NeuroNEXT Network

Standard Operating Procedure (SOP)

Routine Monitoring Visits

Version 2.0

SOP NN SS 403

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NN SS 403

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR ROUTINE MONITORING VISITS

SOP: NN SS 403 Version No: 2.0 Effective Date: 21Oct2016	ROUTINE MONITORING VISITS	Supercedes Document: Version 1.0 Effective Date: 06May2012

1. POLICY

This SOP describes procedures regarding scheduling, frequency, preparing for, and conducting a routine monitoring site visit for NeuroNEXT clinical trials. Routine monitoring visits to Clinical Study Sites (CSS) will be scheduled according to the requirements of the approved study monitoring plan. Guidelines for scheduling monitoring visits for each NeuroNEXT CSS will be determined by the NeuroNEXT Data Coordinating Center (DCC) in consultation with the Clinical Coordinating Center (CCC) and according to the stage of development and complexity of the studies at the CSS, the rates of subject accrual, and other factors.

These visits are conducted for routine monitoring only and are intended to ensure that the protocols and applicable regulatory requirements are being followed, that subjects' rights and safety are being protected, and to confirm data integrity and quality.

The objectives of routine monitoring visits are to:

- document and report on clinical study progress;
- document that the protocols and associated forms are current;
- update the site team of any changes in study conduct/documentation;
- ensure that the PPI/Sponsor requirements and investigator obligations are met;
- ensure continued acceptability of the investigator, site team and facility;
- obtain and review current clinical data, reports, and source documents;
- ensure adequate investigational product inventory and accountability, if applicable.

Activities conducted during the preparation for a monitoring visit include reviews of study documents, data queries, data reports, previous monitoring reports, and supplies of study materials (if applicable).

During the monitoring visit, the monitor performs the following activities:

- assesses the overall status of the study, staff, and facilities to determine whether the study is being conducted per protocol and in compliance with regulatory requirements;
- conducts a CRF review that includes checks of all adverse event documentation;
- verifies the presence of all essential documents and records related to investigational products and clinical supplies (if applicable); and
- determines if protocol violations have occurred and, if so, are documented properly.

After the monitoring visit, the monitor documents the results of the monitoring visits and completes a post-visit monitoring letter for each study that conveys any issues discovered during the visit and the need for data corrections, if appropriate.

2. SCOPE

This SOP has been developed to be in alignment with federal regulations and Good Clinical Practices (GCP) as set forth in the 1996 ICH E6 Consolidated Guidance. The policies and procedures described in this SOP apply to the NeuroNEXT CCC and DCC within the context of their oversight and advisory roles for the NeuroNEXT Network, and to all NeuroNEXT investigators, staff, subcontractors, or other

entities associated with the NeuroNEXT Network who manage, oversee, and conduct research regulated by FDA and/or applicable review committees.

3. ROLES AND RESPONSIBILITIES

The DCC is responsible for designating a trained and qualified member of the research team to serve as study Monitor. The DCC Monitor is responsible for preparing for, conducting, and documenting all monitoring visits.

The responsibility to conduct any or all of these activities will be delegated at the discretion of the Sponsor/PPI to the DCC, or to subcontractors of the DCC where applicable. Those individuals and entities also take on responsibility for meeting regulatory requirements on behalf of the Sponsor, but the Sponsor has the ultimate responsibility, and must therefore supervise those delegated activities effectively.

4. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.53	Selecting Investigators and Monitors
21 CFR 312.56	Review of Ongoing Investigations
ICH E6, 4.1	Investigator's Qualifications and Agreement
ICH E6, 5.5	Trial Management, Data Handling and Record Keeping
ICH E6, 5.18	Monitoring
FDA	Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (August 2013)

5. REFERENCES TO OTHER APPLICABLE SOPS

NN RA 202	Trial Master File Maintenance
NN RA 203	Site Regulatory File Maintenance
NN SS 402	Site Initiation Visits and Site Training
NN SS 404	Site Performance Monitoring
NN PM 501	Communication
NN PM 504	Investigational Site Staff Training
NN PM 505	Investigational Product Management
NN SM 602	Central Institutional Review Board Reporting
NN SM 603	Subject Eligibility and Enrollment
NN DM 1001	Clinical Data Management

6. ATTACHMENTS AND REFERENCES

NN SS 403 - A	Document History

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

AE	Adverse Events
CCC	Clinical Coordinating Center at Massachusetts General Hospital
CIRB	Central Institutional Review Board
CRF	Case Report Forms that are completed for each study subject at the sites
CSS	Clinical Study Site(s)
DCC	Data Coordinating Center at The University of Iowa

FDA	U.S. Food and Drug Administration
ICH	International Council for Harmonisation
PPI	Protocol Principal Investigator
RMF	Regulatory Master File

8. SPECIFIC PROCEDURES

A. Scheduling/Frequency of Monitoring Visits

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Lead Coordinator, DCC Monitor	Develop a monitoring plan that includes conducting a minimum of one monitoring visit at each CSS with an ongoing protocol per year.		
2.	DCC Monitor	Review study reports to determine when to schedule CSS visits according to the monitoring plan.		
3.	DCC Monitor	Conduct unscheduled or more frequent monitoring visits to CSS as needed.		
4.	DCC Monitor	Contact the investigator or designee and study coordinator regarding scheduling and conducting monitoring visits.		NN PM 501
5.	DCC Monitor	Confirm date and logistics of the monitoring visit in writing and provide the investigator with a list of source documents and records (e.g., medical records, laboratory records, etc.) to be reviewed.		NN PM 501
6.	DCC Monitor	Create a monitoring report to track CSS visits.		

B. Preparing for a Monitoring Visit

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Monitor or CCC Project Manager	Review the relevant contents of the project and site files in the study RMFs, if applicable, prior to the monitoring visit.		NN RA 202
2.	DCC Monitor	Review the current version of the clinical protocols and informed consent forms prior to the monitoring visit, if applicable.		
3.	DCC Monitor	Review the data reports and data queries for any data received to date for each study.		
4.	DCC Monitor	Review previous monitoring reports for any outstanding items that must be addressed prior to, or during, the next scheduled visit.		
5.	DCC Monitor	Determine the CSS inventory of study supplies, including forms or other relevant materials and investigational products (if applicable). Arrange to provide additional items as necessary.		

C. Conducting a Monitoring Visit

1. Overall Study Status

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Monitor	Verify that the CSS subject files for the study contain all required documents and records, and that they are accurate, complete, and current.		NN RA 203
2.	DCC Monitor	If requested by the CCC, confirm with the investigator that the CSS routinely files and forwards essential and required information to other required parties (e.g. CIRB) appropriately.	RA 203-B	NN SM 602
3.	DCC Lead Coordinator and DCC Monitor	Assess subject enrollment rates and examine unexpectedly high or low recruitment.		NN SM 603
4.	DCC Monitor	Review study screening and enrollment logs for information on subjects who failed to meet inclusion criteria, did not give informed consent, or withdrew from the study for any reason.		NN SM 603
5.	DCC Monitor	Confirm eligibility of enrolled subjects.		
6.	DCC Monitor	Confirm that all subjects have signed the correct version(s) of the informed consent form.		
7.	DCC Monitor	Evaluate status of follow-up plans and visits for subjects and identify problems.		
8.	DCC Monitor	Confirm that safety and efficacy assessments are conducted per the study protocols.		
9.	DCC Monitor	Verify that all specimens for protocol-specific laboratory studies are being stored and forwarded properly and that specimen preparation documentation is maintained.		NN PM 505
10.	DCC Monitor	Meet with investigator and key staff to discuss any scientific or administrative problems and possible solutions.		

2. CRF Review

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Monitor	Verify that CRFs[1] are being completed in a timely manner and per protocol requirements.		NN DM 1001
2.	DCC Monitor	Review the CRFs scheduled for review (as outlined in the monitoring plan) to ensure that they are complete, legible, consistent with protocol specifications, and signed by the appropriate site personnel.		
3.	DCC Monitor	For randomized studies, verify that the randomization procedures are being carried out per the study protocols.		
4.	DCC Monitor	Evaluate allocation of investigational products, if applicable.		NN PM 505

#	Who	Task	Attachment/ Reference	Related SOP
5.	DCC Monitor	Check data in the CRFs scheduled for review against source documents to assess accuracy and completeness of the information.		
6.	DCC Monitor	Review and address omissions and queries, and ensure that corrections to the CRFs are properly completed prior to departure.		
7.	DCC Monitor	Tabulate changes and corrections for updating the study databases.		
8.	DCC Monitor	Assess whether all adverse events (AEs) have been documented and reported as specified by the protocols, and that other relevant regulatory procedures have been followed.		NN SM 602
	Note: [1] CRF(s) can be paper or electronic.			

3. Investigational Products and Other Clinical Supplies (if applicable)

#	Who	Task	Attachment	Related SOP
1.	DCC Monitor	Verify storage of investigational products and other clinical supplies.		NN PM 505
2.	DCC Monitor	Assess investigational product dispensing and accountability records.		NN PM 505
3.	DCC Monitor	Examine storage freezers and other storage equipment to confirm they are appropriate for the clinical protocol's requirements, and that calibration and temperature logs are maintained in the CSS study files.		NN PM 505

4. Staff and Facilities

#	Who	Task	Attachment	Related SOP
1.	DCC Monitor	Confirm each study investigator's control of the study and assess his/her ongoing participation and any responsibility delegations not previously reported.		
2.		Assess the ongoing suitability of facilities and staff for conducting the study.		
3.		Note and record any changes in staff or facility not previously reported.		NN SS 402
4.		If applicable, discuss scheduling additional study training for new staff.		NN PM 504

5. Communications Records

#	Who	Task	Attachment	Related SOP
1.	DCC Monitor	Confirm that copies of all critical correspondence (electronic, paper), including facsimile correspondence and notes of telephone conversations, are maintained on file at the CSS.		NN RA 203

6. Protocol Violations

#	*Who*	*Task*	*Attachment*	*Related SOP*
1.	DCC Monitor	Note whether the records show any evidence that protocol violations have occurred, and record the nature of these violations.		
2.	DCC Monitor	For each study, review any issues related to study conduct or other incidents of noncompliance with the investigator and other key study personnel, and document the issues on the monitoring report.		
3.	DCC Monitor	If needed, an ongoing process of counseling, re-education and re-training shall be undertaken by the appropriate Study staff to ensure trial CSS compliance.		NN SS 404

7. Documenting Results of Monitoring Visits

#	*Who*	*Task*	*Attachment*	*Related SOP*
1.	DCC	Document all visits by monitors and other authorized parties on a Site Visit Log.		NN SS 402
2.		Document the outcome of all scheduled and unscheduled monitoring visits.		
3.		Complete a post visit monitoring letter for each study. The letter may include and address the following, if applicable: • Protocol Compliance • Subject enrollment and study timelines • Review of regulatory documents and findings • Review of subject files and source documents • Investigational product accountability • Data corrections • Pending issues and action items		
4.		Provide the CCC with copies of the completed Monitoring Visit Checklists, Reports, and the CSS post-visit monitoring letters for review.		
5.		Provide the CSS Study PI and Study Coordinator with the post-visit monitoring letter(s).		
6.		Instruct site to place the post-visit monitoring letter(s) in the study Regulatory binder.		
7.		File the completed reports and letters in the appropriate site files in the RMF.		NN RA 203

Attachment NN SS 403 - A. Document History

NeuroNEXT Network Standard Operating Procedure (SOP) Routine Monitoring Visits SOP NN SS 403				
Version	**Description of Modification**	**Reason or Justification for Modification**	**Issue Date**	**Effective Date**
1.0	New	N/A	06Apr2012	06May2012
2.0	Clarified that scheduling for monitoring visits is according to the study monitoring plan. Added CCC Project Manager responsibilities for reviewing study RMF files, and removed responsibility for DCC Monitor to reconcile the CSS study files with the RMF. Deleted obsolete FDA Guidance for monitoring, and added 2013 FDA Guidance on risk-based monitoring. Several other minor administrative edits.	Updates for version 2.0	21Sep2016	21Oct2016