

Division of Microbiology  
and Infectious Diseases

# REGULATORY FILE DOCUMENT GUIDELINES

**Version 5.10 February 10, 2004**



National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
Department of Health and Human Services

The Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), and National Institutes of Health (NIH) supports through both contract and grant mechanisms, a large number of clinical studies and trials. This guidance is provided to aid DMID supported investigators in establishing a regulatory file of essential documents for each of their studies. Sections with specific documents are presented as well as sample forms. Study specific forms may be provided by the study management in a multicenter trial. Sites may organize their documents differently, but all of the essential documents must be in the file.

A regulatory file must be established at the beginning of each study and kept updated throughout the life of the study. Study files (except for future use consent forms) must be maintained for a minimum of two years after a licensing application has been filed with the Food and Drug Administration or until two years have elapsed since the formal discontinuation of clinical development of the investigational product. The site must contact DMID for authorization prior to the destruction of any study records.

During or after the trial, if parts of the regulatory file are not kept centrally, a notation must be placed in that part of the file or a list provided of where those documents are kept and in whose custody.

The assumption in this document is that the study will be performed under a US IND and that DMID will be the IND sponsor. In cases where DMID is not the IND sponsor, the investigator still has reporting/submission requirements to an IND sponsor. The principles of setting up a regulatory file are the same for studies not under IND.

The presented guideline has been assembled by using the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines and incorporating the regulatory requirements for performance of a study under 21 CFR 312. For more information on these guidelines and requirements, please reference the DMID GCP handbook or the websites for ICH and FDA ([www.ich.org](http://www.ich.org) and [www.fda.gov](http://www.fda.gov)). Search engines will take you to various regulations and the GCP guidelines. DMID requires adherence to GCP standards for all studies sponsored by the Division.

According to the ICH guidelines Section 8: "Essential Documents are those documents that 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 regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and integrity of the data collected."

Sites that are participating in multicenter or industry-sponsored IND trials should consult their Manual of Procedures for specific instruction and forms for the regulatory file.

# CLINICAL STUDY REGULATION DOCUMENTS

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CLINICAL STUDY REGULATION DOCUMENTS

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## **ABBREVIATIONS**

AE	Adverse Event
CAP	College of American Pathologists
CLIA	Clinical Laboratories Improvement Amendments
CRFs	Case Report Forms
CVs	<i>Curricula vitae</i>
DMID	Division of Microbiology and Infectious Diseases
DMID-CAR	DMID – Clinical Agents Repository
FWA	Federalwide Assurance
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
MOP	Manual of Procedures
OCRA	Office of Clinical Research Affairs
ORA	Office of Regulatory Affairs
PI	Principal Investigator
PID	Participant Identifier
SAE	Serious Adverse Event
SR	IND Safety Report

## **ESSENTIAL DOCUMENTS**

The following statements apply to all documents listed in this guideline:

This Regulatory Document Guideline reflects the submission and maintenance of regulatory documents supporting clinical trials. This guideline is not intended to reflect the entire review process from concept to programmatic oversight that must take place during development and execution of a clinical study.

Protocols, consents, protocol amendments, Manual of Procedures, and site registration documents must be sent to DMID through the Protocol Champion for the study or a designated contractor. Specific directions for Serious Adverse Events will be delineated in the Protocol. The Office of Regulatory Affairs (ORA) must receive copies of all IND regulatory documents. To meet DMID's IND sponsorship obligations, ORA may request documents directly from the sites.

Monitoring report letters to PIs will direct where documents not previously collected need to be sent.

**Essential Documents Maintenance List**

<b>Document</b>	<b>Maintain in:</b>
Study Identification	Site Regulatory File Only
Federalwide Assurance	Site Regulatory File Only
Form FDA 1572 (if under IND)	Site Regulatory File and ORA
Study Personnel Signature/ Responsibility List	Site Regulatory File (Monitor to Collect at Study Close-out Visit)
Study Specific Procedures Manual Manual of Procedures	Site Regulatory File and ORA
Subject Screening/Enrollment Log	Site Regulatory File Only
ID Code List	Site Regulatory File Only
Test Article Accountability Records	Site Regulatory File (Monitor to Collect at Study Close-out Visit)
Temperature Log	Site Regulatory File Only
Monitor Log/Monitoring Reports	Site Regulatory File and ORA (reports only)
Specimen Retention Records	Site Regulatory File (Monitor to Collect at Study Close-out Visit)
CRFs	Site Regulatory File and ORA IRB/IEC (per their guidelines)
Regulatory Review History	Site Regulatory File Only
IRB Approvals for: Protocols, Protocol Amendments, Informed Consents, Advertisements and Subject Information Materials	Site Regulatory File and ORA
Protocols	Site Regulatory File and ORA (after IRB/IEC approved)
Informed Consents	Site Regulatory File and ORA (after IRB/IEC approved)
Approvals from Collaborating Research Laboratories	Site Regulatory File and ORA (per criteria noted on Page 18)
Advertisements and Subject Information Materials	Site Regulatory File and ORA (after IRB/IEC approved)

**Essential Documents Maintenance List (con't)**

<b>Document</b>	<b>Maintain in:</b>
Investigator's Brochure (IB)/Addendums/ Package Insert	Site Regulatory File ORA (verification that documents were submitted to the IRB/IEC)
Periodic Reports and Annual Renewals	Site Regulatory File and ORA (once acknowledged by the IRB/IEC)
Final Report to the IRB/IEC	Site Regulatory File and ORA
Final Report to Sponsor	Site Regulatory File and ORA
Local Regulatory Approvals	Site Regulatory File and ORA
Serious Adverse Events (SAEs)	Site Regulatory File and ORA (SAEs <b>must</b> be reported to DMID and the IRB/IEC)
IND Safety Report (SR) (IND Safety Reports are SAEs that have been reported to the FDA)	Site Regulatory File and ORA (Sites must submit to their IRB/IEC as directed by the IND Sponsor)
Protocol Deviations	Site Regulatory File and ORA (Sites to submit to their IRB/IEC per their IRB/IEC policy) (See Page 25)
<i>Curricula vitae</i>	Site Regulatory File: All study personnel  ORA: PI and all sub-investigators listed on Form FDA 1572
Medical Licenses	Site Regulatory File: Current medical licenses for the PI and all sub-investigators listed on Form FDA 1572  ORA: PI license (if MD) or license of primary physician associated with the study (if the PI is not an MD)
Laboratory Normals and Accreditations	Site Regulatory File and ORA
Site Correspondence with the Sponsor	Site Regulatory File Only
Telephone Contact Report	Site Regulatory File Only
Internal Correspondence	Site Regulatory File Only
Notes to File	Site Regulatory File Only
Site Specific Information	Site Regulatory File Only

## STUDY IDENTIFICATION

This section will contain the identification of the study site, including name of the Principal Investigator (PI), study site location(s), Division of Microbiology and Infectious Diseases (DMID) Protocol Number, Investigational New Drug (IND) number and Protocol title. Include the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Protocol number and any other identifying numbers if they are different from the DMID Protocol number.

Any contact information for large or multicentered studies should also be included here.

Please complete a new form when any of the information changes. Retain a copy of the previous version in the regulatory file.

**Please complete a study identification form for each Protocol at each separate study site.**

A sample form is provided.

STUDY IDENTIFICATION

IND No.: \_\_\_\_\_  
DMID PROTOCOL No.: \_\_\_\_\_  
IRB/IEC STUDY No.: \_\_\_\_\_  
DATE STUDY STARTED: \_\_\_\_\_  
DATE STUDY COMPLETED: \_\_\_\_\_  
FWA ASSURANCE No.: \_\_\_\_\_

PROTOCOL TITLE: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

PRINCIPAL INVESTIGATOR: \_\_\_\_\_

SITE LOCATION: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

PHONE: \_\_\_\_\_

FAX: \_\_\_\_\_

**SAMPLE FORM**

FEDERALWIDE ASSURANCE

(FWA)

Maintain a record of your Institutional Review Board's (IRB) Federalwide Assurance number in the regulatory file. Be sure to have the expiration date for the Assurance as well. You may obtain this information by searching the following website:

<http://ohrp.cit.nih.gov/search/asearch.asp#ASUR>

FORM FDA 1572 (if under IND)

If the study is under a US IND, a Form FDA 1572 is required. The Form FDA 1572 must be signed and dated by the Principal Investigator and include the names of all sub-investigators for the study and location of all sites where the study will be conducted (all sites where subjects will be examined). Be sure to complete Sections 1 – 11 of the Form. For Section 4, only clinical laboratory facilities need be included. Research laboratories **must be identified in the Protocol**, but not on the Form FDA 1572. Sub-investigators are usually physicians or other professionals responsible for making Protocol decisions. Independent Safety Monitors or DSMB members are not considered sub-investigators. Please ensure that the DMID Protocol Title and Protocol Number in Section 7 are correct.

A new form must be completed when the following occurs:

1. Change in Principal Investigator
2. Change in sub-investigator
3. Change in address of study site
4. Change in clinical laboratory
5. Change in Institutional Review Board

Keep all Versions, with the newest in front.

The weblink to the current Form FDA 1572 is:

<http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>

Previous Versions of Form FDA 1572 should not be used. The current Form FDA 1572 must be hand signed and hand dated on a double-sided form. The original signed and dated form may stay at the clinical site and a copy sent to DMID for ORA.

STUDY PERSONNEL SIGNATURE/RESPONSIBILITY LIST

The signature list must contain the signatures and initials of all study personnel, including those who are making entries or corrections on the case report forms, as well as all ancillary study personnel (e.g., laboratory personnel, data personnel, and pharmacy personnel). The signature list must include name, title, signature, initials, responsibilities, phone number, e-mail, 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 sign study documents. The list must be kept current.

**A completed copy of this form will be collected upon monitoring close out.**

A sample form is provided.

STUDY PERSONNEL SIGNATURE/RESPONSIBILITY LIST

PRINTED NAME	TITLE	SIGNATURE	STUDY TASKS	INITIALS	START DATE/ END DATE	ID CODE If applicable	PHONE # and E-MAIL ADDRESS														
	Principal Investigator																				
	Sub-investigator																				
	Sub-investigator																				
	Site Pharmacist																				
	Study Coordinator																				
<p>List individuals delegated study related tasks (ICH GCP 4.1.5). Signature/initials required for all persons authorized to make entries and/or corrections to Case Report Forms (ICH GCP 8.3.24). All personnel listed on Form FDA 1572 <u>must</u> be listed on this form. In addition, you may need to list other supporting study personnel. Update as personnel, roles and/or study tasks change. Original, completed form to be collected by Monitor at study closeout.</p>			<p>*Key Delegated Study Task Codes:</p> <table border="0"> <tr> <td>1. Obtain Informed Consent</td> <td>8. CRF Completion</td> </tr> <tr> <td>2. Obtain Medical History</td> <td>9. CRF Signature</td> </tr> <tr> <td>3. Perform Physical Exams</td> <td>10. Query Completion</td> </tr> <tr> <td>4. Inclusion/Exclusion Assessment</td> <td>11. Query Signature</td> </tr> <tr> <td>5. Drug Dispensing</td> <td>12. Update/Maintain IRB docs</td> </tr> <tr> <td>6. Drug Accountability</td> <td>13. Other _____</td> </tr> <tr> <td>7. Ongoing AE/Con Med Assessment</td> <td>14. Other _____</td> </tr> </table>					1. Obtain Informed Consent	8. CRF Completion	2. Obtain Medical History	9. CRF Signature	3. Perform Physical Exams	10. Query Completion	4. Inclusion/Exclusion Assessment	11. Query Signature	5. Drug Dispensing	12. Update/Maintain IRB docs	6. Drug Accountability	13. Other _____	7. Ongoing AE/Con Med Assessment	14. Other _____
1. Obtain Informed Consent	8. CRF Completion																				
2. Obtain Medical History	9. CRF Signature																				
3. Perform Physical Exams	10. Query Completion																				
4. Inclusion/Exclusion Assessment	11. Query Signature																				
5. Drug Dispensing	12. Update/Maintain IRB docs																				
6. Drug Accountability	13. Other _____																				
7. Ongoing AE/Con Med Assessment	14. Other _____																				

STUDY SPECIFIC PROCEDURES or MANUAL OF PROCEDURES

This section (or alternate location if other file system is used) must contain the study specific procedures (SOP) or manual, if applicable. **Each study specific procedure or Manual of Procedures (MOP) must have a Version number and date.**

All Versions used throughout the study must be maintained in the file.

The Study Specific Procedures or Manual of Procedures may include the Laboratory Procedures Manual, Laboratory Specimen Handling instructions, test article handling and/or preparation, and Protocol-specific instructions.

**Note: Deviations from the Study Specific Procedures or Manual of Procedures must be documented in a similar fashion as Deviations of the Protocol.**

### SUBJECT SCREENING/ENROLLMENT LOG

List all subjects considered for this study (e.g., all subjects from your IRB/IEC approved institution that you screened for this study). A study number or screening number must be used on this list and an ID Code list that links those numbers must be kept. For study purposes, records cannot be maintained by name or other personal (non-study) identifier.

**Note:** Subjects cannot be screened until they have signed an informed consent document or an IRB/IEC approved screening consent.

**Be sure to note the reason a subject was not enrolled, when applicable.**

For all subjects enrolled, minority and gender data must be collected per the reporting requirements for gender/minority tracking consistent with current NIH policy.

A sample form is provided.

DMID Protocol No.:  
Protocol Title:

6a

**SCREENING/ENROLLMENT LOG**

NO.	DATE SCREENED	SUBJECT IDENTIFIER*	SEX	MINORITY DATA	ENROLLED? Y/N	SUBJECT ID NO.**	REASON <u>NOT</u> ENROLLED
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							

\*Screening number

\*\*Study number if enrolled

Duplicate this page as needed, continuing the numerical sequence

**SAMPLE FORM**

DMID Regulatory File Guidelines  
Version 5.10 February 10, 2004

### ID CODE LIST

Per the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) guideline 8.3.21, the investigator/institution must maintain a confidential list of names of all subjects allocated to study numbers upon enrollment in a study. This list allows the investigator/institution to reveal the identity of any subject. The list should also contain subject contact information. For study purposes, study records must not be maintained by name or other personal (non-study) identifier.

The ID Code List is a confidential document that contains the information described above, remains at the site, and is for study use only. This list must be kept in a secure location. It must be kept in a different location than where subject Source Documents are kept. Please reference the location of the ID Code list.

Subject names corresponding to study ID codes must not be entered into the database or shared with anyone.

The site may also keep subject or demographic information that provides identifiable data, such as hospital identification numbers, social security numbers, and birthdates. This information may be considered a source document (i.e. birthdate) or maintained for contact and compensation purposes. In order to be in compliance with the Privacy Act of 1974, this information is not considered study data and is the property of the site. This information must not be entered into the study database or transferred from the site.



## TEST ARTICLE ACCOUNTABILITY RECORDS

This section (or alternate location if other file system is used) must include the following documentation:

1. Site copy of shipping receipts for test article. The provider of test article may require an investigator signed copy of the receipt.
2. Records documenting the receipt date, quantity, lot numbers of all test articles (if open label study), and a copy of the label.
3. Records showing that all study material that is unused at the end of the study has been returned to DMID-CAR, designated central repository, manufacturer, or destroyed per the IND sponsor's instructions. This must include the date of shipment (or destruction), means of shipment (or destruction), quantity, and lot numbers (if known) of the returned or destroyed study material.
4. Accurate records must be kept documenting the date and amount of test article dispensed to the subject, the amount used, and, if applicable, the date and quantity of study drug returned by the subject. The inventory balance recorded on the test article disposition record should agree with the actual inventory on hand. Results of the physical inventory are recorded on the test article disposition record; if the recorded balance and actual inventory are not the same, the reason must be determined and recorded on the disposition record.
5. Physical inventories are recommended on a monthly basis during active enrollment and on a regular basis thereafter and may be documented on the accountability log or as recommended by DMID-CAR. Time specific inventories may be required for certain Protocols. Investigators should verify the requirements in the Protocol or study Manual of Procedures.
6. Records to verify cold chain for all materials stored at other than room temperature.
7. Per ICH GCP 8.2.13, a copy of the test article sample label to document compliance with applicable labeling regulations and appropriateness of instructions provided to subjects.
8. Copy of any locally purchased drug, vaccine, diluent, or placebo label.

## TEST ARTICLE ACCOUNTABILITY RECORDS

**Note:** Unless specifically directed otherwise, used test article vials/containers should never be destroyed until the monitor has completed accountability. After the monitor verifies the site's test article accountability, the monitor will instruct the site to destroy used test article vials per the site's hazardous waste policies, unless otherwise directed.

Disposition of any unused vials remaining at the end of the study will be determined by DMID.

Sample forms for receipt, disposition at the end of a study, accountability records, and refrigerator/freezer logs are provided. These sample forms can be modified as necessary for your study. Some multicenter studies may include a standard form in the Manual of Procedures that should be used.

For blinded studies, expiry dates and lot numbers are confidential to maintain blinding and are not entered onto the accountability log.

**Transfer of test article from one study to another is not allowed.** In the rare cases where an exception is granted, a site must obtain authorization from DMID (may include getting permission from the manufacturer) prior to transferring study drug from one Protocol to another Protocol using the same test article. Documentation of the authorization of transfer must be included in the Regulatory File and the transfer must be reflected on the Test Article Accountability Log.

**The monitor will collect the final disposition and accountability records at the close-out monitoring visit.**

**RECEIPT OF TEST ARTICLE**

SITE: \_\_\_\_\_

PROTOCOL NO.: \_\_\_\_\_

INVESTIGATOR: \_\_\_\_\_

TO BE COMPLETED BY SUPPLY SOURCE

NAME OF SUPPLIER: \_\_\_\_\_

LABEL CODE	LOT/LABEL NO.	DESCRIPTION	UNIT SIZE	QUANTITY	INITIALS

TO BE COMPLETED BY SITE

LABEL CODE	LOT/LABEL NO.	DESCRIPTION	UNIT SIZE	QUANTITY	INITIALS

- |   |          |          |
|---|----------|----------|
| 1. Was/were test article(s) received undamaged?                   | Yes      | No       |
| 2. Has the shipment temperature appeared to have been maintained? | Yes      | No       |
| 3. Was a temperature monitor included in the shipment?            | Yes      | No       |
| 4. If "Yes," was the temperature monitor readable at the site?    | Yes      | No       |
| 5. If "Yes," what was the readout?                                | Min.____ | Max.____ |

I HEREBY ACKNOWLEDGE THAT THE TEST ARTICLES LISTED ABOVE WERE RECEIVED ON

\_\_\_\_\_ AT \_\_\_\_\_ AM/PM  
 (MM/DD/YY)

\_\_\_\_\_  
 SIGNATURE

**SAMPLE FORM**



Site: \_\_\_\_\_

9c

### Test Article Accountability Record

<b>Protocol #:</b>	<b>Protocol:</b>			<b>Product</b> <i>(test article/placebo/diluent/product name):</i>
<b>Packaging:</b> <i>(vial/bottle/carton/kit)</i>	<b>Manufacturer:</b>	<b>Lot number:</b>	<b>Storage Temperature:</b>	<b>Name/Strength/Dosage Form:</b>
<b>Received by:</b>		<b>Date of Receipt (mm/dd/yy)</b>	<b>Number received</b> <i>(vials/containers/kits):</i>	<b>Expiration</b> <i>( if known):</i>

Date mm/dd/yy	PID or Vial No. Dispensed (for)	Quantity Dispensed	Received/ Dispensed By	Comments	Balance Forward	Date of Physical Inventory
<b>End Balance →</b> <i>(take forward to next page)</i>						

Page \_\_\_\_\_ of \_\_\_\_\_

*A new form should be started for each new shipment of product.*

**SAMPLE FORM**



**DISPOSITION OF TEST ARTICLE AT END OF TRIAL**

SITE: \_\_\_\_\_

PROTOCOL: \_\_\_\_\_

INVESTIGATOR: \_\_\_\_\_

I HEREBY ACKNOWLEDGE THAT THE REMAINING TEST ARTICLES LISTED BELOW WERE DESTROYED ON \_\_\_\_\_  
(MM/DD/YY)

TEST ARTICLES WERE DESTROYED. SPECIFY METHOD:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

LABEL CODE	LOT/LABEL NO.	DESCRIPTION	UNIT SIZE	QUANTITY	INITIALS

\_\_\_\_\_  
SIGNATURE

\_\_\_\_\_  
(MM/DD/YY)

\_\_\_\_\_  
SIGNATURE

\_\_\_\_\_  
(MM/DD/YY)

**SAMPLE FORM**

### TEMPERATURE LOG

This section (or alternate location if other file system is used) must include the temperature log for all refrigerators/freezers that hold study-related items (examples: vaccine, drug, study specimens).

Be sure to monitor any refrigerator/freezer containing test article or study specimens on a daily basis during the normal work week.

Use a different page for each refrigerator/freezer that holds study-related items.

A sample form is provided.

# TEMPERATURE LOG

SITE: \_\_\_\_\_

REFRIGERATOR ID#: \_\_\_\_\_

REQUIRED TEMP: \_\_\_\_\_

FREEZER ID#: \_\_\_\_\_

ACCEPTABLE RANGE: \_\_\_\_\_

YEAR: \_\_\_\_\_

ENTER TEMPERATURE AND INITIALS DAILY

	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

NOTE: Cross out weekends and Holidays.

**SAMPLE FORM**

# TEMPERATURE LOG

SITE: \_\_\_\_\_

REFRIGERATOR ID#: \_\_\_\_\_

REQUIRED TEMP: \_\_\_\_\_

FREEZER ID#: \_\_\_\_\_

ACCEPTABLE RANGE: \_\_\_\_\_

YEAR: \_\_\_\_\_

ENTER TEMPERATURE AND INITIALS DAILY

	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
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21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

NOTE: Cross out weekends and Holidays.

**SAMPLE FORM**

### MONITOR LOG/MONITORING REPORTS

This section (or alternate location if other file system is used) must include a list of study site visits made by external monitors and a copy of all site visit letters and reports. For the Monitoring Log, the designated monitor will "sign-in" as each site visit is made and the study site designee must countersign. A new Monitor Log must be utilized at each different study site for each Protocol.

Any correspondence (letters/e-mails/phone records) concerning site monitoring visits, either to or from the site monitor or the sponsor, should also be included here.

A sample form is provided.



### SPECIMEN RETENTION RECORDS

Per ICH GCP Guideline 8.3.25, maintain a record of the Protocol-specified retained body fluids/tissue samples (if any) to document the location and identification of retained samples if assays need to be repeated.

**The monitor will collect this record at the close-out monitoring visit.**

Once a study has been completed and the final report has been submitted to the FDA, consult with DMID regarding the relocation, destruction, or anonymization of any remaining clinical specimens. Unused specimens must be destroyed or anonymized unless consent has been granted for future use of stored specimens.

- If consent for future use is not granted, then a method of destruction or anonymization must be part of the file. If samples are to be anonymized, the SOP must also be part of the file.
- If consent for future use is granted, then a list of PID numbers and a certified copy of the consent granting future use needs to be maintained in the regulatory file.

Records must be maintained for all samples released for future use not stipulated in the Protocol along with a copy of the IRB Approval for that use. IRB Approval must be obtained from both the center with custody of the samples and the user institution, if different.

### CASE REPORT FORMS

Per ICH GCP Guideline 6.4.9, the Protocol should have a description of the trial design that should include: “The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of the data) and to be considered source data.” Therefore, if any of the forms will be used as source documents, this must be stated in the Protocol.

**All documents must have a Version number and date.**

**Paper CRFs:** Include in this section a blank copy of all final (actually used) versions of case report forms (CRFs), subject diaries, or other forms used for entering study data, including forms for screening study subjects. Include full copies of all blank versions - newest in front.

**eCRF Studies:** All versions (actually used) of the Source Document Workbook that is provided by the Sponsor must be kept in this section. Dated documentation of all changes to the database during the active period of the trial must be maintained. At the end of the trial, a CD, disk, or hard copies of all final versions of case report forms (eCRFs) must be added to the file.

# **IRB/IEC REGULATORY SUBMISSIONS**

### REGULATORY REVIEW HISTORY

This section should include a listing of all documents submitted to the IRB/IEC, the Version number, Version date, a description of the change (if applicable), and the date of submission.

**Prepare a separate entry on the Regulatory Review History Form for each IRB/IEC submission for the study, if applicable.**

A sample form is provided.



### SUBMISSION LETTER/SUBMISSION PACKAGE/IRB/IEC APPROVAL

This section (or alternate location if other file system is used) must include a copy of the original IRB/IEC approved Protocol for the study and any subsequent IRB/IEC approved revisions/amendments to the Protocol. Include full copies of all final versions – newest in front.

**Starting with the original Protocol and each Protocol revision or amendment afterward, maintain the ENTIRE PACKET PHYSICALLY TOGETHER in the file – the submission letter, submission package, any response to stipulations, comments, or questions, and the final IRB/IEC Approval.**

**All documents must have a Version number and date. Suggestion for all IRB/IEC submissions: The memo to the IRB/IEC should state clearly what documents are being submitted for review, including Version number and date of all Protocol, Informed Consents, advertisements, and amendments. If known, also include the date of the IRB/IEC review meeting.**

To facilitate verification of regulatory compliance, DMID recommends that the following bulleted items be identified in the IRB/IEC Approval letter. If these elements are not included in the Approval letter, please write a note to the file indicating the items approved, including Version and date of all submitted documents.

- At a minimum, the IRB/IEC Approval letter should contain the following, per GCP Guideline 3.1.2:
  - DMID Protocol name and number, clearly identifying the trial
  - Approval date
  - A list of the documents approved
- In addition, DMID suggest these be included:
  - IRB/IEC chairperson or designee's signature
  - Should be addressed to the PI
  - Should list all sites covered by IRB/IEC Approval
  - Version number and date of documents submitted

**Note:** If contingent Approval is granted, evidence of final Approval must be present before the study can be implemented.

## PROTOCOL AND PROTOCOL AMENDMENTS

This section (or alternate location if other file system is used) must include a copy of the original IRB/IEC approved Protocol for the study and any subsequent IRB/IEC approved revisions/amendments to the Protocol. Drafts that were never submitted to the IRB do not need to be maintained.

**All documents must have a Version number and date.**

Please note the following:

- Foreign Regulations for non-US sites and non-DMID IND sponsored Protocols may require that the Investigator(s) sign the Protocol.
- If the Principal Investigator, any sub-investigator, study coordinator, or study team member is a member of the IRB/IEC, documentation must be in the file of their voting abstention for all Approvals relating to this Protocol. Examples: a letter from the IRB 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.
- Protocol changes must be approved by DMID and the IRB/IEC prior to implementation unless the change is intended to eliminate an apparent immediate hazard to subjects.
- Sites must obey any local or country-specific regulatory authorization relating to the Protocol.

### CONSENT FORMS

This section (or alternate location if other file system is used) must include a copy of the original IRB/IEC approved consent forms for the study and any subsequent IRB/IEC approved revisions/amendments to the consent forms. This section must also include Assents for Minors or other consent addenda, if applicable. Include full copies of all final versions - newest in front. Drafts that were never submitted to the IRB do not need to be maintained.

**All documents must have a Version number and date.**

Other consent forms: copies of screening consents, future use consents, or consents for procedures mandated by the study are also maintained in this file.

If any Consent Form is prepared in a language other than English, include copies of the translated Consent Form in the Regulatory File with copies sent to ORA.

**Note:** Consents for future use must be maintained for the lifetime of the sample and 2 years post-closure of any study for which the samples have been used.

### COLLABORATING RESEARCH LABORATORIES

If identifiers such as names, hospital numbers, or pathology accession numbers permit specimens to be linked to individual people and perhaps also to associated medical information, then IRB Approval must be obtained to conduct research with these specimens. If identifiable samples are to be sent to other collaborators, IRB Approval must be obtained by both your IRB and the collaborator's IRB. Information concerning samples sent to collaborators must be filed in this section (or alternate location if other file system is used).

**Note:** Identifiable specimens include any specimen that is linked to subject identity via a readily available identifier such as a name, social security number, medical record number, etc., or coded by use of classification that **links the samples to their source through a key available to the investigator or collaborator.**

**Note:** Commercial laboratories are not collaborators, but should be listed in the Protocol.

ADVERTISEMENTS AND SUBJECT INFORMATION MATERIALS

This section (or alternate location if other file system is used) must include all study advertisements (examples include television, radio, newspaper, and internet advertisements; and “Dear Patient” letters) or flyers used to recruit study subjects.

Regulations require IRB/IEC Approval prior to use of any study advertisement. Any revisions to an IRB/IEC approved study advertisement or flyer require IRB/IEC Approval prior to use.

INVESTIGATOR'S BROCHURE/PACKAGE INSERT

This section (or alternate location if other file system is used) must include a copy of the original and all revisions of the Investigator's Brochure (IB) and/or Package Insert (if test article is an approved product). All versions of the IB or Package Insert must be submitted to the IRB/IEC to aid in Protocol review and acknowledged by the IRB/IEC.

The IB must be available to all study staff. It is the site's reference to potential reactions and side effects that might be expected during use of the study drug.

The IB must be provided to the PI by the manufacturer or by DMID unless the test article is a licensed product and is purchased locally. If the test article is purchased locally, obtain a package insert for the regulatory file.

IND sponsors are required to notify sites of IND Safety Reports that have been submitted to the FDA. These IND Safety Reports must be submitted to the IRB/IEC and filed with the IB.

Any other informational letters issued by the manufacturer to investigators must also be filed in this section.

## PERIODIC REPORTS AND ANNUAL RENEWALS

This section (or alternate location if other file system is used) must include the Principal Investigator's periodic reports to the IRB/IEC and any other reports to the IRB/IEC, as well as annual and/or periodic Approvals from the IRB/IEC. Maintain the entire packet together in the file – the submission letter, submission report package, and IRB/IEC Approval. It is suggested that the newest packet should be in the front.

FINAL REPORT TO THE IRB/IEC

This section (or alternate location if other file system is used) must contain the Investigator's final report to the IRB/IEC upon completion/termination of the study. The basic requirements of the final report to the IRB/IEC are analyzed data; the number of subjects screened, enrolled, and dropped; and a listing of SAEs.

**Note:** This final report is not usually sufficient to serve as the final report for the IND sponsor.

### LOCAL REGULATORY APPROVALS

All other local, state, and/or special authorizations relating to the Protocol can be maintained in this section.

If the study is done outside of the United States, documentation of national approval for the conduct of the study must be collected and renewed per local regulations.

**IRB SAFETY SUBMISSIONS**

**IND SAFETY REPORTS**

SERIOUS ADVERSE EVENT REPORTING  
and  
IND SAFETY REPORTS

This section (or alternate location if other file system is used) must contain copies of the SAE report forms. All SAEs must be recorded and reported to DMID as stated in the Protocol.

**SAEs that are causally related, serious, and unexpected must be reported to the local IRB/IEC and DMID immediately.**

All other SAEs must be reported to the IRB/IEC per the IRB/IEC policy. Include the initial correspondence as well as follow-up reports to DMID and the IRB/IEC when notifying them of SAEs. Include supporting documentation (examples: progress notes, autopsy reports, death certificates). Copies of fax confirmation, e-mail printout, or cover memo that SAE reports were submitted to DMID and the IND sponsor, if applicable, need to be included in this section.

The IND sponsor may also provide IND Safety Reports to your site from other sites participating in the same or different studies using the same investigational product. These IND Safety Reports concern events that may be causally related to the product and must be submitted to the IRB/IEC.

## PROTOCOL DEVIATION REPORTING

(Formerly known as Protocol Violations and/or Protocol Deviations/Departures)

### **Protocol Deviations**

Protocol Deviations occur when there is non-adherence to the Protocol and includes Informed Consent, enrollment, and other occurrences of non-adherence to the Protocol.

**DMID does not allow any exemptions or eligibility criteria waivers for enrollment.** These are enrollment deviations.

Protocol Deviations:

- May result in a significant added risk to the study subject.
- Occur when the subject or investigator has failed to adhere to Protocol requirements impacting on enrollment eligibility, safety surveillance, endpoint outcomes, and test article handling and accountability.
- Occur when there is non-adherence to GCP.

All deviations from the Protocol must be addressed in study subject source documents. The documentation should include the reason(s) for the deviation and all attempts to prevent or correct them. For example, documentation of a missed visit would properly consist of a note explaining the missed visit and the site's attempts to locate the study subject to request that he/she come in to make up that visit.

The site must complete a DMID Deviation Form documenting each Protocol Deviation. The completed form must be sent to DMID unless specific instructions are provided by the study team or are included in the Protocol or Manual of Operations. If the IND sponsor is other than DMID, the form must also be sent to the sponsor according to their requirements. A completed copy of the DMID Protocol Deviation (PD) Form must be maintained in the Regulatory File as well as in the subject's source document. Copies of fax confirmation or e-mail printout that PD Forms were submitted to DMID and the IND sponsor, if applicable, need to be included in the Regulatory File. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

A sample form is provided.

**PROTOCOL DEVIATION**

IND NO.: \_\_\_\_\_

DMID PROTOCOL NO.: \_\_\_\_\_

SUBJECT NUMBER: \_\_\_\_\_

**Complete a new form for each Deviation from the Protocol.**

Date of Protocol Deviation (MM/DD/YY): \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Description of Deviation from Protocol: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_Reason for Deviation from Protocol: \_\_\_\_\_  
\_\_\_\_\_Did this Deviation result in an adverse event?  **No**  **Yes**Will the subject continue with the study?  **No**  **Yes**Does this Deviation meet IRB reporting requirements?  **No**  **Yes****Based on your IRB/IEC reporting guidelines, when does this Protocol Deviation need to be reported to your IRB/IEC?**

Should be reported promptly to the IRB.

Should be reported within 30 days of knowledge by the investigator.

Should be reported within 60 days of knowledge by the investigator.

Should be reported within 90 days of knowledge by the investigator.

Should be reported annually.

Does not require reporting.

Other reporting schedule. Please indicate \_\_\_\_\_

What steps were taken to resolve this Deviation and prevent reoccurrence? \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

COMPLETED BY (print and sign): \_\_\_\_\_

(MM/DD/YY) \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Investigator's Signature: \_\_\_\_\_ / \_\_\_\_ / \_\_\_\_ (MM/DD/YY)

Date Submitted/Faxed To: \_\_\_\_\_ (MM/DD/YY)

 **DMID** \_\_\_\_\_ / \_\_\_\_ / \_\_\_\_ **IRB** \_\_\_\_\_ / \_\_\_\_ / \_\_\_\_ **Data Center** \_\_\_\_\_ / \_\_\_\_ / \_\_\_\_ **Other, specify:** \_\_\_\_\_ / \_\_\_\_ / \_\_\_\_**SAMPLE FORM**

# **LICENSES and ACCREDITATIONS**

CURRICULA VITAE AND MEDICAL LICENSES

*Curricula vitae:* This section (or alternate location if other file system is used) must include complete and current *Curricula vitae* (CVs) for the Principal Investigator and all sub-investigators. A current CV must be dated within five years of the current date. Basic requirements of the CV include current work address, professional title, degrees, and current relevant licensure. Provide a copy of the CVs for the PI and all sub-investigators listed on the Form FDA 1572 to the IND Sponsor, and retain a copy in the regulatory file as noted above. For IND studies, copies of current CVs of additional sub-investigators must be added to the regulatory file when the Form FDA 1572 is revised. A copy must also be provided to DMID.

Medical Licenses: Provide a copy of the PI's current licensure to DMID. If the PI is not an MD, a medically responsible physician must be identified and current license collected. For IND studies, the PI is responsible for maintaining the current licensure for all sub-investigators/study staff.

Maintain a copy of current medical licenses for the PI and all sub-investigators listed on the Form FDA 1572 in the regulatory file.

### LABORATORY NORMALS AND ACCREDITATIONS

Per ICH GCP Guideline 8.2.12, certification of accreditation or established quality control and/or external quality assessment or other validation (where required) are required to document competence of the facility to perform required tests and support reliability of results.

This section (or alternate location if other file system is used) must contain the current laboratory normal ranges used by all clinical laboratories for study data and a copy of the laboratory's current certification(s). Remember, if your laboratory is being recertified, include the new certification and retain the original forms. Place the laboratory normal ranges with the pertinent certifications.

Domestic laboratory certifications must include:

- 1) The Clinical Laboratories Improvement Amendments (CLIA) accreditation and a private agency certification (College of American Pathologists [CAP], or the Joint Commission on Accreditation of Healthcare Organizations [JCAHO]), or
- 2) The CLIA certification of compliance (which is a stand alone document), or
- 3) If the laboratory is in a CLIA-exempt state, the state Department of Health certification.
- 4) Labs designated by CLIA as research labs do not require accreditation.
- 5) CLIA exemptions for certain tests.

Non-US laboratories should include their national equivalent for laboratory certification. If no national equivalent is available, include a statement to that effect and a description of the standard that is being used.

The laboratory normal reference ranges must include all clinical laboratory tests required by the Protocol and the unit of measurement. The laboratory name and the date of the document must be provided.

**CORRESPONDENCE**

**and**

**NOTES TO FILE**

### SITE CORRESPONDENCE WITH DMID/SPONSOR

This section (or alternate location if other file system is used) must include all correspondence (e-mails, letters, faxes, memoranda, and phone contacts) between the investigator or research staff and DMID/sponsor relating to the clinical conduct of the study, especially correspondence pertaining to Protocol decisions, serious adverse events, deaths, Protocol Deviations, and Protocol modifications.

Correspondence relating to financial matters should not be kept in the regulatory file, but should be kept in a readily available file.

A sample telephone contact form is provided that may be used to standardize collection of these reports.

Date: \_\_\_\_\_

### Telephone Contact Report

Investigator: \_\_\_\_\_

Sponsor IND No./Protocol No.: \_\_\_\_\_

Contact Person: \_\_\_\_\_ Title: \_\_\_\_\_

Institution: \_\_\_\_\_ Phone: \_\_\_\_\_

**Summary of Conversation:**

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**Action/Follow-up:**

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Signature: \_\_\_\_\_ Date: \_\_\_\_\_

cc: \_\_\_\_\_  
\_\_\_\_\_

### INTERNAL CORRESPONDENCE

This section (or alternate location if other file system is used) must contain site specific correspondence (e-mails, faxes, letters, memoranda, and phone contacts) and will be kept separate from DMID and/or sponsor correspondence. Correspondence between different research facilities should be included here.

### NOTES TO THE FILE

This section (or alternate location if other file system is used) will contain any additional information that is not pertinent to one of the other identified file sections. Notes to the file that are relevant to one of the identified sections should be filed in that particular section. Notes to the file can be used to document Protocol decisions and to clarify Protocol logistics.

If a participant must be unblinded for safety reasons, documentation of the process and approvals for the unblinding must be present.

### SITE SPECIFIC INFORMATION

This information must be present in the site regulatory file (or noted where at the site the file exists) but does not need to be duplicated in each Protocol regulatory file.

This information should include general SOPs for the site, IRB/IEC policies, clinical laboratory procedures, and clinical pharmacy procedures.

### CLINICAL DATABASE VALIDATION

If your site has developed a clinical database for the study, the regulatory file must contain information that documents the validation of the system.

**Note:** Database systems used in clinical trials should be compliant with 21 CFR 11.