

## Clinical Monitoring and Site Verification

### Procedure Overview

To define the standard procedures for preparation and documentation of site visits for clinical monitoring and spoke verification for any NETT entity.

In compliance with GCP, the NETT CCC will perform independent site monitoring to verify regulatory compliance and data accuracy through periodic visits to each Hub/spoke complex. Visits are only made to Hub/spoke complexes as a whole, but information monitored can be from any component of the Hub/spoke complex, usually on a randomly selected basis. Sampling, if performed, will be determined by the SDMC.

In addition, Hubs are responsible for the completeness of regulatory documentation and the accuracy of data at their spokes. Verification of these is required and involves Hub personnel visiting their spokes and completing a standardized quality assurance process defined by the CCC for each trial.

### Purpose

The purpose of this document is to describe the clinical monitoring and verification expectations of participants in the NETT. Roles and responsibilities are defined.

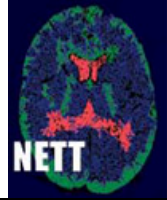
### Responsible Individuals

Qualified NETT and Hub Complex personnel (including, but not limited to, Site Manager and Project Monitor); Contracted Clinical Research Associates; NETT Director of Site Operations and/or designee.

#### 1. Definitions

- a. Monitoring – An onsite review of human subjects, regulatory, and data quality conducted by a NETT Project Monitor (or Contracted Clinical Research Associate of the NETT CCC) visiting a Hub/spoke complex.
- b. Hub complex - The NETT Hub institution and the spokes affiliated with the Hub.
- c. Institutional review board – The board within an institution providing oversight of research as described in 45 CFR Part 46.
- d. NETT entity. Any hub complex, affiliate hub, coordinating center, vendor, or subcontracted agent of the NETT network.

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- e. Verification – Quality assurance onsite visits performed by Hub personnel at spokes within their own Hub-spoke complex using standard processes defined by the NETT CCC.

## 2. Clinical Monitoring Visits

### a. Frequency of Clinical Monitoring Visits

- i. Monitoring visits to investigative sites are made at a frequency specified in the protocol-specific Data Safety Monitoring Plan (DSMP). The frequency should be sufficient to assure that the obligations of both the NETT Clinical Coordinating Center (CCC) and the investigator are fulfilled, data quality and integrity are ensured, and safety of subjects is maintained. Visits will occur at least once per year.
- ii. Monitoring visits can occur more frequently than specified in the study DSMP if requested by the Hub Complex PI, NETT Director of Site Operations, or the sponsor.
- iii. If the time interval between visits becomes longer than specified, the Project Monitor will document the reasons for the longer interval and report the variation to the Director of Site Operations.

### b. Procedures for Clinical Monitoring Visits

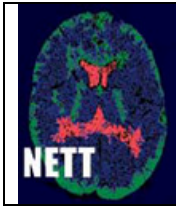
Prior to conducting the site visit, the Project Monitor will:

- i. Correspond with the Hub PI or designee to determine the location and time of the clinical monitoring.
- ii. Provide an agenda of activities, including a list of site personnel required for each, in the form of a Pre-Visit Site letter.
- iii. Obtain a list of subject IDs to be reviewed during the visit and provide the list to hub complex personnel.
- iv. Confirm that source and/or shadow documents will be available in order to conduct the visit.

### c. The following tasks are performed during a routine site visit:

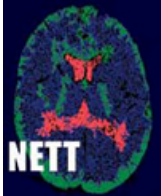
- i. Meet and consult with site personnel
  - 1) Verify adherence to applicable GCP, FDA regulations, and/or applicable regulations of the governing/regulatory agencies with jurisdiction over the clinical trial and investigative site regarding the obligations of the investigator.
  - 2) Conduct meetings with the Hub Complex and/or study investigators, and/or study staff to ensure that the obligations of the investigator are being fulfilled.

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- 3) Discuss enrollment strategies, reason(s) for early subject discontinuation, and identify any challenges at the site.
  - 4) Review Screening and Enrollment logs with investigator and/or study staff.
- ii Examine regulatory binder for identified regulatory materials not uploaded to the NETT WebDCU™
- 1) Inventory the on site regulatory binder for completeness based upon the requirements outlined in the study manual of procedures (MOP)
  - 2) Establish that subject related documents are maintained in compliance with study and institutional requirements.
  - 3) Determine that reports submitted by the investigator in support of the safety and/or efficacy of the test article are timely, adequate, and accurate
- iii Verify CRF data against source documents
- 1) Review relevant documentation (CRFS, source documents, shadow documents etc.) to confirm adherence to the study protocol or investigational plan.
  - 2) Ensure institutional review board approved informed consent documents are available and signed appropriately for each enrolled subject.
  - 3) Verify that enrolled subjects were eligible at time of enrollment, and that study procedures or interventions were initiated based on the timeline and enrollment procedures described in the study protocol.
  - 4) Review SAEs with investigator and site personnel and verify to source/shadow document
  - 5) Review CRFs and/or data entered into the NETT WebDCU™ for accuracy and completeness of information, illegible entries, and missing data by comparing the case report forms to the subject source records.
- iv Verify adequacy of facility (records locked up, visit pharmacy for study kit storage and pharmacy log)
- 1) Continued acceptability of the facilities (e.g. no significant changes in resources, storage space, patient population, etc.)
  - 2) Verify adequate maintenance of records on subject identification, clinical observations, laboratory tests, and study specific source documents

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- 3) Ensure the adequacy of CRFs, investigational product, and other clinical supplies
- v Review the findings with the site personnel
  - 1) Review and reconcile investigational product receipt, disposition, and inventory for protocol and institutional adherence
  - 2) Review of findings and actions items with study staff
- vi Resolve outstanding queries
  - 1) Resolve any pending data queries and verify changes to CRF entries as appropriate.
- d. The following tasks are performed after the site visit:
  - i Completion of the clinical monitoring report (as described in SOP “Records of Project Monitor”) The report will include:
    - 1) Visit participants
    - 2) Physical location of the visit
    - 3) A list of subject IDs reviewed during the visits
    - 4) Documentation for subjects who did not complete the study and the reason(s) for early discontinuation.
    - 5) Findings of investigational product review (if applicable)
    - 6) Identification, description, and reasons for protocol deviations or exemptions
    - 7) Action items and time lines for resolution
  - ii. Dissemination of report findings
    - 1) The report will be provided to the Hub Complex PI, Director of Site Operations, and the Study PI.
    - 2) The report will be retained in WebDCU™

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3. Site Verification
  - a. Each Hub Complex will provide oversight of their affiliated spokes via the site verification process.
  - b. The NETT CCC will provide a study specific list of tasks that must be reviewed during the site verification visit, prior to study initiation.
  - c. The Hub complex will submit a site verification plan to the NETT CCC for approval.
  - d. The personnel conducting the visit must complete the site verification report using the template after each visit into the WebDCU™.
  - e. The Project Monitor will review the site verification reports for action items.
  
4. Approval for Process Exemption
  - a. The Director of Site Operations or designee must approve and document exemption from the processes outlined in sections two and three of this policy.