Management Services (NCRMS) Site Essential Regulatory Documents (SERD) online portal is the centralized resource which facilitates document submission of clinical site essential regulatory documents for DMID supported clinical studies. Sites conducting DMID clinical research submit their essential regulatory documents directly to the NCRMS SERD, submit the documents to the designated Essential Document Collection Organization (EDCO), or to another Coordinating Center which will upload the documents on the site's behalf (as applicable). The designated EDCO is responsible for review and management of site essential document files prior to filing in the DMID files (e.g. DMID-CROMS Document Library or in a Trial Master File (TMF)). The documents uploaded to NCRMS SERD will be retrieved by the DMID Clinical Research Operations and Management Support (CROMS) contract Essential Regulatory Documents Group (ERDG) for document management.

Resources

The DMID Essential Regulatory Document Review Worksheet is available to assist site staff, clinical site monitors, and DMID contractors in the review of essential regulatory documents. The worksheet may be used as a checklist by the site to verify required essential regulatory documents are complete prior to document submission.

On-demand training modules addressing Essential Regulatory Documents and Regulatory File Document Guidelines are available through the DMID CROMS Learning Management System (LMS). Logon credentials are required.

All non-exempt NIH funded human subjects research must follow requirements in 45 CFR 46. The regulations that govern the conduct of clinical studies regulated by the Food and Drug Administration (FDA) are included in the Code of Federal Regulations, Title 21 (21 CFR):

- 21 CFR 312, Investigational New Drug Application (IND), covers the procedures and requirements for the conduct of clinical studies with investigational new drug . 21 CFR 812, Investigational Device Exemptions (IDE), covers the procedures for the conduct of clinical studies with medical devices. 21 CFR 50, Protection of Human Subjects, provides the requirements and general elements of informed consent. 21 CFR 56, Institutional Review Boards, covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols.
- 21 CFR 54, Financial Disclosure by Clinical Investigators, covers the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.
- 21 CFR 11: Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records covers records that are created, modified, maintained, archived, retrieved, or transmitted submitted to the FDA.

Additional clinical research resources are publicly available through the DMID-CROMS WebLibrary, Clinical Research Support. Links to related resources are contained in each document section in these guidelines.

2.0 Overview of Guidelines

Each section in these guidelines highlights the related requirements, general guidance for organization and document maintenance and supporting resources.

- Organize the site file (electronic or paper) to meet the needs of the site and for each specific DMID protocol:
    - Include only sections pertinent to the protocol.
    - Organize and order the sections to facilitate ease of use and reference.

  - Store confidential Financial Disclosure and related documents in a separate site file location.
  - Add additional tabs and/or documents to each section, as needed.
  - If documents are not maintained in the Regulatory File, include a memo referencing the alternate storage location.

- Keep the documents current and complete.
- Identify an individual(s) responsible for maintaining the study's essential regulatory document files. List this person on the protocol-specific Site Signature List/Delegation of Authority Log and 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 all Essential Regulatory Documents in a secure and accessible location throughout the study and make it available to the clinical site monitors during the scheduled visit. It is recommended that this location limit the possibility of accidental damage or destruction by fire or water.
- Binders or hanging files should be in a locked cabinet or locked room with restricted access to study staff.
- Electronic records used as the primary source for a regulatory document must be generated and/or maintained in a secure system/platform with audit trail and meet the requirements of 21 CFR Part 11 for FDA-regulated studies.
- Maintain subject-specific documentation and information, e.g., signed consent forms, test results, and completed case report forms, separately in subject-specific charts.

2.1 What Sections Apply to Your Research Protocol?

Depending on the research, some sections may not be required. If other file systems (e.g., electronic) are used for filing/maintaining essential regulatory documents, those systems must comply with the recordkeeping requirements for essential regulatory documents, and

additional applicable regulations and standards. Within each guidance section, a table labeled MAINTENANCE includes requirements for document filing and other related information. For questions, contact the DMID Point of Contact or Clinical Project Manager (CPM) for the protocol.

2.2 Electronic Signature

The use of electronic signatures is acceptable on essential regulatory documents as long as they meet all applicable requirements under 21 CFR Part 11 Subpart C and will be considered equivalent to handwritten signatures.

- Accepted signature methods by FDA are:
    - Scanned signatures
    - Digital signatures (e.g. signed with PIV card)
    - Flattened digital signatures. A flattened digital signature must include:
        - The printed name of the signer
        - The date and time when the signature was executed
        - The reason for signature

2.3 Location Memo

Any regulatory document not filed in the site's Regulatory Binder must have a reference memo created and placed in the binder's section that documents the location where the regulatory document is filed.

2.4 DMID Language and Translation Requirements

Essential documents in a language other than English, must be filed with either a translation certificate or a translation summary with a DMID Translation Equivalence Form. For the

protocol, subject facing documents including informed consent form (ICF) not in English, a full translation of the document with certificate is required. For additional essential documents including IRB/IEC approval letters, investigational product labels, and PI/Sub-I CVs not in English, a summary of the information contained within the document will be accepted with the Translation Equivalence Form according to DMID policy.

- For Informed Consents, if the original document was written in English and study participants do not speak English, once translated, it must be back translated from the local language to English.
- For other documents, if the original document was written in a language other than English, a translation certificate or the DMID Translation Equivalence Form must be submitted according to DMID policy.

DMID Resources

- DMID Language and Translation Requirements Summary

3.0 Resources

The primary FDA regulations that govern the conduct of FDA-regulated clinical studies are included in the Code of Federal Regulations, Title 21 (21 CFR):

- 21 CFR 312, Investigational New Drug Application (IND), covers the procedures and requirements for the conduct of clinical studies with investigational new drug.
- 21 CFR 812, Investigational Device Exemptions (IDE), covers the procedures for the conduct of clinical studies with medical devices.
- 21 CFR 50, Protection of Human Subjects, provides the requirements and general elements of informed consent.
- 21 CFR 56, Institutional Review Boards, covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols.

- 21 CFR 54, Financial Disclosure by Clinical Investigators, covers the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.
- 21 CFR 11, Electronic Records and Electronic Signatures, covers criteria for electronic records and electronic signatures.
- 45 CFR 46, Protection of Human Subjects, covers criteria that applies to all research involving human subjects conducted, supported, or otherwise subject to Federal regulations.

DMID Resources

- DMID Essential Regulatory Document Review Worksheet is available to assist site staff, clinical site monitors, and DMID contractors in the review of essential regulatory documents. The worksheet may be used as a checklist by the site to verify required essential regulatory documents are complete prior to document submission.
- DMID CROMS Learning Management System (LMS), on-demand training modules addressing Essential Regulatory Documents and Regulatory File Document Guidelines. Logon credentials are required.
- DMID-CROMS WebLibrary, Clinical Research Support, is a central resource to DMID and extramural investigators to facilitate and support the conduct and management of clinical research.

Additional Links

- International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice E6 Guidelines
- United States Government Publishing Office, Electronic Code of Federal Regulations, Title 21, Food and Drugs
- United States Food and Drug Administration (FDA) Guidance for Industry

- Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP)
- NIH Certificate of Confidentiality

4.0 Acronyms

AE	Adverse Event	IND	Investigational New Drug (Application)
CAP	College of American Pathologists	**IRB**	Institutional Review Board
CLIA	Clinical Laboratories Improvement Amendments	**LMS**	Learning Management System
CRF	Case Report Form	**MOP**	Manual of Operational Procedures
CV	Curriculum Vitae	**N-CRMS**	NIAID Clinical Research Management System
CROMS	Clinical Research Operations and Management Support contract	**NIAID**	National Institute of Allergy and Infectious Diseases
DMID	Division of Microbiology and Infectious Diseases	**OCRA**	Office of Clinical Research Affairs
eCRF	Electronic Case Report Form	**ORA**	Office of Regulatory Affairs
EDCO	Essential Document Collection Organization	**PI**	Principal Investigator
ERDG	Essential Regulatory Documents Group	**PID**	Participant Identifier
FWA	Federalwide Assurance	**SAE**	Serious Adverse Event
GCP	Good Clinical Practice	**SDCC**	Statistical and Data Coordinating CenterCenterSerious Adverse Event
IB	Investigator's Brochure	**SERD**	Site Essential Regulatory Documents moduleStatistical and Data Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human UseInternational Council for Harmonisation	**SUSARSERD**	Suspected Unexpected Serious Adverse Reaction (IND Safety Report) Site Essential Regulatory Documents module
IDE	Investigational Device Exemption	**SUSAR**	Suspected Unexpected Serious Adverse Reaction (IND Safety Report) Trial Master File
IEC	Independent Ethics Committee	**TMF/eTMF**	Trial Master File/ Electronic Trial Master File

5.0 Essential Documents for Conducting a Clinical Trial

5.1 Form FDA 1572

The FDA 1572 form is completed by the principal investigator conducting a clinical trial and regulated by the FDA. The investigator provides documentation that he or she has the experience and background needed to conduct the trial and that it will be done in compliance with all applicable FDA regulations.

Regulatory Requirements

A current, valid Form FDA 1572 for studies conducted under an IND.

- The form must be signed and dated by the Principal Investigator. Items 1-11 must be complete.
- In accordance with the DMID Office of Regulatory Affairs requirement, each time there is a change in Principal Investigator, Study site address(es)/location, Clinical laboratory, Institutional Review Board and/or addition of new Sub-Investigator a new Form FDA 1572 must be completed, signed and dated by the Principal Investigator, and submitted to DMID.

Maintenance

Keep all accepted versions of the Form FDA 1572 used for activation and the duration of the study in the site regulatory file. Drafts do not need to be retained.

Document	Site File	DMID Sponsor File	Other information
Form FDA 1572	X	X	Submit via N-CRMS SERD portal

Guidance

The following must be included on the Form FDA 1572:

- A separate Form FDA 1572 is required for the Co-Principal Investigator.
- Names of all Sub-Investigators for the study.
- Any reviewing and approving IRB.

- The locations for all the sites and facilities where study participants are seen, consenting locations, protocol activities are conducted, and clinical data is generated or collected. These sites/facilities may include healthcare facilities where the study product will be managed. This includes shipment location, preparation of the study product, and administration of the study product to study participants, and/or where physical exams will be performed. Facilities where other important clinical investigation functions are performed may also be identified in Section #3 (e.g., analytical research labs).
- Title of the study and the study number, if applicable.
- The original signed and dated Form FDA 1572 must be kept in the site regulatory file.
- Use the Continuation Page to add additional information or locations to Items 3-6.

Additional Information:

- Use of correction fluid (e.g., "White Out") is not acceptable anywhere on the form. There must not be significant typographical errors, and no 'write-overs'; this may impact the interpretation or intended use of the information.
- Research labs can be listed in the addresses of the form such as labs used for end points (e.g., efficacy data) and PK sampling.
- All clinical labs used for a study must be listed. This includes labs with a CLIA waiver or Point of Care testing under a CLIA waiver.
- State-specific license or waivers should be provided for states that do not provide CLIA wavers or certificates (New York & Washington).

Resources

- Form FDA 1572
- Form FDA 1572 Frequently Asked Questions (FAQs)
- Instructions For Filling Out Form FDA 1572 – Statement of Investigator
- Federal Regulations:
    - 21 CFR 312.22 General principles of the IND submissions

- 21 CFR 312.23 IND content and format
- 21 CFR 312.53 Selecting investigator and monitors

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance:
  - ICH GCP E6 Section 8 Essential documents for the conduct of a clinical trial

5.2 DMID Investigator of Record (IoR)/Investigator Agreement

A form that must be completed for DMID studies that are not conducted under an Investigational New Drug (IND) or when local laws or regulations prohibit the signing of a 1572. All clinical investigators must submit an IoR for each new non-IND protocol. The Investigator Agreement is an equivalent form completed for studies that are under an Investigational Device Exemption (IDE).

Requirements

- An IoR/Investigator Agreement is required when local laws or regulations prohibit the signing of a 1572 for studies conducted under an IND (45 CFR 46), or studies not conducted under an IND, this includes studies that are under an IDE (21 CFR 812 Investigational device exemptions).
- In accordance with the DMID Office of Regulatory Affairs requirement, each time there is a change in Principal Investigator, Study site address(es)/location, Clinical laboratory, Institutional Review Board and/or addition of new Sub-Investigator a new IOR/Investigator Agreement must be completed, signed and dated by the Principal Investigator, and submitted to DMID.

Maintenance

Keep all versions of the IoR in the site regulatory file.

Document	Site File	DMID Sponsor File	Other information
Investigator of Record Form	X	X	Submit via N-CRMS SERD portal

Document	Site File	DMID Sponsor File	Other information
Investigator Agreement	X	X	Submit via N-CRMS SERD portal

Guidance

The following must be included on the IoR/Investigator Agreement:

- The original signed and dated form may stay in the regulatory file at the site.
- A separate form is required for the Co-Principal Investigator.
- Names of all Sub-Investigators for the study.
- Any reviewing and approving IRB/IEC.
- The locations for all the sites and facilities where study participants are seen, consenting locations, protocol activities are conducted, and clinical data is generated or collected. These sites/facilities may include healthcare facilities where the study product will be managed. This includes shipment location, preparation of the study product, and administration of the study product to study participants, and/or where physical exams will be performed. Facilities where other important clinical investigation functions are performed may also be identified in Section 4 and 5 (e.g., analytical research labs).
- Title of the study and the study number, if applicable.

Additional Information:

- Use of correction fluid (e.g., “White Out”) is not acceptable anywhere on the form. There must not be significant typographical errors, and no ‘write-overs’; this may impact the interpretation or intended use of the information.
- Research labs can be listed in the addresses of the form such as labs used for end points (e.g., efficacy data) and PK sampling.
- All clinical labs used for a study must be listed. This includes labs with a CLIA waiver or Point of Care testing under a CLIA waiver.

- State-specific license or waivers should be provided for states that do not CLIA waivers or certificates (New York & Washington).

Resources

- DMID Investigator of Record Agreement (IoR)
- DMID Investigator of Record Agreement (IoR) Instructions
- Federal Regulation:
    - 21 CFR 312.53 Selecting investigator and monitors
    - 21 CFR 812 Investigational device exemptions
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance:
    - ICH GCP E6 Section 8 Essential documents for the conduct of a clinical trial

5.3 Federalwide Assurance (FWA)

Regulatory Requirements

- All institutions that are engaged in human subject research that is conducted or supported by HHS that is non-exempt are required by 45 CFR 46 to:
    - Hold or obtain an Office for Human Research Protections (OHRP)-approved FWA.
    - Certify to the Health and Human Services (HHS) agency conducting or supporting the research that the protocol has been reviewed/approved by the IRB designated in the FWA and will be subject to continuing review by an IRB.

Maintenance

Document	Site File	DMID Sponsor File	Other information
FWA number with expiration date.	X	X	Submit via N-CRMS SERD portal

Guidance

- Each facility must have an active FWA number assigned and maintain a record of the FWA number and its expiration date in the regulatory file, matches the facility name(s) listed in either:
    - Sections #1 and #3 of the Form FDA 1572 (IND study)
    - Sections #2 and # 4 of the IoR (non-IND study)
    - If the locations listed on the Form FDA 1572 or the IoR have separate or different FWAs, all records are required to be submitted and filed in the regulatory file.
- Each site must have a linked IRB. The IRB name must correspond to the IRB name listed in either:
    - Section #5 of the Form FDA 1572 (IND study)
    - Section #6 of the IoR (non-IND study)

  - For single IRB/central IRB studies, the site will have to provide documentation for the reliance agreement if the IRB is not designated on the site's FWA.

- The expiration date of the FWA number should be present on the documentation and match the current information on the OHRP website.

Resources

- OHRP Regulations and Policies:
  - 45 CFR 46
  - Engagement of Institutions in Human Subjects Research (2008)
  - Status of IRBs & FWAs
  - Federalwide Assurance Instructions

5.4 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Requirements

- A copy of the initial IRB/IEC-approved study protocol and any subsequent IRB/IEC-approved revisions/amendments to the protocol.
- Protocol changes must be approved by DMID and the IRB/IEC prior to implementation.
- All documents must have a version number and version date as this is a DMID required element for IRB/IEC approval documentation.
- The DMID protocol number must be clearly displayed.

Maintenance

Document	Site File	DMID Sponsor File
Protocol	X	X
All Protocol Amendments	X	X

Guidance

- The following must be present and correct on the Protocol:
    - Protocol number
    - Protocol version number
    - Protocol version date
- Drafts which were never submitted to the IRB/IEC are not required in the regulatory file.

Resources

- Federal Regulation:
    - 21 CFR 312.30 Protocol amendments
    - 21 CFR 312.50 General responsibilities of sponsors
    - 21 CFR 312.60 General responsibilities of investigators
    - 21 CFR 812.35 Supplemental applications
    - Federal Regulations for Clinical Investigators
- Federal Guidance:
    - FDA Inspections of Clinical Investigators
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use(ICH) Guidance:
    - ICH GCP E6 Section 8 Essential documents for the conduct of a clinical trial
- NIAID Clinical Terms of Award

5.5 Protocol Signature Page/Statement of Compliance

Requirements

- The Protocol Signature Page/Statement of Compliance must be signed and dated by the PI for all versions of the protocol that the site participated in.
- Each signed Protocol Signature Page/Statement of Compliance should contain the protocol number, protocol version and date.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Protocol Signature Page/Statement of Compliance *(for all protocol versions submitted to the IRB)*	X	X	Site to submit via N-CRMS SERD portal

Guidance

- The Protocol must contain a Protocol Signature Page/Statement of Compliance.
- The Protocol title may or may not be present on the Signature Page; however, if present, it must also be correct.
- The Protocol Signature Page/Statement of Compliance must be completed and signed by each site Principal Investigator for the study.

Resources

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human (ICH) Guidance:
    - ICH GCP E6 Section 8 Essential documents for the conduct of a clinical trial

5.6 Investigator Brochure / Package Insert / Device Manual

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Requirements

- A copy of the initial version submitted to the IRB and all revisions of the Investigator's Brochure and/or Package Insert or Device Manual (if study product is FDA-approved/marketed).
- All versions of the Investigator's Brochure and/or Package Insert or Device Manual in effect during the conduct of the protocol must be submitted to the IRB/IEC for review and acknowledgement.
- The IRB/IEC submission and acknowledgement should be filed in the site regulatory file. IRB/IEC acknowledgement should be submitted to the regulatory-document collection entity (if applicable).
    - If the sponsor submits the Investigator's Brochure and/or Package Insert or Device Manual to the single/central IRB on the site's behalf, the IRB acknowledgement should be filed in the site regulatory file if a Single IRB issues an acknowledgement.

Maintenance

Document	Site File	DMID Sponsor File	Other information
IB, IB Addendums, Package Insert, Device Manual	X	X	These documents should be submitted to the IRB/IEC.

Guidance

- As the site's reference to known and unknown adverse effects of the study product/drug, the Investigator's Brochure and/or Package Insert or Device Manual must be available to all staff.

- IND/IDE sponsors are required to notify sites of Safety Reports (e.g., IND/Unanticipated Adverse Device Effects (UADE) submitted to the FDA. The Principal Investigator is responsible for submitting Safety Reports to the IRB/IEC according to their guidelines and filing copies in the site files.
- Any other information letters/correspondence issued by the manufacturer to the Investigators must also be filed in this section.

Resources

- Federal Regulation:
  - 21 CFR 312.23 IND content and format
  - 21 CFR 312.58 Inspection of sponsor's records and reports
  - 21 CFR 312.64 Investigator reports
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human (ICH) Guidance:
  - ICH GCP E6 Section 7 Investigator's Brochure
  - ICH GCP E6 Section 8 Essential documents for the conduct of a clinical trial

5.7 Curriculum Vitae (CV)/BioSketches

CVs/BioSketches document the qualifications to conduct the trial and/or provide medical supervision of subjects.

Requirements

- CVs/Biosketches must be provided to DMID for the Principal Investigator listed in either:
  - Sections #1 of the Form FDA 1572 (IND study)
  - Sections #2 of the IoR (non-IND study)
- CVs/Biosketches must be provided to DMID for Sub-Investigator(s) listed in either:
  - Sections #6 of the Form FDA 1572 (IND study)
  - Sections #7 of the IoR, only if it is an *IDE study*

- CVs/Biosketches must be provided to DMID for Investigators acting as Protocol Chairs or equivalent.
- All CVs/Biosketches must be signed and dated current within 3 years and updates should be made available for the DMID files as needed.

Maintenance

Document	Site File	DMID Sponsor File	Other information
CVs/Biosketches for all study personnel listed on site staff signature log	X	N/A	N/A
CVs/Biosketches for PI and all Sub-Investigators listed on Form FDA 1572	X	X	Site to submit via N-CRMS SERD portal
CVs/Biosketches for PI and all Sub-Investigators listed on the IoR	X	X	Site to submit via N-CRMS SERD portal

Guidance

- The names of investigators must be spelled correctly and correspond to the name(s) in the applicable sections of the Form FDA 1572 or the IoR.
- The CV should indicate an affiliation to a site or facility where the study will be conducted, as indicated in either:
    - Section #3 of the Form FDA 1572 (IND study)
    - Section #4 of the IoR (non-IND study)
- The CV should show the relevant education, experience, and training that qualifies the investigator(s) for the study.

Resources

- 21 CFR 812.43 Investigation Device Exemptions, Selecting Investigators

- 21 CFR 312.53 Selecting Investigators
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.8 Principal Investigator / Sub-Investigator Licensure

Requirements

- Current professional licensure (e.g., medical, nursing, pharmacy) must be provided to DMID for all investigators listed in either:
    - Section #1 and #6 of the Form FDA 1572 (IND study)
    - Section #2 and #7 of the IoR (non-IND study)
- If the Principal Investigator is not an MD, a medically responsible physician must be identified, and current licenses collected and submitted to DMID.
- Professional licenses must be provided to DMID for Investigators acting as Protocol Chairs or equivalent.
- Professional licenses for Clinical Staff (e.g., nursing, pharmacy, and laboratory) listed on the Site Signature Log (SSL)/ Delegation of Authority (DOA) log should be filed in the site regulatory file (if applicable).

Maintenance

Document	Site File	DMID Sponsor File	Other information
Current licenses for PI and all Sub-Investigators listed on Form FDA 1572	X	X	Site to submit via N-CRMS SERD portal
PI medical license (if MD) or license of primary physician associated with the study (if the PI is not an MD)	X	X	Site to submit via N-CRMS SERD portal

Document	Site File	DMID Sponsor File	Other information
Professional license for Clinical Staff (medical, nursing, etc.) listed on the Site Signature List/Delegation of Authority Log, if licensed	X	N/A	N/A

Guidance

- As applicable, a photocopy of the current license or information from the state licensing board is acceptable.

Resources

- 21 CFR 812.43 Investigation Device Exemptions, Selecting Investigators
- 21 CFR 312.53 Selecting Investigators
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.9 DMID Financial Disclosure Form

A form that must be completed for DMID studies to identify whose financial interests and arrangements need to be reported.

Requirements

A DMID Financial Disclosure Form must be provided to DMID for all investigator(s) (i.e., Principal Investigator, Sub-Investigator) listed in either:

- Sections #1 and #6 of the Form FDA 1572 (IND study)
- Sections #2 and #7 of the IoR (IDE study).
    - Not needed for non-IND studies unless requested by DMID.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Financial Disclosure Form for PI and all Sub-Investigators listed on Form FDA 1572 or IoR	X*	X	Site to submit via N-CRMS SERD portal

*Filed separately from the site regulatory file.

Guidance

- The names of investigators must be spelled correctly and correspond to the name(s) in the applicable sections of the Form FDA 1572 or the IoR.
- Investigators are obligated to promptly update their financial disclosure information when relevant changes occur during the study and for one year following study completion.
- The original signed and dated DMID Financial Disclosure Form may stay at the site and should be filed separate from the regulatory file.

Resources

- DMID Financial Disclosure Form

- Federal Regulations:
    - 21 CFR 54 Financial Disclosure by Clinical Investigators
    - 21 CFR 312.53 Selecting investigator and monitors
    - 21 CFR 312.64 Investigator reports
- Federal Guidance:
    - Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators
    - Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection

5.10 IRB/IEC Approval Documentation

All Institutional Review Board (IRB) and Independent Ethics Committee (IEC) approvals must meet ICH GCP 8.2.7 requirements to document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. The approval should identify the version number and or date of the document(s).

Requirements

Approval documentation must include:

- The full Protocol title as listed in the Protocol; it may also list the DMID Protocol number (Protocol number only, is not sufficient).
- IRB letterhead with identifiers (e.g., name [abbreviations are acceptable], address) that correspond with the Form FDA 1572 or the IoR of at least one of the participating investigators or sites. (E-mail correspondence stating approval is not sufficient).
- The site name and the PI name at the site.
- The IRB name that corresponds to the IRB associated with the site on the FWA number

- If IRB name does not match information on the FWA number, then a reliance agreement will need to be provided.

- The study documents that were reviewed such as:
  - DMID Protocol (identified with version number/date).
  - Protocol Amendment(s) (identified with version number/date).
  - Informed Consent Form (identified with version number/date).
    - If applicable, Informed Consent Form in foreign language with required English Informed Consent Form or English translation included (identified with version number and/or date).
  - Written information provided to the subject (identified with version number and/or date).
  - Recruiting materials (e.g., advertising) (identified with version number and/or date).
    - Examples include, but are not limited to television, radio, newspaper, internet advertisements, and “Dear Patient” letters or flyers.

- Dates of all approvals
  - Initial and Continuing Review approvals must have the duration of approval (e.g., approved on [date], approval expiration on [date] or approved on [date] and in 12 months must be renewed). If renewal date is not listed, IRB documentation (e.g., SOPs, Guidelines, Policies, or Memo) stating approval/renewal timeframe must be included.

- For conditional approval, IRB/IEC-issued documentation is present to indicate that the stated conditions were met and final approval granted.

- For In-Country Approval Letter for Non-U.S. Sites

- Documentation of national and local approval for the conduct of the study must be collected and renewed per country regulations.

Maintenance

Document	Site File	DMID Sponsor File	Other information
IRB Memorandum of Understanding/ Reliance Agreement of Single/Central IRB	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Approval Letter from Local IRB/IEC not listed on Form FDA 1572/IoR (if applicable)	X	X	N/A
IRB/IEC Roster (if applicable)	X	X	Site to submit via N-CRMS SERD portal
Initial IRB/IEC Approval Letter	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Amendment Approval Letter	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Modification Approval Letter	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Approval Letter	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Continuing Review/Annual Review Letter**	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Acknowledgement Letter	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Approved Advertisements and Subject Information Materials	X	X	Site to submit via N-CRMS SERD portal
IRB/IEC Notification of Study Closure	X	X	Site to submit via N-CRMS SERD portal
Translation Documentation/Translation Certificate/DMID Translation Equivalence Form	X	X	Site to submit via N-CRMS SERD portal

**Sites not within the United States can submit an IRB/IEC approval or acknowledgement letter for the yearly progress report in lieu of the Continuing Review Approval Letter if in-country regulations do not have an annual review process.

Guidance

1. If the IRB approval letter does not list the version and/or date of the Protocol, Informed Consent Form (ICF), or other documents, any of the following are also accepted:
    A. A revised IRB/IEC approval letter including the version requirements listed above for all approved study documents.
    B. The listing of the documents submitted for review by the IRB which includes the following information:
        - Document name
        - Version number and/or version date
        - Version information must match the version information as it appears in the header/footer of the approved document. Example: Radio Advertisement document name = Radio Ad_v2.0_12Mar2008.
    C. A DMID IRB Approval Certification Form may be used. The form must include the following:
        - List of documents submitted and approved by the IRB/IEC
        - Signature of the Principal Investigator
2. If the Principal Investigator, any Sub-Investigator, Study Coordinator, or study team member is a member of the IRB/IEC, the regulatory file must contain documentation of their voting abstention for all approvals relating to this protocol.
    A. Example: a letter from the IRB/IEC at the beginning of the study stating voting abstention for the Investigator; each IRB/IEC Approval Letter can state that the Investigator did not vote; or the IRB/IEC minutes can be included to show voting abstention for the Investigator.
3. Site must comply with any local or county-specific regulatory authorization related to the Protocol.

4. IRB/IEC documentation generated from electronic submission and approval systems are mostly acceptable if all components listed above are present. (Electronic signatures are acceptable).

Resources

- Federal Regulations:
    - OHRP: Engagement of Institutions in Human Subjects Research (2008)
    - OHRP: Status of IRBs & FWAs
    - 21 CFR 50 Protection of Human Subjects
    - 21 CFR 56 Institutional Review Boards
    - 21 CFR 312 Investigational New Drug Application
    - 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:
    - Guidance for IRBs, Clinical Investigators, and Sponsors
    - E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.11 Informed Consent/Assent Form

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate (refer to ICH E6, 45 CFR46, 21 CFR 50 for all requirements). Informed consent is documented by means of a written, signed and dated informed consent/assent form (ICF) in a language understood by the participant. "Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the subject's parents or guardian.

Requirements

- All pages of the document must be present.
- DMID Protocol title must be listed correctly.
- The document must be approved by the IRB/IEC.
- The document(s) should display an IRB/IEC approval stamp somewhere on the document, or have a notation present to indicate the IRB approval and effective approval date(s). The document should contain a date (e.g., version, revision) and/or a version number.
- All documents required for DMID review will be provided to DMID in English.
- Informed consents in any language other than English must be accompanied by a Translation Certificate or DMID Translation Equivalence Form.
- If state-specific and/or IRB-specific documents are required to be given to study participants during the informed consent process in addition to the study consent, these documents must be present. For example, the state of California requires the California Bill of Rights to be included with the consent.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Informed Consents/Assent	X	X	Site to submit via N-CRMS SERD portal
Translation Documentation/Translation Certificate/DMID Translation Equivalence Form	X	X	Site to submit via N-CRMS SERD portal

Guidance

- Principal Investigators (PIs) conducting DMID-supported clinical research are responsible for coordinating the translation process and providing translated documents to DMID, Institutional Review Boards (IRBs), study volunteers, and study staff, as appropriate.

- Principal Investigators and study teams are responsible for ensuring that additional consents are included for optional tests (e.g. pregnancy partner, secondary use, genetic testing).
- If the document does not contain an approval stamp or other approval notation, the IRB approval letter *must* specifically identify the approval of the document and correctly match the version listed on the document.
- If the protocol includes additional optional tests, this should be included in the informed consent.

Resources

- Federal Regulation:
  - 45 CFR 46.116 General Requirements for informed consent
  - 45 CFR 46.117 Documentation of informed consent
  - 21 CFR 50 Protection of human subjects
  - 21 CFR 56 Institutional review boards
  - 21 CFR 312 Investigational New Drug Application
  - 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:
  - A Guide to Informed Consent
  - Informed Consent Information Sheet
  - Informed Consent Tips
  - Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial
- NIAID Clinical Terms of Award

5.12 Laboratory Documents

In accordance with ICH GCP 8.2.11, ICH GCP 8.2.12, and DMID-CROMS ERDG Information Sheet, study essential document files must include documentation that identify all laboratories used during the course of a study. The laboratory normal values or ranges for all clinical laboratory tests done, and documentation of CLIA, CAP, COLA, or State laboratory certification in effect during the entirety of the study should be filed at the site and submitted to DMID.

Requirements

1. CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 (CLIA)
    - A current CLIA certification or equivalent is required and is present for each clinical laboratory listed on the Form FDA 1572 or the IOR.
    - CLIA certificates are **not** required for the following:
        - Foreign (outside the U.S.) country laboratories
        - All labs in the state of Washington
        - All hospital labs in the state of New York (NY practices require a CLIA)
        - All Veteran Administration (VA) hospital labs
    - State certifications or foreign country equivalents are required in lieu of CLIA certification.
2. THE COLLEGE OF AMERICAN PATHOLOGISTS (CAP) & COMMISSION ON OFFICE LABORATORY ACCREDITATION (COLA)
    - As applicable, private inspection agency certifications (e.g., CAP, COLA, or other certifications) are present and current for each clinical laboratory listed on the Form FDA 1572 or the IOR.
    - CAP or COLA **may be present** along with CLIA Certification of Accreditation and should be submitted if available.
    - CAP or COLA **may not be present** with:

- CLIA Certificate of Compliance
- CLIA Certificate of Registration
- CLIA Certificate of Waiver
- CLIA Certificate for Provider-Performed Microscopy Procedures

- If the site is waiting for a renewed certification, a memo from the organization can be provided as proof that the laboratory is still in good standing with the private inspection agency.

3. LABORATORY NORMAL VALUES OR REFERENCE RANGES

- Laboratory normal values/reference ranges are required for all laboratories performing study related clinical labs.
- Site should keep any laboratory normal values/reference ranges from the time of study activation through study completion.
- Package inserts may be used as normal values/reference ranges for point-of-care testing (e.g., pregnancy tests, rapid tests for COVID and hemoglobin).
- Any normal values/reference ranges must have a date identifier as well as the name/location of the lab and must be attributable to a lab listed on the 1572/IOR.

Maintenance

Document	Site File	DMID Sponsor File	Other information
CLIA, state certification equivalent, or in-country certification equivalent	X	X	Site to submit via N-CRMS SERD portal
CLIA Waiver or alternate documentation	X	X	Site to submit via N-CRMS SERD portal
CAP, COLA or other private certification	X	X	Site to submit via N-CRMS SERD portal
Laboratory normal values/reference ranges (Package inserts)	X	X	Site to submit via N-CRMS SERD portal

Document	Site File	DMID Sponsor File	Other information
Translation Documentation	X	X	Site to submit via N-CRMS SERD portal

Guidance

- CLIA certification is **not** relevant/applicable for Research Laboratories when the following apply:
    - Research laboratories test human samples per protocol requirements, but the results of such testing are not available routinely for the diagnosis, treatment, prevention, or assessment of the health of research subjects.
    - Research laboratory tests cannot be ordered as part of routine medical care and are available only in the context of a research protocol.
- Research testing can be either excepted from CLIA or subject to CLIA. Specifically, testing facilities may qualify to be excepted from CLIA certification if they meet the description of "research laboratories" provided by the CLIA regulations at 42 C.F.R. § 493.3(b)(2); only those facilities performing research testing on human specimens that do not report patient-specific results may qualify to be excepted from CLIA certification.
- All Point-of-Care testing done at a clinical site falls under the surveillance of the respective institution's laboratory department or a CLIA Certificate of Waiver. Although FDA does not enforce CLIA requirements, the Form FDA 1572 should include any addresses for point-of-care testing.

Resources

- DMID CROMS ERDG Laboratory Information Sheet
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial
- Laboratory Accreditation Organizations:
    - Clinical Laboratory Improvement Amendments (CLIA)

- College of American Pathologists (CAP)
- Commission on Office Laboratory Accreditation (COLA)

5.13 Laboratory Normal Reference Ranges

Requirements

- The laboratory normal ranges required must include all clinical laboratory tests required by the Protocol, and the unit of measurement.
- The full name of the laboratory must match the laboratory(s) listed in the Form FDA 1572/IoR.
  - Section #4 of the Form FDA 1572 (IND study)
  - Section #5 of the IoR (non-IND study)
- The current date is indicated on the laboratory normal ranges.
- Package inserts are required in lieu of laboratory reference ranges when there is a CLIA Certificate of Waiver and point-of-care (POC) will be performed by the staff.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Laboratory Normal Reference Ranges	X	X	For study samples tested locally on site. Site to submit via N-CRMS SERD portal
Translation Documentation/Translation Certificate/DMID Translation Equivalence Form	X	X	Site to submit via N-CRMS SERD portal

Guidance

- Studies under an IND also require completion and maintenance of an FDA Form 1572 including clinical laboratories and locations where subjects will be seen, study procedures will be performed, and clinical data will be generated or collected.
- Memos clarifying lab reference range issues are obtained from the site and are signed and dated by investigator staff or laboratory personnel.

Resources

- DMID CROMS ERDG Laboratory Information Sheet
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.14 Site Signature List/Delegation of Authority Logs

According to FDA guidance for decentralized trials, as part of preparing and maintaining adequate case histories, investigators must maintain a task log of study staff who perform trial-related activities.

Requirements

- The Site Signature List/Delegation of Authority (DoA) log must contain the signatures and initials of all study personnel performing trial related activities, including all personnel listed on Form FDA 1572 or IoR form (e.g., anyone obtaining informed consent, completing study specific source documentation, or updating case report forms/ electronic case report forms, etc.).
- The DoA log must include name, study role, signature, initials, responsibilities, start date, and end date.
    - The start and end dates refer to the period for which that member of the study staff is authorized to perform study related activities. The list must be kept current.

- The SSL/DOA will be reviewed during visits and copies may be collected.
- A completed copy of the DoA signed by the Principal Investigator will be collected at the study closure.
- If the log includes staff at a location other than the primary study site, the log should include:
    1. names and affiliations of the study staff
    2. a description of their roles and assigned tasks
    3. the dates staff are added to the log, and
    4. the locations where these activities are conducted.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Site Signature List/Delegation of Authority Log	X	X	A final copy will be collected at Study Closeout. Sites retaining DoA after the close-out visit must submit a copy of the completed DoA with PI's end of study signature to the EDCO.

Guidance

- Signature format captured on the SSL/DOA must include the format of signatures used through throughout the study (electronic and handwritten).
- Update logs in a timely manner. Individuals and tasks delegated should be added prior to the person performing them. According to FDA guidance, the log should be signed and dated by the investigator when initially created and updated as individuals are added.

Resources

- Federal Regulations:
    - 21 CFR 312 Investigational New Drug Application
    - 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:
    - Investigator Responsibilities
    - ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial
    - FDA Guidance on Decentralized Clinical Trials

5.15 Site Staff Training Logs

According to ICH GCP, "each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks". Staff training logs or other training forms are used to document staff training.

Requirements

- Appropriate study related training (i.e., Protocol, amendments, MOP, device manual, etc.), Good Clinical Practice, and Protection of Human Subjects must be completed prior to performing delegated responsibilities.
- Additional trainings may be required based on the responsibilities delegate including Dangerous Goods Training and database training (if applicable).
- All staff noted on the Site Signature List/Delegation of Authority Log are expected to have training documentation on file according to DMID policies.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Staff clinical research and study training, etc.	X	N/A	Documentation should be available upon request

Guidance

- Documentation of training should be completed timely and updated throughout the course of the study as new information becomes available.

Resources

- Federal Regulations:
    - 21 CFR 312 Investigational New Drug Application
    - 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:
    - Investigator Responsibilities
    - ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.16 Subject Screening/Enrolling Logs

The subject screening log documents all subjects that signed an informed consent for the study; both those that resulted in screen failures and those that were enrolled/randomized in the trial. The Subject screening/Enrollment Log should not include subjects that did not sign an informed consent.

Requirements

- Screening
    - Subjects cannot be added to the screening log until they have signed an informed consent document.
    - A study number or screening number must be documented on this log for every subject screened.
    - All subjects that signed an informed consent document must be entered into the data management system.

- All screen failures must be documented.

- Enrollment
  - For all enrolled subjects, the subject number and date of enrollment must be collected at a minimum.
  - Additional data may be required on the enrollment log as required by the protocol and/or MOP.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Subject Screening/Enrollment Log	X	X	Monitor to collect at Study Closeout All personal identifiable information (PII) must be redacted before document is uploaded to the N-CRMS portal. Number of subjects noted on the screening log should equal the number of subjects screened and enrolled in the database.

Guidance

- 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.

Resources

- Federal Regulations:
- 21 CFR 312 Investigational New Drug Application
- 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:

- Investigator Responsibilities
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.17 Temperature Log(s)

The temperature logs for all equipment storing study related product or specimens should document the storage conditions throughout the trial. The logs will be used to ensure conditions are acceptable. All temperature logs should be made available for review during monitoring visits and regulatory inspections.

Requirements

- Temperature logs being maintained for study product (e.g., including ambient/room storage, refrigerators, and freezers) must follow the specifics from the DMID-approved Study Product Management Plan (SPMP).
- Temperature logs should be maintained for any equipment used for storage of research specimens, this includes temporary storage such as incubators, etc. as required by the MOP/Protocol.
- All study-related items transported must comply with cold chain and custody requirements stated in the protocol, manual of procedures (MOP), and DMID Guidelines for Clinical Study product management.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Temperature Log	X	N/A	Maintained only at the site and made available upon request.

Guidance

- 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.

Resources

- Federal Regulations:
    - 21 CFR 312 Investigational New Drug Application
    - 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:
    - Investigator Responsibilities
    - ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.18 Study Product Records

The Study Product Records include several documents according to ICH GCP that are needed to document the appropriate use of study product or investigational product (IP) and placebo or comparator as necessary. Section 8 of ICH GCP E6 guidelines describe these documents including the Accountability Log, shipping records, and product label to document that investigational product(s) have been received and used according to the protocol at a site. Please reference the DMID Guidelines for Study Product Management for additional guidance.

Product/ Device Records:

- Study Product/ Device Accountability
    - Records documenting the receipt date, expiration date, quantity received, lot or batch numbers of all study products/devices, and a copy of the sample label.
    - Documentation should support that study product/device use was in accordance with the approved protocol. Records should include when it was used and the specific dosage/device the participant(s) received.
    - Records should show the final disposition of all unused study materials documenting that it has been returned to DMID Clinical Agent Repository (CAR), designated central repository, manufacturer, or destroyed.

- Records to verify cold chain for all materials (as applicable).
- Transfer records and shipping records for study product and any locally purchased drug, vaccine, diluent, or placebo (as applicable).
- For blinded studies, expiry dates and lot numbers are confidential to maintain blinding and are not entered onto the accountability log.
- If a study subject/participant must be unblinded for safety reasons, documentation of the process and approvals for the unblinding must be present.

Requirements

- Drugs/devices used for the study must be labeled investigational and differentiated from standard clinical inventory.
- If medications or supplies are sourced by the pharmacy or commercially, the storage and accountability requirements will be specified in the protocol and/or MOP.
- The accountability of study product needs to be in accordance with all DMID Product Support Team Guidelines.
- Documentation of site staff check of expiration of study product must be maintained as per the DMID Guidelines for Clinical Study Product Management.
- The Study Product Preparation Steps should be documented and include the times for each step so that protocol compliance, preparation, and storage can be assessed against the MOP and protocol.
- Temperature Logs should be kept for temporary storage equipment used to store product prior to dosing.
- The storage area should be locked/secure with access limited to authorized study staff only.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Photocopy of sample Device/Product Label for studies	X	X	Site to submit via N-CRMS SERD portal if not in the MOP

conducted under an IDE/IND			
Study Product Records: Accountability, receipts, dispensing, administration, and disposition	X	X	Monitor to collect at Study Closeout Study Product Records (may be kept in the research pharmacy to protect the blind).
Study Product Preparation Steps	X	N/A	Maintained only at the site and made available upon request.

Guidance

- Maintain accurate records documenting the date and amount of study product dispensed to the subject, the amount used, and, if applicable, the date and quantity of study drug returned by the subject.
- For blinded studies, expiry dates and lot numbers are confidential to maintain blinding.
- The inventory balance recorded on the study product disposition record should agree with the actual inventory on hand. Results of the physical inventory are recorded on the study product disposition record; if the recorded balance and actual inventory are not the same, the reason must be determined and recorded on the disposition record.
- Physical inventories are recommended monthly during active enrollment and on a regular basis thereafter that should be documented as recommended by DMID-Product Support Team. Investigators should verify the requirements in the Protocol or study Manual of Operational Procedures.
- The Monitor will review study product accountability records throughout the lifecycle of the protocol and collect the final disposition and accountability records.
- Records may be maintained via hard copy, electronically, or a combination of both.

Resources

- DMID-CROMS Study Product Information
- DMID Guideline for Clinical Study Product Management
- DMID Product Support Team Information:
- Address:

DMID Product Support Team,

Office of Regulatory Affairs, Division of Microbiology and Infectious Diseases,

National Institute of Allergy and Infectious Diseases

5601 Fishers Lane

Bethesda, MD 20892-9826

(express delivery: Rockville, MD 20852)

Telephone: (301) 496-2126

Email: DMIDProductSupportTeam@niaid.nih.gov

5.19 Secondary Use/Specimen Retention Records

Specimen Retention records document the location and ID of the samples that have been retained by the site or sponsor for secondary use. This includes any repeated assays or future testing as identified in the study informed consent.

Requirements

- Records must be maintained for all samples collected during the conduct of the study for secondary research.
- Once a study is complete and the clinical study report has been submitted to the FDA, documentation of instructions from DMID regarding the relocation, destruction, or anonymization of any clinical specimens remaining at a site must be filed.
- Maintain records of destruction of the unused specimens after the CSR or final study report where participants did not agree to secondary research.

  - The method of destruction or anonymization must be part of the file. If it is not part of the file, the site-specific SOP must also be part of the file.
- If consent for secondary use is obtained, it is recommended that a list of PID numbers granting future use is maintained in the regulatory file.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Laboratory Specimen tracking/retention log	X	X	A copy collected at Study Closeout * Sites retaining specimens after the close-out visit must submit a copy of the specimen tracking log to the EDCO at the time of the IRB study closure submission.
Site storage temperature log	X	N/A	N/A

Guidance

- 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.

Resources

- Federal Regulations:
  - 21 CFR 312 Investigational New Drug Application
  - 21 CFR 812 Investigational Device Exemptions
- Federal Guidance:
  - Investigator Responsibilities
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.20 Site Monitoring

Site monitoring documents are essential components of regulatory binder that document monitoring activities over the course of the study.

Requirements

- The site will maintain a protocol-specific site monitoring visit log documenting each monitoring visit.
- Copies of all monitoring visit documents should be stored within the site regulatory file.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Monitoring Visit Documentation	X	X	Filed in the DMID Sponsor file by the Monitor
Monitoring Log	X	X	Monitor to collect at Study Closeout

Resources

- Federal Regulation:
  - 21 CFR 312.53 Selecting investigator and monitors
  - ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial

5.21 Study Manual(s) of Operational Procedures

A Manual of Operating Procedures (MOP) is a handbook dedicated to detailing a study's operations and conduct to facilitate consistency in protocol implementation and data collection across sites.

Requirements

- Study-specific procedures or Manual of Operational Procedures (MOP) maintained throughout the lifecycle of the study.
- The document (s) must have a version number and date. All final sponsor-approved versions are to be maintained in the study records.
- If the MOP is not stored in the regulatory file, a memo should note the storage location of all versions of the MOP.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Manuals of Operational Procedures	X	X	

Resources

- Federal Regulation:
  - Federal Regulations for Clinical Investigators
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial
- DMID Guidelines for Clinical Study Product Management

5.22 Correspondence (Relevant Communications)

All communication should be evaluated for relevance and significance. Documents determined to be relevant are those that are important to reproducing the activities of preparation for, implementation, or closure of the study.

Requirements

- Internal correspondence should be maintained separately from external correspondence and as required by site-level processes.

- External correspondence (e.g., with sponsor, SDCC or any regulatory body)
    - All correspondence (e.g., e-mails, letters, faxes, memoranda, and phone contacts) between the investigator or research staff and external entities relating to the clinical conduct of the study, especially correspondence pertaining to protocol decisions, serious adverse events, deaths, Protocol Deviations, and protocol modifications should be in the regulatory file.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Correspondence – External (e.g., with Sponsor)	X	X	N/A
Correspondence – Internal	X	N/A	N/A

Guidance

- For relevant emails, all necessary threads must be maintained including attachments and responses.
- For hard copy documents, the integrity of communication should be maintained, and a certified copy should be provided to DMID.
- Any document provided for the sponsor files should be titled with the purpose (significance of the e-mail relating to the trial's reconstruction) and date.
- Correspondence relating to financial matters is confidential and should not be kept in the regulatory file but should be kept in a readily available site file.

Resources

- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial
- DMID Guidelines for Clinical Study Product Management
- DMID Guidelines for Relevant Communications For The Electronic Trial Master File (eTMF)

5.23 Notes to Study File

Notes to the Study File (NTF) are written to clarify or add information regarding site-specific regulatory file requirements and source documentation standards; document and address any issue that is protocol and/or site specific that cannot be resolved without a change from previously approved procedures; describe the immediate and preventative corrective action(s) taken to resolve the issue; and explain a site-specific process that is not documented in any previously approved procedures.

Requirements

- NTFs should be:
    - Typed (not handwritten) and should include the elements from the NTF template found in the DMID NTF guidelines.
    - Kept on file in the site regulatory file.
    - Made available to the clinical site monitors reviewing the site's documents and procedures.
    - Written by the individual responsible for its content, and the author should sign and date the note. If the Note to File pertains to an item for which the PI is responsible (subject protection, data integrity, etc.), the PI should co-sign and date the note to acknowledge his/her awareness of the issue.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Notes to Study Files (NTF)	X	X	Site staff will send a PDF of the signed and dated NTF to the following groups: • DMID CPM • DMID Office of Clinical Research Affairs (OCRA) • DMID Product Support Team (as applicable • Data Coordinating Center (as applicable)

Resources

- DMID Notes to the Study File Guideline and Template

5.24 Reporting

The reporting section of the regulatory file should include notification by the investigator to sponsor and IRB(s)/IEC(s) of serious adverse events, adverse drug reactions, and other safety information in accordance with protocol requirements and applicable regulations.

Requirements

- Serious Adverse Event Reporting Form submission:
    - For DMID, any adverse event that meets a protocol-defined serious criterion must be submitted within 24 hours of site awareness on the appropriate Serious Adverse Event (SAE) Form.
    - Upon submission of SAE, sites must retain a copy of the completed SAE form (e.g. PDF or other format) in the regulatory file.

- Additional contacts and local regulatory authorities should be notified as specified in the protocol.
- All SAEs must be recorded and reported to DMID, as stated in the Protocol, and to the local IRB/IEC per its policy/guidance.
- Both initial correspondence and follow-up reports must be included when submitting safety reports to DMID and the IRB/IEC.
- The following supporting documents with PII removed may be submitted if specifically requested by DMID-CROMS Pharmacovigilance to be included, if applicable:
  - Progress notes
  - Hospital records
  - Clinical records
  - Medication administration records
  - Autopsy reports
  - Death certificates
  - Confirmation documents that SAE reports were submitted to DMID/IND sponsor, either:
    - Fax confirmation
    - E-mail printout
    - Cover memo (use if SAE was report via telephone)

- Suspected Unexpected Serious Adverse Events Reporting (SUSAR):
  - If the IND sponsor provides IND Safety Reports to clinical sites participating in the same study or to sites under different studies using the same study product, then these should be in the regulatory file.

- SUSARs and the associated cover letter are provided to the sites through email and via the Safety Distribution Mailer (SDM). The sites will file the SUSARs in the site regulatory file.
- Monitors will verify all SUSARs are filed in the site regulatory file during each site monitoring visit.
- Site staff will submit the SUSAR to the local IRB/IEC as per their local requirements. A copy of the submission documentation and IRB responses or acknowledgement (as applicable) will be filed in the site regulatory file.
- When a Central IRB or Single IRB is used, the Sponsor or Single IRB Responsible Organization will submit the SUSAR to the Central IRB/Single IRB on the site's behalf.

- Unanticipated Problems

  Unanticipated problems, in general, are considered any incident, experience, or outcome that meets all the following criteria:
  - Unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents.
  - Related or possibly related to participation in the research.
  - Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.
  - Unanticipated problems need to be reported to DMID according to the protocol.

- Protocol Deviation
  - All protocol deviations must be reported according to the protocol.
  - Either a completed copy of a Protocol Deviation (PD) Form or a contemporaneous log of protocol deviations must be maintained in the regulatory file.

- The completed protocol deviation form may also be considered a source for certain data elements and should be maintained with other source documents.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Safety Reports/SUSARs	X	X	IND Safety reports – initial and follow up; correspondence to IRB/IEC.
Serious Adverse Event Reporting Form	X	X	N/A
Protocol Deviation Form	X	X	N/A
Unanticipated Problems	X	X	N/A

Guidance

- If study data is captured by the DMID Statistical and Data Coordinating Center (SDCC) contractor, protocol deviations will be posted to the contractor's web portal. No other reporting is required. The SDCC will automatically notify DMID of the reported protocol deviation.
- For those studies not utilizing the DMID Statistical and Data Coordinating Center (SDCC) electronic data capture system (e.g., AdvantageEDC™), protocol deviations must be reported to DMID via the Protocol Deviation Reporting on the DMID-CROMS Clinical Research Support.
- IND/IDE sponsors are required to notify sites of Safety Reports (e.g. IND/Unanticipated Adverse Device Effects (UADE) submitted to the FDA. The Principal Investigator is responsible for submitting Safety Reports to the IRB/IEC according to their guidelines and filing copies in the site files.

Resources

- Federal Regulation:

  - 21 CFR 312.53 Selecting investigators and monitors
  - 21 CFR 312.66 Assurance of IRB review
- Federal Guidance:
  - Establishment and Operation of Clinical Trial Data Monitoring Committees
- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial
- DMID-CROMS Protocol Deviation Reporting
- DMID Serious Adverse Event (SAE) Form
- DMID SAE Form Guidelines

5.25 Sample Case Report Forms

Sample Case Report Forms (CRFs) should be on file to document the protocol required information reported to the sponsor on each trial subject.

- Case Report Forms:
  - A printed, optical, or electronic document designed to record all the protocol required information to be reported to the sponsor on each study participant.
  - The regulatory file should Include a blank copy of all versions of:
    - CRFs
    - Electronic Case Report Forms (eCRFs)
    - Data Collection Forms (DCFs)
    - Source document worksheets
    - Subject diaries
    - Memory aids
    - Other forms used for collection of study data, including forms for screening study subjects provided by the Sponsor.

- At the end of the trial, an electronic version or hard copies of all final versions of CRFs and/or eCRFs must be added to the file.

Maintenance

Document	Site File	DMID Sponsor File	Other information
Case Report Forms/eCRFs	X	X	DMID contract Statistical and Data Coordinating Center may retain Sponsor copy

Guidance

- The difference between data collection sheets (synonyms: forms, worksheets) and case report forms is data collection sheets typically act as source documentation. Protocol-required information is transferred to eCRFs or CRFs from data collection sheets unless it has been predefined in the protocol that data will be directly entered into the eCRF.
- The study protocol must include a statement as to which eCRFs/CRFs will function as a source document(s) for the study.
- For study purposes, eCRFs/CRFs must not be maintained by name or other personal (non-study) identifier. Subject names corresponding to a study ID code must not be entered into the database or shared with anyone.
- Additional items related to data management may be maintained on site but outside of the regulatory binder:
  - Items like the ID Code List that details personal identifiers for each screened/enrolled study subject/participant.
  - This list allows the investigator/institution to reveal the identity of any subject, if required.

Resources

- Federal Regulation:

  - 21 CFR 312.53 Selecting investigators and monitors
  - 21 CFR 312.62 Investigator recordkeeping and record retention

- Federal Guidance:
  - Computerized Systems Used in Clinical Investigations
  - Electronic Source Data in Clinical Investigations
  - FDA Inspections of Clinical Investigators

- ICH GCP E6 Section 8. Essential Documents for the Conduct of a Clinical Trial