

**National Institute of Arthritis and
Musculoskeletal and Skin Diseases**

**Guidelines for Developing a Multi-site
MANUAL OF OPERATIONS AND PROCEDURES
(MOOP)**

Appendices

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APPENDIX A:

Sample Schedule of Study Visits and Evaluation

APPENDIX B:

Sample Adverse Event Form

SAMPLE ADVERSE EVENT FORM

Study Name _____

Site ID: _____

Participant ID: _____

Has the participant had any Adverse Events (AEs) during this study? Yes No *(If yes, please list all AEs below)*

Severity	Study Intervention Relationship*	Action taken with Study Intervention due to AE	Outcome of AE	Expected*	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly/Probably related 3 = Not related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Dose decreased 5 = Dose increased 6 = Dose delayed 7 = Other, specify	1 = Recovered, without treatment 2 = Recovered, with treatment 3 = Still Present, no treatment 4 = Still Present, being treated 5 = Residual effect(s) present-no treatment 6 = Residual effect(s) present-being treated 7 = Subject Died	1 = Yes 2 = No	1 = Yes 2 = No (If yes, complete SAE form)

Event	AE Onset Date	AE Stop Date	Severity	Relatedness	Action taken with study intervention due to AE	Outcome	Expected?	Serious?	Initials

*Please note if an AE is unexpected **and** is related/possibly related **and** suggests that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized (if the AE is serious, then the answer to the third criteria is always yes) it is an **unanticipated problem**.

APPENDIX C:

Sample Serious Adverse Event Report Form

SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

1.

Protocol number:

Protocol title:

2.

Principal Investigator Name:
Site Investigator Name:
Site ID #:
Site Phone #:
Site Fax #:
Site E-mail:

3.

Participant ID:

 4.

Age:

5. **Sex:**
 Male
 Female

6. **Type of report:**
 Initial
 Follow-up

7.

Date of report: ____/____/____

8.

Serious adverse event (SAE) term (e.g., diagnosis): <i>(Note: Additional space to describe SAE can be found in Question 20.)</i>

9.

SAE onset date: ____/____/____

 10.

Date discovered: ____/____/____
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11.

SAE stop date: ____/____/____

 or check if ongoing

12. **Did the participant receive the study intervention prior to this SAE?**
 Yes No N/A

If yes, last date study intervention given:
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13. **Action taken with study intervention due to SAE:**
 None
 Dose decreased
 Dose increased
 Dose delayed
 Discontinued permanently
 Discontinued temporarily
 Other, specify:

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14. What medications or other steps (i.e., procedures, tests) were taken to treat this serious adverse event?

15. Was this an unexpected adverse event?

- Yes
- No

16. Criteria of the SAE¹:

- Death - date ____/____/____
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital anomaly / birth defect
- Disability / incapacity
- Required intervention to prevent permanent impairment
- Other, specify:

17. Relationship of SAE to study intervention :

- Not related (clearly not related to the intervention)
- Possibly/Probably (may be related to the intervention)
- Definitely (clearly related to the intervention)

18. Have similar SAEs occurred on this protocol?

- Yes
- No

If yes, how many?

Please describe:

19. What steps do you plan to take as a result of the SAE reported above? Provide documentation to the IRB for review and approval of any of the steps checked below.

- No action
- Modification of consent documents to include a description of newly recognized risks (site and/or study wide)
- Revise protocol to eliminate apparent immediate hazards to subjects
- Notify currently enrolled subjects
- Suspension of enrollment of new subjects
- Other (describe):

¹ From HHS Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).
<http://www.hhs.gov/ohrp/policy/advevntguid.html>

20. Brief description of the nature of the serious adverse event (attach description if more space needed):

21. Signature of Principal Investigator: _____ **Date:**
____/____/____

APPENDIX D:

Confidentiality and Conflict of Interest Statement for Monitoring Body Members

**CONFIDENTIALITY AND CONFLICT OF INTEREST STATEMENT FOR
MONITORING BODY MEMBERS**

“STUDY TITLE”
[PRINCIPAL INVESTIGATOR]
[SITE]
[GRANT/CONTRACT #]

Conflict of Interest:

As noted below:

- I am not a part-time, full-time, paid, or unpaid employee of any organization (e.g., study site institution(s) or commercial innovator, distributor, manufacturer, sponsor, or any other affiliated organization) that is involved in the studies under review;
- I am not an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations and have not received research support, honoraria, royalties, or other payment from such organizations;
- I do not have any financial or academic interests or assets in any organizations meeting the above criteria, nor does any immediate family member, nor any organization with which I am connected; and
- I am not a current collaborator associated with the Investigators or commercial innovator, distributor, manufacturer, sponsor, or any other affiliated organization. I have noted below any past or anticipated future collaborations with the Investigators or commercial innovator, distributor, manufacturer, sponsor, or any other affiliated organization

Having read the above: *(please check the appropriate box)*

- I have no relevant interests or activities.
- I have noted any exceptions in the space below:

Confidentiality:

I will notify the NIAMS promptly if:

- A change occurs in any of the above during the tenure of my responsibilities, or
- I discover that an organization with which I have a relationship meets the criteria for a conflict of interest.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

[Name] _____
[DSMB Member/Safety Officer] Signature Date

[Name] _____
NIAMS [Program Director (*for grants*)/ Signature Date
Program Officer (*for Contracts*)/
Project Officer (*for U-funded grants*)]

Laura K. Moen, Ph.D. _____
Director, Division of Extramural Signature Date
Research Activities

APPENDIX E:

Sample Protocol Deviation/Violation Log

SAMPLE PROTOCOL DEVIATION/VIOLATION LOG

Protocol Title: _____

Protocol Number: _____ Site: _____ Principal Investigator: _____

Protocol Deviation/ Violation Code:	Participant Initials	Participant ID#	Date Deviation / Violation Occurred: mm/dd/yyyy	Date Protocol Deviation / Violation Form Completed: mm/dd/yyyy	Contact Person (if applicable)

SAMPLE PROTOCOL DEVIATION / VIOLATION CODES

<p>Consent Form:</p> <ol style="list-style-type: none"> 1. Missing or not obtained 2. Not signed and dated by participant 3. Does not contain all required signatures 4. Outdated, current IRB-approved version not used 5. Not protocol specific 6. Does not include updates or information required by the IRB <p>Randomization:</p> <ol style="list-style-type: none"> 7. Ineligible participant enrolled and/or randomized 8. Participant is randomized prior to determining whether eligible for study 9. Occurs outside protocol window 	<p>IRB:</p> <ol style="list-style-type: none"> 10. Not reporting a serious complication within 24 hours 11. Approvals not kept up to date 12. Enrollment and/or treatment occurs prior to IRB approval or during period when "on hold." 13. Reportable serious adverse events not reported to IRB <p>Participant</p> <ol style="list-style-type: none"> 14. Receives wrong treatment 15. Visits occur outside expected follow-up window 16. Entered into another study <p>Study Data and/or Forms</p> <ol style="list-style-type: none"> 17. Missing data and/or forms 18. Missing radiology and/or operative reports 19. Forms or data not sent from clinical site to coordinating center
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APPENDIX F:

NIAMS Clinical Trial Closeout Procedures Multi-site

NIAMS CLINICAL TRIAL CLOSEOUT PROCEDURES MULTI-SITE

I. INTRODUCTION

Purpose

The purpose of this document is to describe an orderly approach to the separation of participants from a clinical trial and the administrative procedures associated with the trial's completion.

Types of Close-out

- A. ***Scheduled*** - upon completion of the trial.
- B. ***Unscheduled*** - as a result of failure to obtain continuation funding, negative or positive findings, findings in other studies that impact on the clinical trial, or other unforeseen events.

II. SITE CLOSE-OUT

The study site is responsible for ensuring the following activities are completed prior to study close-out along with the Participant Close-out Procedures described in Section III below.

A. ***Study Forms***

- All outstanding Case Report Forms (CRFs) should be collected, organized, and any corrections made, where necessary.
- All data queries should be corrected and resolved.

B. ***Safety Reporting***

- All adverse events (both serious and non-serious) should be recorded and followed up to resolution in accordance with procedures detailed in the protocol.
- All serious adverse events (SAEs) should have been reported to the Data and Safety Monitoring Board (DSMB) or Safety Officer, Institute, Institutional Review Board (IRB), and other organizations, as specified in the protocol and Safety Monitoring Plan.
- All adverse events should have been reported as specified in the protocol.

C. ***Study Files***

- The investigator's study files should be complete and up-to-date with originals of the following maintained in the Study Binder, as relevant:
 - Investigators Curriculum Vitae(s) (CVs), Investigator's Brochure(s) as relevant
 - IRB approval letters for the protocol, all amendments, Informed Consents, annual reviews and advertisements (including updated approvals)

- IRB membership list
- All IRB correspondence
- Institute correspondence
- Site signature log
- Drug accountability records documenting the investigational product received, dispensed and returned or destroyed
- Copy of randomization code for randomization, if applicable
- All informed consents should be signed and on file.
- Record retention procedures should be documented with respect to type and length of retention, and consequences of improper record retention, and should conform to protocol and institutional requirements. The site should be completely familiar with required record retention policies.

D. ***Clinical Supplies***

- Clinical supplies, including any treatment intervention materials, must be shipped or disposed of according to protocol directions.
- As relevant, drug accountability records (shipping, receipt, dispensing, return or destruction) should be up-to-date.

E. ***Laboratory Records and Specimen Retention***

- The site should ensure that the laboratory records are complete and up to date (reference ranges, laboratory certifications, specimen tracking records, specimen storage records).
- If specimens are to be stored, a plan should be in place to address issues such as specimen retention, use, and methods for protecting patient confidentiality. As relevant, study specimens should be transmitted to the analysis center, analyzed, results recorded for the study, and specimens stored with proper documentation.

F. ***Notifications and Equipment Removal***

- A final report should be submitted to the IRB and should conform to institutional reporting requirements. The report is likely to include, but is not limited to, study conduct and outcome, pertinent safety and efficacy observations, complete disclosure of any SAEs experienced during the course of the study, and the study close-out date.
- As relevant, arrangements should be made for the removal and shipment of any study-specific equipment received by the site (e.g., computers, diagnostic equipment, and participant monitoring devices).

Figure 1 provides a sample study documentation list, and Figure 2 provides a sample Close-Out Checklist.

Figure 1: Sample Study Documentation List

Document	Purpose
Completed Participant Identification Code List	Permits identification of all participants enrolled in the trial in case follow-up is required. List should be kept in a confidential manner (double locked system) and for agreed upon time.
Treatment allocation and decoding documentation	Study Records
Treatment intervention product(s) accountability at site	Documents that the treatment intervention product(s) have been used according to the protocol. Documents the final accounting of treatment product(s) received at site, dispensed to participants, returned by the participants, and returned or destroyed.
Final report by investigator to IRB, as required	To document completion of the trial
Final Trial Closeout Monitoring Checklist, if relevant	To document that all activities required for trial closeout are completed, and copies of essential documents are held in the appropriate files
Audit Certificate (if relevant)	To document that audit was performed

Figure 2: Sample Study Close-out Checklist

- Investigator has signed and dated all Case Report Forms (CRFs).
- CRFs for all participants have been filed or transmitted as described in the Manual of Procedures.
- All appropriate documents are in the study files.
- As relevant, study drug has been shipped or destroyed, as described in the study protocol and/or Manual of Procedures.
- Report has been submitted to the IRB.
- Documents are retained as specified in the Manual of Procedures or IRB directives, whichever is longer.
- There is a plan in place in the event of an audit by the NIAMS, as relevant.
- Final report has been submitted to the NIAMS.

III. PARTICIPANT RIGHTS AND NOTIFICATION

The study site should prepare a letter that thanks each study participant and could include the following information:

- Study findings
- Treatment assignment, as relevant
- Treatment options, as relevant, whether continued treatment with the assigned intervention is indicated, and how and where treatment may be obtained
- Transfer of care responsibilities
- Rights to confidentiality, privacy, and to no further contact from study staff, if that is participant's preference
- Subsequent updates or recalls if new and important information emerges following separation
- Contact information of study staff

A copy of the letter should be included in the participant's file.

IV. INSTITUTE RESPONSIBILITIES

The NIAMS may wish to send staff or a Contractor to ensure that close-out procedures are appropriately conducted at the study site.