National Institute of
Neurological Disorders
and Stroke

NINDS Standard Operating Procedure
NINDS SOP 12

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NINDS Clinical Director

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1. PURPOSE

This standard operating procedure describes and outlines the process for conducting and participating in a NINDS Quality Assurance (QA) protocol audit. The purpose of the QA audit is to ensure research participant safety, verify accurate data collection and protocol adherence, assess compliance with applicable regulatory requirements and good clinical practice (GCP) guidelines, as well as to provide recommendations for improving the management of clinical research data.

2. POLICY

The Deputy Director of Intramural Research, NIH Quality Officer, Institutes and Centers (IC), Office of Human Subjects Research Protections (OHSRP), IRBO, and investigators all work together to carry out the NIH Human Research Protection Program (HRPP). The primary mission of the HRPP program is to protect the rights and safeguard the welfare of human subjects who participate in its research studies. Each IC is responsible for ensuring compliance with federal regulations (45 CFR 46 and 21 CFR parts 50, 56, 312, and 812) and NIH policies, as well as establishing quality improvement activities to address deficiencies in compliance and to improve the quality, effectiveness, and efficiency of HRPP activities.

The NIH has established standards requiring each Institute to develop a quality assurance program to assure that investigators are conducting research in compliance with the protocol, good clinical practices, and the applicable regulatory requirements. Quality assurance programs provide the Institute with data about the quality of execution of their clinical research and provides investigators an opportunity to learn through external evaluation. According to the standards set forth by the Medical Executive Committee of the NIH Clinical Center, each IC is responsible for developing a quality assurance/quality improvement plan which includes conducting routine and for-cause audits of research activities.

3. PROCEDURES

3.1 Site Initiation Visit

Following IRB approval of the protocol, the NINDS Quality Assurance and Data Management (QADM) Office will contact the PI to schedule a Site Initiation Visit (SIV) (see Appendix A: Site Initiation Visit Checklist). The SIV should occur following the development of the data collection/data management system and prior to initiating subject enrollment, to ensure that all components of subject protection and data collection are in place prior to the first participant being consented to the protocol.

A SIV includes a detailed discussion and review of the protocol recruitment and consent process, protocol procedures, requirements for oversight and reporting of research related events, investigator training, applicable regulatory requirements, and good documentation practice. It is also an opportunity to review completed case report forms to ensure all required and desired data is captured. During the SIV, the NINDS Clinical Trials Unit (CTU) Data Manager may be present to review the data management system. At times, the auditor will tour laboratory facilities used during the protocol, as well as ancillary service areas such as the pharmacy, sample storage facilities (e.g., freezers), and phlebotomy, as applicable.

3.2 Quality Assurance Plan

The NINDS QADM Office is available to assist investigators in determining an appropriate quality assurance plan for their protocol. The NINDS QADM Office employs a decision algorithm (see Appendix B) to determine the need for auditing or on-going (external or internal) monitoring of the protocol. The process of on-going external QA protocol monitoring is described in a separate SOP, i.e., Quality Assurance Monitoring.

In general, protocols undergo quality assurance audits based on the protocol classification of risk. All applicable open protocols may be selected for routine or random audit. Repository protocols, protocols designated by the IRB as exempt, and protocols which are in "Data Analysis Only" are exempt from NINDS QADM Office review. The Principal Investigator (PI) is responsible for the oversight of data included in the protocols exempt from NINDS QADM Office review.

3.2.1 Routine Audits
Protocols involving procedures that are more than minimal risk and/or include a vulnerable population are audited most frequently, with a *target* of once within the first year and at least once every 3 years thereafter. However, protocols that include more than minimal risk procedures that are considered "standard of care" in the targeted patient population by the medical community, (e.g., the use of gadolinium during MRI, lumbar puncture for diagnostic purposes, neurological surgery), may undergo random audit similar to a minimal risk protocol.

3.2.2 Random Audits
Protocols classified as minimal risk, i.e., the protocol includes no more than minimal risk procedures, in non-vulnerable populations, and protocols that are classified as more than minimal risk but the procedures are considered standard of care in the targeted patient population (as noted above) may be selected for random audit.

3.2.3 For-Cause QA audits
A for-cause audit can be conducted on any protocol when issues of concern are raised. For-cause audits may be requested by an investigator, study coordinator, participant, or any individual with concern regarding the conduct of a protocol (see OHSRP Policy 802).

3.3 Scheduling a Quality Assurance Audit

3.3.1 Routine Audits

The PI is responsible for following the Quality Assurance Plan described in the protocol and must notify the NINDS QADM Office when study time points have been reached.

3.3.2   Random Audits

The NINDS QADM Office will select the protocol to be audited. Following the selection of the protocol, the NINDS QADM Office will contact the PI with a request to schedule a protocol audit meeting. When an audit date is scheduled, the Investigator should ensure that all key personnel are available on the selected date to participate in the audit.

3.4   Quality Assurance Pre-Audit Procedures

The QA Audit Preparation Checklist (see Appendix C) will be sent to the Principal Investigator describing the documents to be reviewed during the audit.

The QA auditor(s) prepares for the audit by reviewing protocol documents (e.g., initial protocol, amendments to the protocol, and correspondence memos). A checklist is developed detailing all protocol procedures (e.g., inclusion/exclusion criteria, screening and protocol visits and associated procedures) prior to the audit. The checklist is utilized during the record review portion of the QA audit. During the audit, all regulatory, research, and medical records may be reviewed, paying particular attention to consent, eligibility, safety measures, and procedures addressing the primary and secondary outcome measures.

3.5   Quality Assurance Audit

3.5.1   Attendance

The Principal Investigator and/or key study personnel should be present at the meeting and available to answer questions, retrieve documents, and facilitate the completion of the audit.

3.5.2   Meeting Structure

The audit meeting begins with the PI or study investigator providing a brief overview of the protocol purpose, visit schedule, enrollment, and data management processes.

Following the presentation, the QA auditor(s) will have an opportunity to ask questions of the investigators and clarify any outstanding issues. The auditor(s) will then proceed in the review of regulatory documents (electronic regulatory documents, and/or paper documents, on-site or remotely) and participant research records.

3.5.3   Focus of Quality Assurance Audit

3.5.3.1   Regulatory Records and Documents

All protocol related documents are reviewed in the research team's regulatory binders, either electronically or on paper.
- Documents reviewed may include:
    - Initial and all versions of the IRB approved protocol, initial and all versions of the IRB approved consents, IRB submission forms/memos (e.g., CR Memo, Study Application, Key Study Personnel Form), amendments, reportable events form (Deviations, Non-compliance, UPs, and SAEs), corrective and preventative action plans (if applicable), radiation safety documents (if applicable), recruitment materials, and all IRB approval &/or acknowledgment letters.
    - Additional protocol management tools such as: screening/enrollment logs, subject code list, delegation of authority/signature log, eligibility checklist, adverse events log, product accountability log (if applicable), normal lab values (if applicable), site visit log and reports, blank data collection tools used such as checklists, questionnaires, and case report forms (CRFs).

- o Investigator Qualification Documentation: CVs and Licenses (where applicable) as well as all institutional and protocol required training certificates.
- o Sample collection (if applicable): sample collection logs, sample tracking and shipping logs, review of stored samples (verify sample tracking log and freezer temperature logs).
- o Study Correspondence: IRB communication, FDA exemption/communication (if applicable), any collaborative agreements or agreements on sharing data, site visit correspondence, or technology transfer agreements.
- o Data and Safety Monitoring (DSM) Documentation: DSM plan, correspondence, meeting minutes, reports.

3.5.3.2 Conflict of Interest and Financial Disclosure

The NINDS QADM Office will rely on the Deputy Ethics Counselors and NIH Ethics Office for Conflict of Interest and Financial Disclosure for audits.

- Covered Individuals: The NIH Deputy Ethics Counselors (DEC) Office reviews Conflict of Interest and Financial Disclosure for all covered individuals (Federal and Non-Federal employees).
- NINDS Leadership: The NIH Ethics Office (NEO) reviews Conflict of Interest and Financial Disclosure for NINDS Leadership.

3.5.3.3 Training

- Required HRPP training certificates as per Policy 201 are inspected.
  - o HRPP training reviewed by NINDS QADM Office:
    - CITI Biomedical Basic course and/or CITI Social-Behavioral-Educational Basic course (depending on the type of research being conducted)
    - CITI Good Clinical Practice (GCP) (US FDA Focus)
- Required protocol specific training certificates are identified and inspected (e.g., Just-In-Time Training).
  - o Site Initiation Visit training and documentation of training for all protocol amendments
- All other training required by the Institute or institution are inspected via study binder.
  - o NINDS & institutional training reviewed by NINDS QADM Office:
    - Elements of a Successful Consent (where applicable) & documentation of first consent monitored (i.e., the Observed Structured Clinical Examination [OSCE])
    - Event Reporting Training (either in-person or on-line with attestation)
    - Responsible Conduct of Research Training
    - Non-Credentialed Staff Competency Checklist documenting procedure specific training, if applicable
    - Other training documentation, as required

3.5.3.4 Participant Record Selection

A representative selection of records is reviewed. The number of records reviewed is determined at the discretion of the NINDS QADM Office.
In general:

- ➢ 10 or fewer subjects enrolled = 100% of records are reviewed
- ➢ 11-20 subjects enrolled = 50% of records are reviewed
- ➢ >20 subjects enrolled = 10-50% of records are reviewed

3.5.3.5 Review of Informed Consent Documents

The following elements pertaining to informed consent are reviewed:

- Signature and date of participant (or guardian or DPA), investigator with consent privileges, and witness (as applicable).
- Presence of DPA document, if indicated.
- Assent document, as indicated, with date and signature.
- Date of informed consent relative to date of initial protocol procedure.
- Version of consent utilized.

- Labeling of consent with subject identifying information, i.e., name and medical record (MR #).
- Original informed consent document in MR/Clinical Research Informatics System (CRIS).
- Documentation of the consent process in the MR.
- Items requiring subject initials/specific consent in the body of the consent document.
- Other consent documents necessary per the protocol and population (e.g., short-form consent for non-English speakers, telephone consent).

3.5.3.6 Review of Eligibility Criteria

- All inclusion/exclusion criteria are determined by reviewing the source documents.
- Documentation of review of inclusion/exclusion criteria (e.g., via progress note, memo, or eligibility checklist).
- If an eligibility checklist is utilized, each criterion should be able to be source verified.

3.5.3.7 Review of Protocol Visits and Procedures

- Research and clinical records are reviewed to ensure adherence to all protocol procedures addressing the primary and secondary outcome measure and safety measures, as stated in the IRB approved protocol.
- If CRFs are utilized, a portion of the data is verified for accuracy with the source documents and the records are reviewed for completeness.
- Progress notes are reviewed to ensure all visits are documented in the clinical record.

3.6 Audit Findings

Findings will be classified according to Major or Minor deficiencies.

3.6.1 Major Deficiencies
A major finding is a significant or recurring deviation from the protocol or institutional policy, such as:

- A deviation that significantly impacts the ability to record valid and accurate data on safety and/or efficacy.
- A deviation that violates the NIH or FDA regulations or policy.
- A deviation that places the participant's safety at risk.

3.6.2 Minor Deficiencies
A minor finding is a deviation from the protocol that is neither deliberate nor recurring, which does not place the subject at risk or does not affect the integrity of the data, such as:

- A minor deviation from the protocol, but there are no safety implications for study participants.
- A minor deviation from the protocol, but the data are usable and valid.

3.7 Follow-up to the Quality Assurance Audit

3.7.1 Audit Report
The NINDS QADM Office will generate a report of findings following the completion of the regulatory and record review. The draft audit report will be sent to the PI and designated study team member with the offer of a follow-up meeting. It is expected that essential documents that were unable to be reviewed during the audit will be located by the investigator and presented to the auditor(s) for review within 2 weeks of receipt of the draft audit report. The audit report will then be updated to account for items located by the study team. Any documentation unable to be located will need to be reported to the IRB by the investigator, if representing a deviation from the protocol.

The NINDS QADM Office will review the audit findings with the NINDS Clinical Director or Director of the CTU. The Clinical Director will sign off on the report once finalized.

The Principal Investigator should receive a complete audit report from the NINDS QADM Office as soon as possible after the audit is completed. Any actions requiring IRB reporting must be submitted upon PI notification of the event, within the required time frame.

The Principal Investigator is responsible for replying in writing within 30 days to each action item listed on the audit report and must acknowledge any recommendations made.

The Investigator will maintain a copy of the audit report and related correspondence in the appropriate section of the regulatory files.

3.7.2   Determination
The audit report will include a determination:

No Deficiencies: No formal response is required from the PI. The report may include recommendations; these should be considered and acknowledged in writing.

Minor Deficiencies: A formal written response is required from the PI to address the action items listed in the audit report, and deficiencies must be reported to the IRB within the appropriate time frame.

Major Deficiencies: A formal written response including a CAPA is required from the PI. In addition, a meeting will be held with the PI, the Clinical Director, and the Lead of the NINDS QADM Office and/or designee, to review the deficiencies and discuss the implementation of the CAPA.

3.7.3   Corrective Action Preventative Action (CAPA)
All significant or major deficiencies must have a Corrective Action Preventive Action (CAPA) created, outlining how the deficiency will be corrected and prevented in the future.

3.7.4   Significant Protocol Non-compliance
If significant protocol non-compliance is noted, a special meeting will be held with the Lead of the NINDS QADM Office and/or designee, the NINDS Clinical Director and the study team to discuss the plan for the implementation of corrective actions and process improvements arising from objectionable audit observations, as needed.

The Investigator will implement those corrective actions and improvements within a mutually agreed upon time period.

NOTE: definitions are available on the "Glossary" page of the CTU intranet.

4. APPENDICES

Appendix A: Site Initiation Visit (SIV) Checklist

Appendix B: QA Monitoring/Auditing Algorithm

Appendix C: QA Audit Preparation Checklist

Appendix A: Site Initiation Visit (SIV) Checklist

The NINDS QA auditor(s) are available to conduct a Site Initiation Visit (SIV) for all NINDS protocols conducted in the intramural research program. The SIV should occur after the protocol has been approved by the IRB, the database and all data collection tools have been developed and prior to enrollment of the first participant. The primary purpose of the SIV is to review the IRB approved protocol with the study team including events reporting requirements as well as discuss good documentation practices, and confirm that all required processes are in place prior to site activation. The auditor(s) will confirm that all action items are resolved prior to beginning enrollment.

The following will be reviewed during the Site Initiation Visit:
- ☐ Protocol Design (documents may be reviewed in an electronic or paper regulatory binder)
  - o Primary/secondary objectives
  - o Study design
  - o Study Population
  - o Inclusion/Exclusion Criteria

- ☐ Recruitment Plan and Consent
  - o Pre-screening for eligibility
  - o Consent
  - o Assent (if applicable)

- ☐ Study Procedures
  - o Screening procedures
  - o Baseline measures
  - o Study visits and procedures
    - ▪ Review each study procedure (e.g., MRI, EEG, Behavior task)
  - o Follow-up procedures
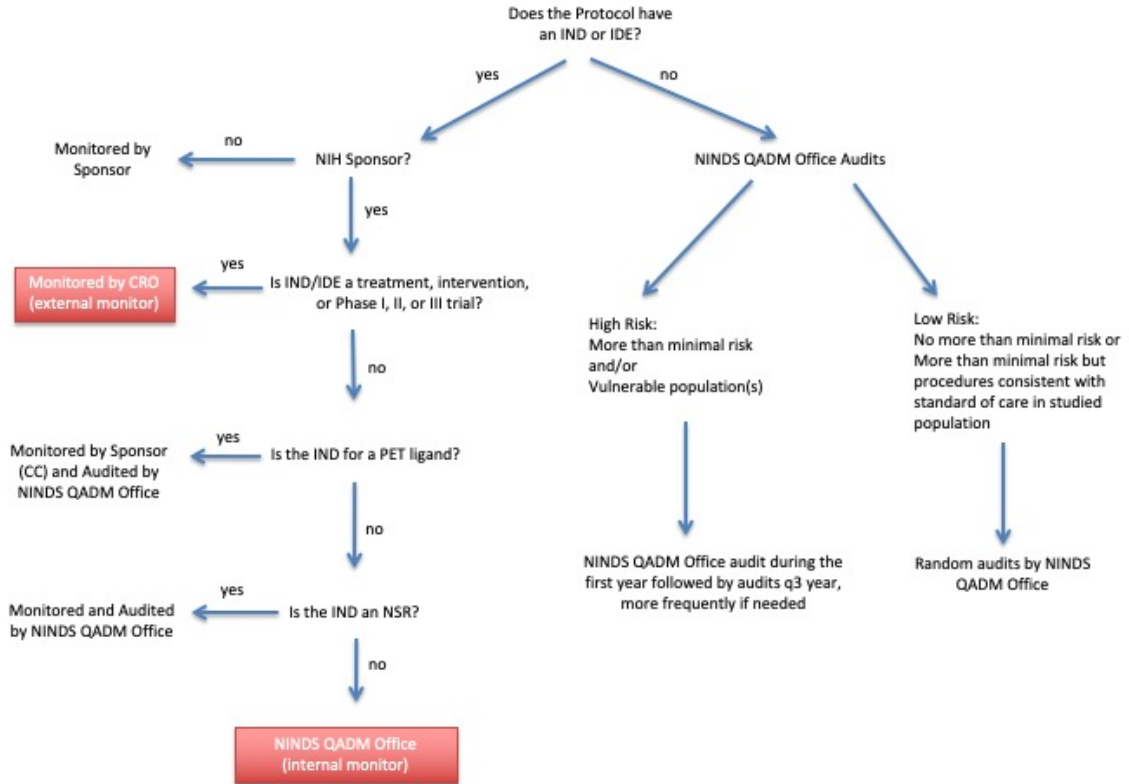 - o End of participation/early termination
  - o Outcome measures

- ☐ Study Oversight
  - o Subject monitoring
  - o Data and Safety monitoring
  - o QA auditing schedule
  - o Event Reporting (UPs, AEs, SAE, PDs)
  - o Stopping procedures
  - o Management of data and samples
  - o Data sharing (if applicable)

- ☐ Investigator Qualifications
  - o Investigator training (CITI GCP, CITI Biomedical, Elements of a Successful Consent, Events Reporting Training, Responsible Conduct of Research, Protocol specified training)
  - o Investigator CVs and Licenses (as applicable)
  - o IRTA and non-Credentialed Staff Competency Checklist, if applicable

- ☐ Data Management and Documentation
  - o Review of good documentation practice including ALCOA-C principles
  - o Identify source documentation
  - o Case Report Forms
  - o Subject logs (screening/enrollment logs)
  - o Adverse Events logs
  - o Non-compliance logs

☐ Regulatory Records Review
- o Review of Regulatory binder (electronic or paper)
  - ▪ See Audit Preparation Checklist (Section 1. Regulatory Review)

Appendix B: QA Monitoring/Auditing Algorithm

Does the Protocol have an IND or IDE?

- **yes** → **NIH Sponsor?**
  - **no** → Monitored by Sponsor
  - **yes** → **Is IND/IDE a treatment, intervention, or Phase I, II, or III trial?**
    - **yes** → Monitored by CRO (external monitor)
    - **no** → **Is the IND for a PET ligand?**
      - **yes** → Monitored by Sponsor (CC) and Audited by NINDS QADM Office
      - **no** → **Is the IND an NSR?**
        - **yes** → Monitored and Audited by NINDS QADM Office
        - **no** → NINDS QADM Office (internal monitor)
- **no** → **NINDS QADM Office Audits**
  - High Risk: More than minimal risk and/or Vulnerable population(s) → NINDS QADM Office audit during the first year followed by audits q3 year, more frequently if needed
  - Low Risk: No more than minimal risk or More than minimal risk but procedures consistent with standard of care in studied population → Random audits by NINDS QADM Office

Updated: 1/13/21

QADM = Quality Assurance and Data Monitoring

Appendix C: QA Audit Preparation Checklist

The primary purpose of a Quality Assurance audit is to ensure compliance with Good Clinical Practice Guidelines and to provide recommendations for the management of clinical research data. According to ICH E6 (R2) GCP Guidelines, an audit is the systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

The items listed below are materials which may be reviewed during the audit. Some items may be substituted or omitted, where appropriate, for the particular study identified for review (e.g., FDA correspondence would not be included in a non-FDA regulated study). The NINDS QADM Office will consider any tools that meet the standard for which it is used to satisfy.

During an audit, investigators should be prepared to provide the auditor(s) with a brief description of the protocol and to describe the schedule of visits (what happens when, what tests/labs are required at what time points). Additionally, investigators should provide the auditor(s) with information regarding the type of data that is generated from the research, how the data is documented and stored, and the origin of the data, (e.g., is the data generated from the subject (completing questionnaires) or instrument (biophysical data)).

Items below are materials to have available for a Quality Assurance Audit, as appropriate for the study under review:

Section 1. Regulatory Review (documents may be reviewed in an electronic or paper regulatory binder)
- ☐ Original protocol with approval
- ☐ All amendments with approvals
- ☐ All continuing reviews with approvals
- ☐ All acknowledgment letters (if applicable)
- ☐ Copies of past and present approved blank consent/assent forms
- ☐ Adverse event/SAE and Unanticipated Problem reporting documents (REF form in iRIS)
- ☐ Non-compliance (Protocol Deviation) documents
- ☐ Delegation of Authority/Signature Log
- ☐ Documentation of current GCP and HSP Training
- ☐ Documentation of Elements of a Successful Consent for Investigators with Consent Privileges
- ☐ Documentation of Events Reporting Training
- ☐ Documentation of Responsible Conduct of Research Training
- ☐ Documentation of any required Just-In-Time Training, as specified in the protocol
- ☐ IRTA and non-Credentialed Staff Competency Checklist (if applicable)
- ☐ Curriculum Vitae according to Delegation of Duties
- ☐ Professional Licenses/Certifications
- ☐ Staff Training Logs
- ☐ Laboratory Accreditations/Certificates (e.g., CLIA, CAP) (if applicable)
- ☐ Monitoring documents (if applicable; e.g., DSMB/SMC/IMM/PI reports and Quality Assurance Monitoring reports)
- ☐ Radiation Safety documents (if applicable)
- ☐ Technology Transfer documents (if applicable)
- ☐ FDA documents (if applicable) – Refer to Start-up Checklist for FDA regulated trials
- ☐ COI certificate for non-federal covered investigators

Section 2. Protocol Management
Overview of data collection tools:

    ☐ Sample data collection tools (e.g., blank questionnaires, checklists, CRFs)
    ☐ Source document review (e.g., progress notes, labs, questionnaires, original data documents or recordings)
    ☐ Screening/enrollment log
    ☐ Adverse Events log
    ☐ Lists of all study participants/codes (linked and unlinked data)
    ☐ Randomization method/code
    ☐ Investigational Product facility and accountability methods
    ☐ Sample Storage facilities and tracking system
    ☐ Data management tools (paper/computer; e.g., CiSTAR, CTDB, Excel spreadsheets, fileMaker)
    ☐ Describe measures taken to ensure data integrity (e.g., internal quality control checks)
    ☐ Describe measures taken to ensure patient confidentiality

Section 3. Participant Records (Individual Subject Data)
    ☐ Signed consent forms (reviewed in CRIS)
    ☐ Completed inclusion/exclusion checklist or equivalent memo documenting review of all eligibility criteria
    ☐ Source documents verifying eligibility, safety measures and primary and secondary outcome measures
    ☐ Verify data included in completed Case Report Forms (when utilized)

Section 4. NIH Medical Record Review
    ☐ Signed consent form in CRIS and properly completed (signatures, date, version)
    ☐ Documentation of informed consent process
    ☐ Documentation of screening procedures in progress notes and/or research records
    ☐ Documentation of each patient contact in progress note (e.g., study visits, study procedures, adverse events, phone calls)
    ☐ Required laboratory tests, EKG, data and safety monitoring measures, other tests at time interval(s), per the protocol
    ☐ Procedure notes for studies performed (PET, MRI, TMS etc.)