NeuroNEXT Network

Standard Operating Procedure (SOP)

Medical Monitoring and Safety Monitoring

Version 4.0

SOP NN RA 206

Originators: NeuroNEXT CCC and DCC Personnel

Reviewed and Approved by:

Signature and Date: Christopher S. Coffey *Electronically signed by: Christopher S. Coffey Reason: I approve this document Date: Mar 8, 2024 08:12 CST* 08-Mar-2024
Name and Title: Christopher S. Coffey, PhD (DCC Principal Investigator)
Signature and Date: Merit Cudkowicz *Electronically signed by: Merit Cudkowicz Reason: I approve this document Date: Feb 29, 2024 20:52 MST* 29-Feb-2024
Name and Title: Merit E. Cudkowicz, MD MSc (CCC Principal Investigator)
Signature and Date: Marianne Chase *Electronically signed by: Marianne Chase Reason: I approve this document Date: Feb 22. 2024 14:52 EST* 22-Feb-2024
Name and Title: Marianne Chase, BA (CCC Senior Director of Clinical Trials Operations)

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR MEDICAL MONITORING AND SAFETY MONITORING

SOP: NN RA 206 Version No.: 4.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	MEDICAL MONITORING AND SAFETY MONITORING	Supersedes Document : Version 3.0 Effective Date : 08Apr2023

Signature and Date:

Dixie Ecklund

Electronically signed by: Dixie Ecklund
Reason: I approve this document
Date: Feb 24, 2024 17:17 CST

24-Feb-2024

Name and Title: Dixie J. Ecklund, RN MSN MBA (DCC Associate Director)

Signature and Date:

Electronically signed by: Stacey Grabert
Reason: I approve this document
Date: Feb 22, 2024 13:55 EST

22-Feb-2024

Name and Title: Stacey Grabert, Pharm.D, MS, (CCC Director of Quality Assurance)

Signature and Date:

Joan Ohayon

Electronically signed by: Joan Ohayon
Reason: I approve this document
Date: Mar 11, 2024 11:18 EDT

11-Mar-2024

Name and Title: Joan Ohayon, RN, MSN, CRNP, MSCN (NINDS, NeuroNEXT Program Official)

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR MEDICAL MONITORING AND SAFETY MONITORING

SOP: NN RA 206 Version No.: 4.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	MEDICAL MONITORING AND SAFETY MONITORING	Supersedes Document : Version 3.0 Effective Date : 2Mar2023

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 participant protection and confidentiality;
- assessing, documenting, and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), and unanticipated 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 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 AE to be considered Serious
    - The criteria for an 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 Clinical Coordinating Center [CCC] or Data Coordinating Center [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 Investigational New Drug (IND) Safety Reports to participating Clinical Study Sites (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 2016 Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 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 Safety Monitor will review relevant SOPs, study protocol, Safety Management Plan, and process for reviewing and evaluating adverse events on the NeuroNEXT private website.

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
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 Council for Harmonisation

SOP: NN RA 206 Version No.: 4.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	MEDICAL MONITORING AND SAFETY MONITORING	Supersedes Document : Version 3.0 Effective Date : 08Apr2023

IND	Investigational New Drug
NINDS	National Institute of Neurological Disorders and Stroke
PPI	Protocol Principal Investigator
PSC	Protocol Steering Committee
SAE	Serious Adverse Event
SIRB	Single Institutional Review Board (Mass General Brigham)
UP	Unanticipated Problem

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 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.		

SOP: NN RA 206 Version No.: 4.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	MEDICAL MONITORING AND SAFETY MONITORING	Supersedes Document : Version 3.0 Effective Date : 2Mar2023

9. SPECIFIC PROCEDURES

B. Medical Monitoring

#	*Who*	*Task*	*Attachment/ References*	*Related SOP*
1.	PPI and DCC	Identify the Safety Monitor for the study, if required.		
2.	PPI and DCC	Train the Safety Monitor by review of the following: a. Relevant SOPs b. Study protocol c. Safety Management Plan d. Study specific guidelines		
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 SIRB 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.		

SOP: NN RA 206 Version No.: 4.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	MEDICAL MONITORING AND SAFETY MONITORING	Supersedes Document : Version 3.0 Effective Date : 08Apr2023

Attachment NN RA 206 – 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**	**Reviewer(s)**
1.0	New	N/A	06Apr2012	06May2012	N/A
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	N/A
3.0	Updated "1996 ICH E6 Consolidated Guidance" to "2016 Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)". Updated signature block to accommodate for electronic signatures. Additional minor updates throughout.	Updated for version 3.0	22Feb2023	08Apr2023	Catherine Gladden
4.0	Minor edits for clarity	Periodic review	01Mar2024	15Apr2024	Preeti Paul

NN RA 206 Medical Monitoring and Safety Monitoring v4.0 2feb2024 clean

Final Audit Report 2024-03-11

Created:	2024-02-22
By:	Tania Leeder (tleeder@mgb.org)
Status:	Signed
Transaction ID:	CBJCHBCAABAAKa9SN7Qq-jy72s9hHg6QYQ-OG1utbaTk
Number of Documents:	1
Document page count:	8
Number of supporting files:	0
Supporting files page count:	0

"NN RA 206 Medical Monitoring and Safety Monitoring v4.0 2feb 2024 clean" History

Document created by Tania Leeder (tleeder@mgb.org)
2024-02-22 - 6:10:32 PM GMT

Document emailed to christopher-coffey@uiowa.edu for signature
2024-02-22 - 6:11:58 PM GMT

Document emailed to cudkowicz.merit@mgh.harvard.edu for signature
2024-02-22 - 6:11:58 PM GMT

Document emailed to Marianne Chase (mchase@mgh.harvard.edu) for signature
2024-02-22 - 6:11:59 PM GMT

Document emailed to dixie-ecklund@uiowa.edu for signature
2024-02-22 - 6:11:59 PM GMT

Document emailed to Stacey Grabert (SGrabert@mgh.harvard.edu) for signature
2024-02-22 - 6:11:59 PM GMT

Document emailed to ohayonj@ninds.nih.gov for signature
2024-02-22 - 6:11:59 PM GMT

Stacey Grabert (SGrabert@mgh.harvard.edu) authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-02-22 - 6:55:37 PM GMT

Document e-signed by Stacey Grabert (SGrabert@mgh.harvard.edu)

Signing reason: I approve this document

Signature Date: 2024-02-22 - 6:55:47 PM GMT - Time Source: server

Marianne Chase (mchase@mgh.harvard.edu) authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-02-22 - 7:51:59 PM GMT

Document e-signed by Marianne Chase (mchase@mgh.harvard.edu)

Signing reason: I approve this document

Signature Date: 2024-02-22 - 7:52:11 PM GMT - Time Source: server

Email viewed by christopher-coffey@uiowa.edu

2024-02-22 - 7:55:46 PM GMT

Tania Leeder (tleeder@mgb.org) added alternate signer cscoffey@iowa.uiowa.edu. The original signer christopher-coffey@uiowa.edu can still sign.

2024-02-23 - 6:54:46 PM GMT

Document emailed to cscoffey@iowa.uiowa.edu for signature

2024-02-23 - 6:54:46 PM GMT

Tania Leeder (tleeder@mgb.org) added alternate signer ecklundd@uiowa.edu. The original signer dixie-ecklund@uiowa.edu can still sign.

2024-02-23 - 6:54:59 PM GMT

Document emailed to ecklundd@uiowa.edu for signature

2024-02-23 - 6:54:59 PM GMT

Email viewed by cscoffey@iowa.uiowa.edu

2024-02-23 - 7:14:11 PM GMT

Email viewed by ecklundd@uiowa.edu

2024-02-24 - 11:16:55 PM GMT

ecklundd@uiowa.edu authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-02-24 - 11:17:10 PM GMT

Signer ecklundd@uiowa.edu entered name at signing as Dixie Ecklund

2024-02-24 - 11:17:24 PM GMT

Document e-signed by Dixie Ecklund (ecklundd@uiowa.edu)

Signing reason: I approve this document

Signature Date: 2024-02-24 - 11:17:27 PM GMT - Time Source: server

Email viewed by cudkowicz.merit@mgh.harvard.edu

2024-03-01 - 3:52:00 AM GMT

cudkowicz.merit@mgh.harvard.edu authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-03-01 - 3:52:28 AM GMT

Signer cudkowicz.merit@mgh.harvard.edu entered name at signing as Merit Cudkowicz

2024-03-01 - 3:52:39 AM GMT

Document e-signed by Merit Cudkowicz (cudkowicz.merit@mgh.harvard.edu)

Signing reason: I approve this document

Signature Date: 2024-03-01 - 3:52:41 AM GMT - Time Source: server

Email viewed by cscoffey@iowa.uiowa.edu

2024-03-08 - 9:19:54 AM GMT- IP address: 172.226.137.0

cscoffey@iowa.uiowa.edu authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-03-08 - 2:11:52 PM GMT

Signer cscoffey@iowa.uiowa.edu entered name at signing as Christopher S. Coffey

2024-03-08 - 2:12:07 PM GMT- IP address: 128.255.113.139

Document e-signed by Christopher S. Coffey (cscoffey@iowa.uiowa.edu)

Signing reason: I approve this document

Signature Date: 2024-03-08 - 2:12:10 PM GMT - Time Source: server- IP address: 128.255.113.139

Email viewed by ohayonj@ninds.nih.gov

2024-03-11 - 3:18:11 PM GMT- IP address: 104.47.64.254

ohayonj@ninds.nih.gov authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-03-11 - 3:18:21 PM GMT

Signer ohayonj@ninds.nih.gov entered name at signing as Joan Ohayon

2024-03-11 - 3:18:34 PM GMT- IP address: 72.83.187.43

Document e-signed by Joan Ohayon (ohayonj@ninds.nih.gov)

Signing reason: I approve this document

Signature Date: 2024-03-11 - 3:18:36 PM GMT - Time Source: server- IP address: 72.83.187.43

Agreement completed.

2024-03-11 - 3:18:36 PM GMT