NeuroNEXT Network

Standard Operating Procedure (SOP)

Adverse Events: Sponsor Responsibilities

Version 3.0

SOP NN RA 205

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 08:11 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 22, 2024 12:13 CST* 22-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 14:55 EST* 22-Feb-2024
Name and Title: Marianne Chase, BA (CCC Senior Director of Clinical Trials Operations)

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR ADVERSE EVENTS: SPONSOR RESPONSIBILITIES

SOP: RA 205 Version No.: 3.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	ADVERSE EVENTS: SPONSOR RESPONSIBILITIES	Supersedes Document : Version 2.0 Effective Date : 08Apr2023

Signature and Date:

Dixie Ecklund

Electronically signed by: Dixie Ecklund
Reason: I approve this document
Date: Feb 24, 2024 17:16 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 13:54 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 ADVERSE EVENTS: SPONSOR RESPONSIBILITIES

SOP: RA 205 Version No.: 3.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	ADVERSE EVENTS: SPONSOR RESPONSIBILITIES	Supersedes Document : Version 2.0 Effective Date : 08Apr2023

1. POLICY

The NeuroNEXT Protocol Principal Investigator (PPI) will typically be the Investigational New Drug (IND) holder/Sponsor for NeuroNEXT protocols. The PPI or industry Sponsor, as the IND holder that is regulated by the US Food and Drug Administration (FDA), will be responsible for investigating and reporting to the FDA all Adverse Events (AE) and Serious Adverse Events (SAE) that occur during the conduct of a clinical study within the period of time defined by federal regulations, and may delegate this responsibility to the study designated Safety Monitor. The PPI will ensure that all participating investigators and their key study personnel are familiar with protocol-defined adverse events for investigational products under investigation, and that they are aware of the protocol-defined process by which AEs and SAEs are to be elicited and documented throughout the study.

For studies not regulated by the FDA, the NeuroNEXT PPI will delegate responsibility of reviewing and reporting AEs and SAEs, as outlined in the study protocol, to the Safety Monitor.

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 policies and 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 Sponsor/PPI, or their designee (i.e., Safety Monitor), is responsible for ensuring the collection and reporting of all AEs as described in the study protocol. If the study is regulated by the FDA, these events are to be reported annually as described in 21 CFR 312.33.

The Sponsor/PPI, or their designee (i.e., Safety Monitor), is responsible for ensuring the collection, evaluation, and reporting all SAEs as described in the study protocol and other applicable study documents (e.g. Safety Management Plan). If the study is regulated by the FDA, the Sponsor/PPI is responsible for reporting these events in an expedited fashion if they meet the regulatory requirement for such reporting, as well as annually as described in 21 CFR 312.32 and 21 CFR 312.33, respectively.

The Sponsor/PPI, or designee (i.e., Safety Monitor), is responsible for ensuring that all participating investigators are aware of their responsibility to recognize and report all AEs and SAEs according to applicable regulations, guidelines, and the requirements of the protocol. All AEs and SAEs are to be reported using appropriate eCRFs and other forms, as required per protocol.

The PPI, or their designee (i.e., Safety Monitor), shall evaluate each reported Serious Adverse Event for the following:

- Serious / non-Serious: Does this event meet the regulatory definition of “Serious”?
- Expected / Unexpected: Is the event, including the severity and duration of the event, listed in the Investigators Brochure / Package Insert provided for this trial?
- Relationship to Study Drug/Intervention: Is there a possible causal relationship between the event and the investigational product?

The NeuroNEXT SOP NN RA 206 for *Medical Monitoring and Safety Monitoring* addresses the monitoring of serious adverse events and other medical events of interest in NeuroNEXT studies.

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/PPI, but the Sponsor/PPI has the ultimate responsibility and must therefore, supervise those delegated activities effectively.

4. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.32	IND Safety Reports
21 CFR 312.33	Annual Reports
21 CFR 312.50	General Responsibility of Sponsors
21 CFR 312.55	Informing Investigators
21 CFR 312.56	Review of Ongoing Investigations
21 CFR 312.64	Investigator Reports
ICH E6, 2.7	The Principles of ICH GCP
ICH E6, 4.3	Medical Care of Trial Subjects
ICH E6, 4.11	Safety Reporting
ICH E6, 5.3	Medical Expertise
ICH E6, 5.5	Trial Management, Data Handling and Record Keeping
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 201	Regulatory Authority Submission and FDA Contact
NN RA 206	Medical Monitoring and Safety Monitoring
NN SS 402	Site Initiation Visits and Site Training
NN PM 504	Investigational Site Staff Training
NN SM 602	Single Institutional Review Board Reporting

6. ATTACHMENTS AND REFERENCES

NN RA 205-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

SOP: RA 205 Version No.: 3.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	ADVERSE EVENTS: SPONSOR RESPONSIBILITIES	Supersedes Document : Version 2.0 Effective Date : 08Apr2023

CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center at The University of Iowa
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IND	Investigational New Drug
PPI	Protocol Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

8. SPECIFIC PROCEDURES

A. Adverse Events Reporting

#	*Who*	*Task*	*Attachment/ References*	*Related SOP*
1.	PPI / CCC / DCC or designee	Train all investigators and key study personnel on protocol-defined adverse events		NN SS 402 NN PM 504
2.	PPI / CCC / DCC or designee	Train all investigators and key study personnel on their role in identifying and reporting all AEs that occur throughout the study, as defined per protocol		NN SS 402 NN PM 504
3.	PPI / CCC / DCC or designee	Provide safety data to any safety oversight committees as defined per protocol		
4.	PPI / Sponsor / CCC / DCC or designee	Report cumulative safety data to FDA, if applicable, per 21 CFR 312.33		NN RA 201

B. Serious Adverse Event Reporting

#	*Who*	*Task*	*Attachment/ References*	*Related SOP*
2	PPI / CCC / DCC or designee	Train all investigators and key study personnel on their role in identifying and reporting all SAEs that occur throughout the study, as defined per protocol		NN SS 402 NN PM 504
3	PPI / CCC / DCC, Safety Monitor or designee	Evaluate each report of a SAE to determine if it meets the definition of “serious”, “unexpected”, and/or “possibly related to the study drug”		

SOP: RA 205 Version No.: 3.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	ADVERSE EVENTS: SPONSOR RESPONSIBILITIES	Supersedes Document : Version 2.0 Effective Date : 08Apr2023

#	*Who*	*Task*	*Attachment/ References*	*Related SOP*
4	PPI / CCC / DCC, Safety Monitor or designee	If study is being conducted under an IND, determine if SAE meets regulatory requirements for expedited reporting to FDA and submit report as appropriate		NN RA 201
5	PPI / CCC / DCC or designee	Provide safety data to any safety oversight committees as defined per protocol		NN SM 602
6	PPI / Sponsor/ CCC / DCC or designee	Report cumulative safety data to FDA, if applicable, per 21 CFR 312.33		NN RA 201

SOP: RA 205 Version No.: 3.0 Issue Date: 01Mar2024 Effective Date: 15Apr2024	ADVERSE EVENTS: SPONSOR RESPONSIBILITIES	Supersedes Document : Version 2.0 Effective Date : 08Apr2023

Attachment NN RA 205 - A. Document History

NeuroNEXT Network Standard Operating Procedure (SOP) Adverse Events: Sponsor Responsibilities SOP NN RA 205					
Version	**Description of Modification**	**Reason or Justification for Modification**	**Issue Date**	**Effective Date**	**Reviewer(s)**
1.0	New	N/A	06Apr2012	06May2012	N/A
1.0	Reviewed – no changes (2016)	N/A	06Apr2012	06May2012	N/A
2.0	Replaced the term 'Data and Safety Monitoring Plan' with 'Safety Management Plan' and replaced references to the IMM with 'Safety Monitor'. Updated "1996 ICH E6 Consolidated Guidance" to "2016 Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)". Additional minor updates throughout. Updated signature block to accommodate for electronic signatures. Additional minor updates throughout.	Updated for version 2.0	22Feb2023	08Apr2023	Catherine Gladden
3.0	Minor updates	Periodic review	01Mar2024	15Apr2024	Preeti Paul

NN RA 205 Adverse Events-Sponsor Responsibilities v3.0 2feb2024 clean

Final Audit Report 2024-03-11

Created:	2024-02-22
By:	Tania Leeder (tleeder@mgb.org)
Status:	Signed
Transaction ID:	CBJCHBCAABAAR1VzQDImsJ8WBUnq6YKrFsXgrD9lFQFV
Number of Documents:	1
Document page count:	7
Number of supporting files:	0
Supporting files page count:	0

"NN RA 205 Adverse Events-Sponsor Responsibilities v3.0 2feb 2024 clean" History

Document created by Tania Leeder (tleeder@mgb.org)
2024-02-22 - 6:08:19 PM GMT

Document emailed to christopher-coffey@uiowa.edu for signature
2024-02-22 - 6:09:51 PM GMT

Document emailed to cudkowicz.merit@mgh.harvard.edu for signature
2024-02-22 - 6:09:51 PM GMT

Document emailed to Marianne Chase (mchase@mgh.harvard.edu) for signature
2024-02-22 - 6:09:51 PM GMT

Document emailed to dixie-ecklund@uiowa.edu for signature
2024-02-22 - 6:09:51 PM GMT

Document emailed to Stacey Grabert (SGrabert@mgh.harvard.edu) for signature
2024-02-22 - 6:09:51 PM GMT

Document emailed to ohayonj@ninds.nih.gov for signature
2024-02-22 - 6:09:51 PM GMT

Email viewed by cudkowicz.merit@mgh.harvard.edu
2024-02-22 - 6:11:53 PM GMT

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

Challenge: The user opened the agreement.

2024-02-22 - 6:12:19 PM GMT

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

2024-02-22 - 6:13:02 PM GMT

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

Signing reason: I approve this document

Signature Date: 2024-02-22 - 6:13:04 PM GMT - Time Source: server

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

Challenge: The user opened the agreement.

2024-02-22 - 6:54:47 PM GMT

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

Signing reason: I approve this document

Signature Date: 2024-02-22 - 6:54:56 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 - 7:54:51 PM GMT

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

Signing reason: I approve this document

Signature Date: 2024-02-22 - 7:55:02 PM GMT - Time Source: server

Email viewed by christopher-coffey@uiowa.edu

2024-02-22 - 7:55:16 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 - 6:55:07 PM GMT

Document emailed to ecklundd@uiowa.edu for signature

2024-02-23 - 6:55:08 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 - 6:55:41 PM GMT

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

2024-02-23 - 6:55:42 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 - 11:16:23 PM GMT

ecklundd@uiowa.edu authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-02-24 - 11:16:36 PM GMT

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

2024-02-24 - 11:16:48 PM GMT

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

Signing reason: I approve this document

Signature Date: 2024-02-24 - 11:16:51 PM 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 - 2:11:06 PM GMT

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

2024-03-08 - 2:11:24 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 - 2:11:26 PM GMT - Time Source: server- IP address: 128.255.113.139

Email viewed by ohayonj@ninds.nih.gov

2024-03-11 - 3:17:36 PM GMT- IP address: 104.47.65.254

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

Challenge: The user opened the agreement.

2024-03-11 - 3:17:46 PM GMT

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

2024-03-11 - 3:17:58 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 - 3:18:00 PM GMT - Time Source: server- IP address: 72.83.187.43

Agreement completed.

2024-03-11 - 3:18:00 PM GMT