NICHD SOP for Intramural Clinical Protocol Monitoring

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1. PURPOSE

The purpose of this Standard Operating Procedure is to describe the process for ongoing monitoring of NICHD clinical research protocols, both for quality assurance as well as for cause. In addition, the purpose of this SOP is to describe the process for ongoing quality assurance/quality improvement of the Intramural Clinical Research program of NICHD. This SOP establishes a system for oversight and monitoring of clinical trials and other clinical research as is required by the NIH Intramural Research Program Standards of Clinical Research.

2. APPLICABLE REGULATIONS AND GUIDELINES

- 45 CFR 46 Protection of Human Subjects
- 21 CFR 312 Investigational New Drug Application
- ICH E 6 Guideline for Good Clinical Practice
- Standards for Clinical Research within the NIH Intramural Research Program (http://www.cc.nih.gov/ccc/clinicalresearch/index.html)
- Standards for Patient Care at the NIH Clinical Center (http://www.cc.nih.gov/ccc/patientcare/standards7.shtml)

3. MONITORING

All open and accruing clinical trials, including IND/IDE studies, non-IND therapeutic interventional studies, natural history studies, teaching, and screening studies, are subject to protocol adherence and human subjects’ protection monitoring. The purpose of Study Monitoring Visits is to verify that:

- the rights and well-being of human subjects are protected
- the reported study data are complete and verifiable from source document
- the study is conducted in compliance with current regulatory requirements
- study subjects have provided consent for study participation
- a person responsible for monitoring the study is designated in the protocol

A risk-based approach to monitoring will be used with a primary focus on the processes that are critical to protecting human subjects, maintaining the integrity of study data, and compliance with applicable regulations. The level of monitoring required is determined by the category of protocol and relative to research interventions or therapeutic interventions. The complexity and scope of the monitoring for each category is outlined below in Section 4. Oversight of monitoring will be performed by the NICHD Quality Assurance (QA) Program.

3.1 Frequency of monitoring

Protocols conducted under an IND/IDE where an NICHD investigator is the sponsor will be monitored by a Contract Research Organization (CRO) at least every two years or more frequently as determined by the CRO. The frequency will depend on the rate of
enrollment, the number of safety events, the complexity of the protocol, the experience of the Clinical Investigator and Sponsor, the relative safety of the IND, the stage of the protocol, and any regulatory activities that need immediate independent review.

Random audits will be performed annually by the NICHD Quality Assurance Program on at least 10% of actively accruing NICHD protocols.

3.2 Clinical Study Monitoring Plans

All protocols will have a study-specific monitoring plan for the lifetime of the study to ensure adequate and systematic monitoring of study data, protocol compliance and maintenance of regulatory documents.

4. MONITORING LEVELS

There are two categories of monitoring with clinical studies: Screening, Teaching and Natural History Studies and Clinical Trial Studies. IND/IDE studies are monitored separately. NICHD OCD can adjust the level of monitoring as needed.

4.1 Screening, Teaching, Natural History Studies

These studies do not have research interventions and are designated as “S”, “T”, or “NH” by the NICHD IRB.

4.1.1 Areas of Focus

- Human subjects’ protection
- Protocol compliance

4.1.2 Random Audit

- Review of Informed Consent Forms
- Randomized sample of at least 20% will be reviewed.
- Protocols with enrollment > 300: 20% from the last 3 years will be reviewed
- Review of inclusion/exclusion criteria, including supporting documentation
- Randomized sample of at least 20% will be reviewed
- Protocols with enrollment > 300: 20% from the last 3 years will be reviewed
- Review reports on Adverse Events (AEs), Serious Adverse Events (SAEs) and UPs. Time of event and time of submission will be tracked for all submissions to evaluate for reporting within the appropriate timeline to IRB
- Ensure reportable deviations and Unanticipated Problems are submitted via the Problem Report Form

4.1.3 Audit Schedule

- Interim auditing on at least 10% of actively accruing protocols at least annually
- If indicated, a specific protocol could be audited more frequently as needed
Audit results for protocols of the leadership (CD, SD) will be provided to the IRB Chair and Vice Chair prior to being given to either the CD or SD. Responses to the audit (CAPA) will also be reviewed by the IRB Chair and Vice Chair.

4.2 Clinical Trial Studies

Clinical Trial Studies include therapeutic interventions of non IND/IDE protocols. These studies are designated as “CT” by the IRB. IND/IDE protocols where NICHD is not the sponsor are also included.

4.2.1 Areas of Focus
- Human subjects’ protection
- Protocol compliance
- Confirmation of protocol auditing by IND/IDE sponsor

4.2.2 Random Audit
- Review of Informed Consent Forms
- Randomized sample of at least 50% will be reviewed
- Protocols with enrollment > 300: 50% from the last 3 years will be reviewed
- Review of inclusion/exclusion criteria
- Randomized sample of at least 50% will be reviewed
- Protocols with enrollment > 300: 50% from the last 3 years will be reviewed
- Review reports on Adverse Events (AEs), Serious Adverse Events (SAEs) and UPs. Time of event and time of submission will be tracked for all submissions to evaluate for reporting within the appropriate timeline to IRB
- Ensure reportable deviations and Unanticipated Problems are submitted via NIH Problem Report Form

4.2.3 Audit Schedule
- Interim auditing on at least 25% of actively accruing protocols at least annually
- If indicated, a specific protocol could be audited more frequently as needed

4.3 IND/IDE Studies

All studies under Investigational New Drug (IND) or investigational device exemptions (IDE) with the FDA, where NICHD is the sponsor, are designated as “CT” by the IRB. These studies will be monitored by an external Contract Research Organization (CRO) and the monitoring will be coordinated through the NICHD Quality Assurance (QA) Program.

4.3.1 Areas of Focus
The CRO will provide onsite audits of ongoing clinical studies to assure quality and compliance with GCP guidelines, and FDA & ICH regulations for clinical research.

4.3.2 Monitoring Plan
• Review of credentials, training records, and delegation of responsibility logs
• Review of Informed Consent Forms
• Verify that study procedures compliant with GCP guidelines and FDA requirements
• Compare CRFs to source documentation to ensure data are accurate and complete
• Verify and compare to source documentation all AEs and SAEs
• Review reports on Adverse Events (AEs), Serious Adverse Events (SAEs) and UPs. Time of event and time of submission will be tracked for all submissions to evaluate for reporting within the appropriate timeline to IRB
• Review Regulatory Files
• Review accountability and storage of Investigational Product
• Review target recruitment goals

4.3.3 Visit Schedule
• Study initiation visit will be conducted with the contractor
• First monitoring visit no more than 8 weeks after first subject enrolled
• Interim monitoring visits on an ad hoc basis based on site activity
• Other monitoring as needed

5. VISIT TYPES

5.1 Study Initiation

The CRO will conduct a Study Initiation visit for all protocols under Investigational New Drug (IND) or Investigational Device Exemptions (IDE) with the FDA. The purpose of this visit is to review the study protocol and all procedures required for appropriate conduct of the study, while using the protocol, CRF, and Study Operations Manual as resources

5.2 Interim Monitoring Visits

The CRO will conduct Interim Monitoring visits. The purpose of these visits is to review regulatory documents, verification between Case Report Form data and source medical records, and to check on adherence to protocol procedures.

5.3 Study Close Out

At the conclusion of a study, a study close out visit will occur. The purpose of this visit is to verify that the study is completed and no more procedures will be performed.

6. MONITORING VISIT FOLLOW UP AND REPORTING

6.1 Follow Up for Protocols Monitored by a Contractor

For protocols monitored by a contractor, a follow-up letter will be sent to the Primary Investigator within 2 weeks of the site visit and will include items reviewed at the visit.
The letter will detail any significant violations that must be addressed as well as any suggestions for improvement. The PI will then be given 30 days to respond to the letter. All correspondence will be included in the Investigator’s Binder/File. The monitoring report along with the investigator response will be made available to the NICHD Office of the Clinical Director and may be made available to the NICHD Office of the Scientific Director, the NICHD Data Safety Monitoring Committee, the Program Head, and the NICHD IRB.

6.2 Follow Up for Study Specific Monitoring Plans by the Investigator

For study specific monitoring plans by the investigator a monitoring report will be filed with the protocol. This report will include: 1) the date the monitoring was performed, 2) who conducted the monitoring; and 3) the findings. All significant or major deficiencies must have a Corrective Action Preventative Action (CAPA) created outlining how the deficiency will be corrected and prevented in the future. The CAPA will also have an anticipated completion date.

6.3 Follow Up for Random Audits

For protocols audited by random audit, a follow-up QA audit memo will be sent to the Principal Investigator or Admitting Physician within 2 weeks of the audit. This memo will detail any deficiency found and a proposed Corrective Action Preventative Action (CAPA) plan created outlining how the deficiency will be corrected and prevented in the future. The Principal Investigator or Admitting Physician will respond to the memo with revisions to the CAPA if necessary. The signed memo will be due to the Office of the Clinical Director (OCD) within 2 weeks of receipt of the memo and will be maintained in the NICHD OCD office by the QA Program. When a deficiency requires a NIH Problem Report Form, the Principal Investigator is notified and the Protocol Coordinator ensures that a form is submitted in PTMS. Principal Investigators that have more than one protocol will have CAPA’s from previous audits reviewed during subsequent random audits to ensure that the former deficiency has been addressed.

6.4 Reporting Requirements

IRB reportable events, which include all Unanticipated Problems (UPs), protocol deviations, and non-compliance reports will be evaluated for reporting within the appropriate timeline to the IRB upon submission in the protocol tracking system (PTMS). The Protocol Coordinator will be the first line of review by checking the dates in PTMS when a problem report form is first submitted. The IRB Chair will also review the date the problem report form is submitted during his pre-IRB review of all problem report forms. The Protocol Coordinator will notify the NICHD Clinical Director (CD) of all late submissions within 3-5 days of submission and a root cause analysis will be done by the NICHD OCD within 2 weeks. If the problem report has boxes checked for notification of either the FDA or Study Sponsor, the Protocol Coordinator will request evidence of this notification. This ensures timeliness of reporting of events to the study sponsor or FDA for FDA-regulated studies. These safety reports will be sent to the NICHD QA.
Committee for review. The NICHD QA Committee will submit these reports to the Clinical Director.

Data and critical feedback from a Root Cause Analysis will be provided to the PI, in the form of an email, by the NICHD QA Committee for every late submission of IRB reportable events. This will occur after every root cause analysis. This feedback may include additional or refresher training for the PI or members of the study team. Ratings on individual PMAP benchmarks for timely reporting will reflect late reporting. Recurrent or chronic late reporting will be addressed by meeting with the Clinical Director. The PI will be asked to establish a corrective action plan to address the underlying reason for the late submission. Results of this QA activity will be reported to the NICHD Clinical Chiefs and NICHD Scientific Director (SD) as part of the quarterly meeting. Results will also be reported to the NICHD Institute Director on a quarterly basis.

The QA Program will submit an annual report of all QA/QI activities to the NICHD Clinical Director.

7. ORGANIZATIONAL PERFORMANCE IMPROVEMENTS

Annually, the NICHD Clinical Director will conduct a review of the monitoring activities, reports, and QA/QI program. The review will identify if there are organization wide common deficiencies or suggestions for improvements contained in the monitoring reports and determine if any opportunities for improvement in the conduct of clinical research and humans subjects protection exist.

8. INTRAMURAL CLINICAL RESEARCH QUALITY ASSURANCE/QUALITY IMPROVEMENT

In accordance with NIH Standards for Clinical Research and Patient Care at the NIH Clinical Center, NICHD supports an ongoing quality assurance/performance improvement program. The committee is an interdisciplinary group, consisting of members from clinical research, nursing, physician, and social work. The purpose of the program is to:

1) Assess the quality and appropriateness of patient care provided within individual NICHD clinical research protocols
2) Identify relevant and important patient care issues specific to individual NICHD protocols.
3) Pursue opportunities to improve patient care.
4) Address problems (or potential problems) that affect the delivery of safe, high quality patient care, develop possible solutions, and evaluate the effectiveness of the intervention.

The NICHD Quality Assurance Committee carries out this mission by:
• Review monthly occurrence reports concerning patients enrolled on NICHD protocols, discuss treatments and interventions. Identify policies or practices that may have contributed to the occurrence and formulate measures to prevent recurrence of these events. A summary of the discussion and follow-up is provided to the Clinical Director, NICHD.
• Provide an opportunity for interdisciplinary team members from each of the key areas in the CC where NICHD patients are seen to discuss issues and concerns related to patient care and protocol implementation.
• Develop plans to address any problems identified, and evaluate the effectiveness of the interventions in a timely manner.
• Routinely, perform brief, checklist-guided audits of randomly selected NICHD patient Medical Records and charts.
• On an annual basis identify performance improvement initiatives, develop plan and implementation, and evaluate progress.

Appendix 1: Regulatory Binder
Appendix 2: Minimal/Medium Risk Monitoring Checklist
Appendix 3: Algorithm for Protocol Monitoring
Appendix 4: Glossary
Appendix 5: Performance Initiative Project Template

June 24, 2017
APPENDIX 1

**Regulatory Binder/File**

The Regulatory Binder/File contains all study-specific information and regulatory documentation. Regulatory Binders/Files are mandatory for any research protocols that have an IND or IDE. This Binder/File will be standardized, and may be maintained in either a paper or electronic version.

The Regulatory Binder/File contains the elements described in the Regulatory Binder Checklist below.

**Regulatory Binder for IND Studies**

Sections should be separated by tabs and arranged in the following order. Note this can be maintained electronically in an organized structure.

1. FDA 1572 Form
2. FDA 3455 Financial Disclosure Form (state if not applicable)
3. NIH 1195
4. IRB Documentation  
   a. Approval memo  
   b. Annual review approval memo  
   c. IRB correspondence
5. Radiation safety approval (state if not applicable)
6. DSMC correspondence (state if not applicable)
7. FDA correspondence with copies of the corresponding 1571 form  
   a. FDA annual reports  
   b. Other
8. Current protocol and amendments
9. Current consent documents
10. Investigator CVs, licenses and appropriate certifications*
11. Investigators brochure (if applicable)
12. Study manual (if applicable)
13. Case report file (organization and standardized forms)
14. Monitoring plan
15. Authorized representative sheet/delegation log
16. Laboratory certifications (available from CLIA certified laboratories)
17. Laboratory normal range values (Can reference CC laboratory web site)
18. Randomization (state if held by PDS) and decoding procedures for blinded study
19. Drug accountability (If performed by PDS/pharmacy, state this)
20. Subject screening log/Enrollment log (May be computerized log but need to refer to location)
21. Adverse event reports  
   a. FDA memo and 1571 form  
   b. NICHD IRB correspondence
22. Site visit log and correspondence
23. Appendix
   a. Previous protocol versions if any*
   b. Previous consent versions if any*
   c. Miscellaneous documentation

*For existing protocols, refer to “other attachments” under initial review in PTMS. Do not copy old files for this. However, begin to maintain these files as the active version is replaced.

APPENDIX 2

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<tr>
<th>MEDICAL RECORDS</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
<th>COMMENTS</th>
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<td>INFORMED CONSENT PROCESS:</td>
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<tr>
<td>Signed by patient</td>
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<td>Correct version used</td>
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<td>All pages have complete patient identifying information</td>
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<td>All consents signed prior to participating in protocol procedures</td>
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**STUDY PROCEDURES:**

| Inclusion/Exclusion criteria documented |   |   |
| H&P documented |   |   |
| H&P in proper time frame |   |   |

**NIH HRPP MANDATORY TRAINING:**

| Training Requirements Met |   |   |

**PROTOCOL MONITORING PLAN**
APPENDIX 3

IND/IDE Protocol Algorithm

Does the Protocol have an IND or IDE?

yes

NICHD Sponsor

no

no

Random Audits by QA Audit Staff

yes

Monitored by CRO

NICHD Sponsor

Monitored by Sponsor

NICHD QA Audit Program
APPENDIX 4

GLOSSARY

AE Adverse Event: Any untoward medical occurrence in a patient or clinical subject administered a pharmaceutical product or other intervention and which does not necessarily have a causal relationship with the product/intervention

CAPA Corrective and Preventative Action: A plan designed to summarize significant deficiencies and develop methods to prevent the occurrence in the future.

CFR Code of Federal Regulations

CRA Clinical Research Associate: (monitor); person who monitors the progress of the investigation and sites participating in a clinical study and who is responsible for determining if a study is being conducted in accordance with the protocol.

CRF Case Report Form/File: A printed, optical, or electronic document/file designed to record all protocol required data to be reported to the sponsor on each study subject.

GCP Good Clinical Practices: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical research studies designed to provide assurance the the data and reported study results are credible and accurate, and that the rights of subjects are protected.

ICH International Conference on Harmonization

IND Investigational New Drug: The clinical investigation of a previously untested drug or biologic that is generally divided into three phases of study. Each phase is designed to ensure the safety and rights of subjects and to help assure that the quality of the scientific evaluation of drugs/biologics is adequate to permit a scientific evaluation of the drug’s effectiveness and safety.

IRB Institutional Review Board: An independent body constituted of medical scientific, and nonscientific members, who responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a study by, among other things, reviewing, approving, and providing continuing review of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the study subjects.
<table>
<thead>
<tr>
<th>Protocol Deviation</th>
<th>A protocol deviation is a variance between the IRB approved protocol and the actual activities or procedures performed.</th>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event: Any untowards medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in a congenital anomaly/birth defect.</td>
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<tr>
<td>Source Documents</td>
<td>Original documents, data and records, such as hospital records, clinical and office charts, laboratory results, notes, memoranda, pharmacy</td>
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**APPENDIX 5**

**NIH CLINICAL CENTER**

**PERFORMANCE IMPROVEMENT (PI) PROJECT INVENTORY**

**Instructions:** In an effort to catalogue the performance improvement activities occurring in the Clinical Center please provide us with the following information about PI projects led by your Department in 2008 – 2009. Projects selected should be *data-driven* and should have had *significant impact* on the services and/or care provided to patients.

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<th><strong>Title of Improvement Project:</strong></th>
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<th><strong>Plan:</strong></th>
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<td><em>Brief description of the issue/opportunity for improvement:</em></td>
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<th><strong>Stakeholders:</strong></th>
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<th><strong>Baseline Measures/Indicators (please include summary data, as appropriate):</strong></th>
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<td><em>Describe improvement and implementation strategies:</em></td>
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<td><em>Describe outcomes used to evaluate improvement strategy (please include summary data, as appropriate):</em></td>
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<td><em>Describe current status of project (e.g., continuous monitoring, redesigning improvement strategy):</em></td>
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March 11, 2014