NeuroNEXT Network

Standard Operating Procedure (SOP)

Medical Monitoring and Safety Monitoring

Version 2.0

SOP NN RA 206

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NN RA 206

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR MEDICAL MONITORING AND SAFETY MONITORING

SOP: NN RA 206 Version No.: 2.0 Effective Date: 21Oct2016	MEDICAL MONITORING AND SAFETY MONITORING	Supercedes Document: Version 1.0 Effective Date: 06May2012

1. POLICY

It is the policy of the NeuroNEXT Network that each study conducted within the Network will have the appropriate level of Medical and Safety Monitoring, based upon the complexity and risk/benefit profile of the study. The level and detail of monitoring will be described in a Safety Management Plan that provides details regarding independent oversight of the study, and includes processes and procedures for:

- ensuring human subject protection and confidentiality;
- assessing, documenting, and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), and unexpected problems (UPs) or events; and
- stopping the study due to safety concerns.

Depending on the nature of the study, the Safety Management Plan may include discussion of the following:

- Inclusion and exclusion criteria
- Potential risks of the study and an overall plan for protection against risks
- A plan for assessing, documenting and reporting AEs, SAEs, and UPs that should include:
    - The method by which Adverse Events (AEs) are to be reported for the study (i.e. paper-based or web-based). In the event that reporting is web-based, instructions for paper-based submissions will also be included should the site be unable to access the web-based system for any reason.
    - The period for the required reporting and tracking of AEs
    - The criteria for an Adverse Event to be considered Serious
    - The criteria for an Serious Adverse Event (SAE) to be considered related/unrelated as well as expected/ unexpected in relation to the Investigational Product or device
    - The review flow of an SAE once it has been reported by a site to the Sponsor (or CCC or DCC designee); reviewers may include: the Independent Medical Monitor or Medical Safety Monitor (to be referred to as the Safety Monitor), Protocol Principal Investigator (PPI) / Sponsor, Protocol Steering Committee (PSC), Data and Safety Monitoring Board (DSMB), or other appropriate oversight committees or entities.
    - The process and responsibility for determining whether an SAE meets the criteria for expedited reporting to the Federal Agency and for completing this expedited reporting
    - AE/SAE/UP reporting forms
- Roles and responsibilities of the DSMB and Safety Monitor.
- Plan for interim reviews of study data
- Interim monitoring plan
- Interim efficacy assessment
- Interim futility assessment

- Stopping rules
- Process for distributing IND Safety Reports to participating CSS

The National Institute of Neurological Disorders and Stroke (NINDS) will assess each study and will appoint a DSMB as appropriate. In addition, some studies may require the services of a Safety Monitor to perform "real time" and periodic safety reviews. A Safety Monitor is not part of the PPI research team. For purposes of developing a budget, the PPI should assume that interventional studies will require an independent DSMB that will be appointed, managed, and funded by NINDS; and a Safety Monitor, who will be named by the PPI and funded through the proposed study budget.

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 procedures described in this SOP apply to the NeuroNEXT Clinical Coordinating Center (CCC) and Data Coordinating Center (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 NeuroNEXT PPI is responsible for recommending the level of medical and safety monitoring required for the study, in consultation with NINDS and relevant members of the CCC and DCC. The PPI will ensure that the study budget includes appropriate funding for their recommended level of medical and safety monitoring, and to provide justification for this budget item in their grant application.

NINDS is responsible for reviewing the PPI's recommended level of safety monitoring and determining the level of funding for this activity.

If medical monitoring is required for a study, the PPI will contract with a Safety Monitor who is qualified by training and experience to perform this role. The PPI, in collaboration with members of the CCC and DCC, will create study-specific guidelines for the Safety Monitor, as appropriate, and ensure that the Safety Monitor is properly trained on the study protocol and his/her role in monitoring the study

The NeuroNEXT DCC will provide the Safety Monitor and the DSMB with safety reports that are appropriate for the study. These may be "real time" Serious Adverse Event (SAE) Reports and/or monthly or quarterly aggregate Serious and non-Serious Adverse Event Reports. The Safety Monitor will forward any concerns that arise due to observed trends to the DSMB for review. The NeuroNEXT DCC will provide the DSMB with blinded safety reports unless the DSMB requests to be un-blinded.

The NINDS will determine the need for a DSMB and will appoint qualified members to fulfill the duties of the DSMB. The DSMB will perform oversight activities that include, but are not limited to, the following:

- Reviewing the study protocol
- Providing recommendations to NINDS regarding protocol revisions prior to study initiation and throughout study implementation.
- Reviewing study data on a periodic basis, as determined by NINDS
- Communicating any concerns to NINDS throughout the study.

The PPI, in collaboration with the CCC and/or DCC, will develop a Safety Management Plan, or similar guidance document, to document Serious and non-Serious Adverse Event reviewing and reporting guidelines for each study.

The responsibility to conduct any or all of these activities may be delegated at the discretion of the Sponsor/PPI to the NeuroNEXT CCC and/or DCC, or to their subcontractors. Those individuals and entities 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 312.50	General Responsibility of Sponsors
ICH E6, 2.7	The Principles of ICH GCP
ICH E6, 4.3	Medical Care of Trial Subjects
ICH E6, 4.7	Randomization Procedures and Unblinding
ICH E6, 4.11	Safety Reporting
ICH E6, 5.16	Safety Information
ICH E6, 5.17	Adverse Drug Reaction Reporting
ICH E6, 6.8	Assessment of Safety

5. REFERENCES TO OTHER APPLICABLE SOPS

NN RA 205	Adverse Events: Sponsor Responsibilities

6. ATTACHMENTS AND REFERENCES

NN RA 206-A	Document History

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

AE	Adverse Event
CCC	Clinical Coordinating Center at Massachusetts General Hospital
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board (Partners Healthcare)
CSS	Clinical Study Site
DCC	Data Coordinating Center at The University of Iowa
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
NINDS	National Institute of Neurological Disorders and Stroke
PPI	Protocol Principal Investigator
PSC	Protocol Steering Committee
SAE	Serious Adverse Event

8. SPECIFIC PROCEDURES

A. Safety Oversight

#	*Who*	*Task*	*Attachment/ References*	*Related SOP*
1.	NINDS	Establish and appoint members to the NeuroNEXT Network DSMB.		
2.	NINDS, PPI	Assess whether the study requires individuals with special expertise to be added to the NeuroNEXT		

#	Who	Task	Attachment/ References	Related SOP
		Network DSMB.		
3.	PPI / CCC or DCC designee	Recommend the level of medical and safety monitoring to be proposed for the study.		
4.	PPI and CCC	Budget appropriately for proposed level of medical and safety monitoring.		
5.	PPI and CCC or DCC	Create a study-specific Safety Management Plan as described in the Policy section of this SOP.		

B. Medical Monitoring

#	Who	Task	Attachment/ References	Related SOP
1.	PPI and DCC	Develop study-specific guidelines for the Safety Monitor, if required.		
2.	PPI and DCC	Identify and train the Safety Monitor, if required.		
3.	DCC	Provide real-time Serious Adverse Event (SAE) reports to the Safety Monitor and assist in obtaining additional information if necessary for review.		
4.	DCC	Provide aggregate Serious and non-Serious Adverse Event reports to the Safety Monitor on an agreed upon frequency in order to identify trends.		
5.	Safety Monitor	Evaluate all reports, whether real-time or aggregate reports, according to an established plan. Communicate any concerns regarding observed trends to the DSMB for review.		

C. NINDS Data and Safety Monitoring Board

#	Who	Task	Attachment/ References	Related SOP
1.	DSMB	Complete review of study protocol prior to or in conjunction with finalization and CIRB submissions.		
2.	DCC	Provide summary blinded safety reports to the DSMB unless requested by DSMB to be un-blinded.		
3.	DSMB	Conduct periodic meetings for review of study data and safety reports.		
4.	DSMB	Make recommendations to NINDS regarding study changes.		
5.	DSMB	Communicate any study concerns to NINDS.		

Attachment NN RA 206 - A. Document History

NeuroNEXT Network Standard Operating Procedure (SOP) Medical Monitoring and Safety Monitoring SOP NN RA 206				
Version	**Description of Modification**	**Reason or Justification for Modification**	**Issue Date**	**Effective Date**
1.0	New	N/A	06Apr2012	06May2012
2.0	Replaced the term 'Data and Safety Monitoring Plan' with 'Safety Management Plan', replaced references to the IMM or the MSM with 'Safety Monitor', and clarified the role of the Safety Monitor in reviewing reports.	Updates for version 2.0	21Sep2016	21Oct2016