NeuroNEXT Network
Standard Operating Procedure (SOP)
Central Institutional Review Board Reporting
Version 1.0
SOP NN SM 602

Originators: NeuroNEXT CCC and DCC Personnel

Reviewed and Approved by:

Christopher S. Coffey, PhD (DCC Principal Investigator)

Merit E. Cudlowicz, MD MSc (CCC Principal Investigator)

P. Pearl O'Rourke, MD (Central IRB Director of Human Research Affairs)

Marianne Kearney, BA (CCC Director of Clinical Operations)

Dixie J. Ecklund, RN MSN MBA (DCC Associate Director)

Katherine B. Gloer, PhD (DCC Quality Management Lead)

Claudia Moy, PhD MPH (NINDS, NeuroNEXT Administrative Program Director)

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NN SM 602

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR CIRB REPORTING

<table>
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<tr>
<th>SOP: NN SM 602</th>
<th>CIRB REPORTING</th>
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<tbody>
<tr>
<td>Version No: 1.0</td>
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<td>Document: N/A</td>
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1. POLICY

Employees, professional staff or other agents of institutions participating as a Clinical Study Site (CSS) for a NeuroNEXT Network human research study overseen by the NeuroNEXT Central IRB (CIRB) are required to report unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that are determined, discovered, or learned by them in connection with the conduct of a NeuroNEXT human research study in accordance with the standards, time frames, and procedures specified in this CIRB Reporting SOP, which includes the attached CIRB Reporting Table (section 8: Procedures).

2. SCOPE

This SOP applies to all employees, professional staff or other agents of institutions participating as a Network or Non-Network CSS for a NeuroNEXT Network human research study overseen by the Partners Human Research Committee (PHRC), the Institutional Review Board (IRB) selected by the National Institute of Neurological Disorders and Stroke (NINDS) to serve as the NeuroNEXT CIRB.

3. ROLES AND RESPONSIBILITIES

A. NeuroNEXT Clinical Study Site Principal Investigator

The NeuroNEXT Clinical Study Site Principal Investigator (CSS PI) or designee is responsible for reporting to the CIRB any unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance, and cessation of research activities that are determined, discovered, or learned by them in connection with the conduct of a NeuroNEXT human research study, in accordance with the standards defined in the CIRB Reporting Table (section 8: Procedures).

Reports are made through the NeuroNEXT Clinical Coordinating Center as follows:

1. The CSS PI or designee completes the appropriate Report Form identified on the CIRB Reporting Table, and submits the completed form to the NeuroNEXT Clinical Coordinating Center IRB Liaison (CCC-CIRB Liaison) or designee via the online data entry system.

2. The CCC-CIRB Liaison is then responsible for completing the CIRB Report Form and for submitting the completed form to the CIRB.

3. CSS and CCC reports are to be made in accordance with the time frames specified in the CIRB Reporting Table.

B. NeuroNEXT Clinical Coordinating Center

The CCC-CIRB Liaison or designee is responsible for submitting reports to the CIRB of unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that they receive from CSSs in connection with the conduct of a NeuroNEXT human research study.
The CCC-CIRB Liaison is responsible for completing the CIRB Report Form and for submitting the completed form to the CIRB in accordance with the time frames specified in the CIRB Reporting Table.

C. NeuroNEXT Data Coordinating Center

The NeuroNEXT Data Coordinating Center (DCC) is responsible for developing the data entry system for reporting by the CSS PI/designee of unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that are determined, discovered, or learned by them in connection with the conduct of a NeuroNEXT human research study for review by the CCC-CIRB Liaison to determine required reporting to the CIRB and in accordance with the standards defined in the CIRB Reporting Table.

DCC and CCC reports are to be made in accordance with the time frames specified in the CIRB Reporting Table.

D. NeuroNEXT Central Institutional Review Board

The CIRB is responsible for reviewing reports of the unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that they receive from the NeuroNEXT CCC in connection with the conduct of a NeuroNEXT human research study.

When reviewing any of the aforementioned reports, the NeuroNEXT CIRB is responsible for making the determination as to whether the report constitutes an unanticipated problem involving risks to subjects or others or serious or continuing noncompliance with applicable laws and regulations or the requirements or determinations of the CIRB and for taking appropriate responsive action, which may include suspension or termination of CIRB approval of the research.

The NeuroNEXT CIRB is responsible for informing the reporting CSS PI/designee through the NeuroNEXT CCC of the findings, determinations, actions taken, and any modifications or remedial action required by the CIRB in response to such reports and, when applicable, informing all NeuroNEXT CSS PIs of any discovery or determination that affects subject safety or the conduct of the trial at all CSSs.

E. External Reporting

Responsibilities regarding any required reporting to sponsors/funding agencies, OHRP, FDA and/or other oversight authorities of any serious or continuing non-compliance, unanticipated problems involving risks to subjects or others, and suspension or termination of CIRB approval in connection with a NeuroNEXT human research study will be coordinated as described in the NeuroNEXT Central IRB Reliance Agreement executed by the CSS.

4. APPLICABLE REGULATIONS AND GUIDELINES

Ethical Principles
All parties shall be guided by the Ethical Principles and Guidelines for the Protection of Human Subjects of Research, generally known as the "Belmont Report."

45 Code of Federal Regulations 46
21 Code of Federal Regulations 56
21 Code of Federal Regulations 50

5. REFERENCES TO OTHER APPLICABLE SOPs

NN SM 601: CIRB Reliance SOP
6. ATTACHMENTS AND REFERENCES
NN SM 602-A Document History

7. TERMS AND ABBREVIATIONS
The following terms and abbreviations are used in this document:

ADE    Adverse Device Effect
AE     Adverse Event
CCC    NeuroNEXT Clinical Coordinating Center at Massachusetts General Hospital
CCC-CIRB Liaison NeuroNEXT Clinical Coordinating Center Central Institutional Review Board Liaison
CFR    Code of Federal Regulations
CIRB   NeuroNEXT Central Institutional Review Board
CSS    Clinical Study Site that conducts research for a particular NeuroNEXT protocol
CSS PI Principal Investigator who is responsible for implementing and conducting a specific NeuroNEXT protocol at a Clinical Study Site
DCC    NeuroNEXT Data Coordinating Center at the University of Iowa
DMC    Data Monitoring Committee
DSMB   Data and Safety Monitoring Board
DSMC   Data and Safety Monitoring Committee
eIRB   Electronic Institutional Review Board (Form)
FDA    US Food and Drug Administration
HIPAA  Health Information Portability and Accountability Act
NINDS  National Institute of Neurological Disorders and Stroke
OHRP   Office for Human Research Protections
PPI    Protocol Principal Investigator of a NeuroNEXT protocol
SAE    Serious Adverse Event
UADE   Unanticipated Adverse Device Effect

8. SPECIFIC PROCEDURES
The specific requirements, timeframes, and procedures for making reports to the NeuroNEXT CIRB of unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities as required by this SOP are outlined in the attached CIRB Reporting Table. Note that certain types of events need only be reported at Continuing Review.
<table>
<thead>
<tr>
<th>Type of Report</th>
<th>Description</th>
<th>Reporting Procedures</th>
<th>Form</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local CSS Adverse Events (AE)</td>
<td>Adverse event means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research.</td>
<td>CSS PI/designee reports all Adverse Events to CCC-CIRB Liaison via the online data entry system</td>
<td>NeuroNEXT Adverse Event Form</td>
<td>Report all Adverse Events within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Event except Serious Adverse Events as noted below</td>
</tr>
<tr>
<td>Serious Adverse Events (SAE)</td>
<td>Serious adverse event means any untoward or unfavorable medical occurrence in a human subject which results in death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, or required an intervention to prevent permanent impairment and temporally associated with the subject’s participation in the research.</td>
<td>CSS PI/designee reports all Serious Adverse Events to CCC-CIRB Liaison via the online data entry system</td>
<td>NeuroNEXT Adverse Event Form</td>
<td>Report Serious Adverse Events (SAEs) within 24 hours of when CSS PI first becomes aware of the Adverse Event</td>
</tr>
<tr>
<td>Unexpected and Possibly Related Adverse Events</td>
<td>Unexpected means that the incident, experience, or outcome in terms of nature, severity or frequency is not described in the protocol-related documents, such as the CIRB-approved research protocol and informed consent document or the characteristics of the study population being studied. Possibly related means there is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research. Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a &gt;50% likelihood that the event is related to the research procedures.</td>
<td>CCC-CIRB Liaison reports all Unexpected Adverse Events that are Possibly Related to the Research to the CIRB via the online data entry system</td>
<td>eIRB Adverse Event Form</td>
<td>Report Unexpected and Possibly Related Adverse Events within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Event</td>
</tr>
</tbody>
</table>
Continuing Review Progress Report - Adverse Events
At continuing review, the CIRB reviews all available information in a summary fashion to prevent unblinding regarding adverse events that have occurred in the trial.

CCC-CIRB Liaison provides updated summary information on Adverse Events
eIRB Continuing Review Form

Continuing Review

Local Adverse Device Effects (ADE)
Adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device.

CSS reports all Adverse Device Effects to CCC-CIRB Liaison via the online data entry system
NeuroNEXT Adverse Device Effect Form

Report all Adverse Events within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Device Effect, except Serious Adverse Device Effects as noted below.

Serious Adverse Device Effects (SAE)
Serious adverse device effect means any untoward or unfavorable medical occurrence in a human subject which results in death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, or required an intervention to prevent permanent impairment and temporally associated with the subject’s participation in the research.

CSS PI/designee reports all Serious Adverse Device Effects to CCC-CIRB Liaison via the online data entry system
NeuroNEXT Adverse Device Effect Form

Report Serious Adverse Device Events (SAEs) within 24 hours of when CSS PI first becomes aware of the Adverse Device Effect.

Unanticipated Adverse Device Effects (UADE)
Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

CCC-CIRB Liaison reports all Unanticipated Adverse Device Effects to CIRB
eIRB Adverse Event Form

Report any Unanticipated Adverse Device Effect within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Event.

Continuing Review Progress Report - Adverse Device Effects
At continuing review, the CIRB reviews all available information in a summary fashion to prevent unblinding regarding adverse device effects that have occurred in the trial.

CCC-CIRB Liaison provides updated summary information on Adverse Device Effects to CIRB
eIRB Continuing Review Form

Continuing Review
Local CSS Unanticipated Problems Involving Risks to Subjects or Others

Unanticipated problem involving risks to subjects or others means any incident, experience, information, outcome, or other problem that is unexpected given the research procedures and that indicates that the research places subjects at a greater risk of physical, psychological, economic, legal, or social harm than was previously known or recognized.

Unanticipated problems include, but are not limited to:

- Medication, procedural or laboratory errors
- Breach of confidentiality or HIPAA violation
- Complaints that indicate subjects’ rights, safety or welfare were adversely affected
- Change initiated without CIRB approval to eliminate apparent immediate hazards to subject/s

<table>
<thead>
<tr>
<th>Safety Monitoring Reports</th>
<th>Safety monitoring report means any DMC, DSMB, DSMC or sponsor analysis that describes a safety problem</th>
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<tbody>
<tr>
<td>CCC-CIRB Liaison</td>
<td>CCC-CIRB Liaison reports to the CIRB</td>
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<tr>
<td>eIRB Other Event Form</td>
<td>eIRB Other Event Form</td>
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<td>Report within 5 working days/7 calendar days of the date the CCC receives the report</td>
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Apparent Serious or Continuing Noncompliance

Noncompliance means any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the PHRC, including institutional policies related to human subject protection.

Serious noncompliance means any noncompliance that negatively impacts the rights and welfare of subjects or compromises the integrity of the study data. For example, serious noncompliance might include, but is not limited to, the following violations: (1) failure to obtain prospective PHRC approval; (2) failure to obtain informed consent of subject(s); (3)

| 1. CSS PI/designee reports to CCC-CIRB Liaison via the online data entry system | NeuroNEXT Reportable Event Form |
| 2. CCC-CIRB Liaison reports to CIRB | eIRB Other Event Form |
| Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem |
enrollment of subject(s) who do not meet all eligibility criteria; (4) obtaining informed consent using an invalid/oudated research consent form that is missing information that might affect the individual’s willingness to participate or continue to participate in the research; (4) failure to perform follow-up as outlined in the protocol where the lack of follow-up places the subject at increased risk of harm; and (5) failure to report a serious unanticipated problem involving risks to subjects or others, including adverse events.

*Continuing noncompliance* means any noncompliance that occurs repeatedly after appropriate remedial education or corrective action has been instituted taking into consideration all relevant factors, including, for example: (1) whether the continuing noncompliance was intentional, or (2) whether the investigator collaborated in remedial activity and the continuing noncompliance was not intentional.

| Major Unapproved Protocol Deviations | Major Unapproved Protocol Deviation means any alteration/modification to the PHRC-approved research that has the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject’s willingness to participate in the study. | 1. CSS PI/designee reports to CCC-CIRB Liaison via the online data entry system | NeuroNEXT Deviation Form | Report within 24 hours of the date the CSS PI first becomes aware of the deviation |
| Changes Initiated Without CIRB Approval To Eliminate Apparent Immediate Hazards To Subject/S, | See Unanticipated Problems | 2. CCC-CIRB Liaison reports to CIRB | eIRB Other Event Form | Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem |

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<table>
<thead>
<tr>
<th>Complaints</th>
<th>Complaints that indicate subjects' rights, safety or welfare were adversely affected - See Unanticipated Problems</th>
<th>1. CSS PI/designee reports to CCC-CIRB Liaison via the online data entry system</th>
<th>NeuroNEXT Reportable Event Form</th>
<th>the date the CSS PI first becomes aware of the problem</th>
<th>Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem</th>
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</thead>
<tbody>
<tr>
<td>Cessation of Research Activities</td>
<td>Cessation of research activities</td>
<td>1. CSS PI/designee reports to CCC-CIRB Liaison</td>
<td>NeuroNEXT Site Close Out Form</td>
<td>Report within 30 calendar days of the date the CSS ceases research activities</td>
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<td></td>
<td>See also Unanticipated Problems when cessation of research is for safety problems</td>
<td>2. CCC-CIRB Liaison reports to CIRB</td>
<td>eIRB Amendment Form</td>
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<tr>
<td>Minor Unapproved Protocol Deviations</td>
<td>Minor Unapproved Protocol Deviation means any deviation from the PHRC-approved research that does not have the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect subject's willingness to participate in the study.</td>
<td>1. CSS PI/designee reports to CCC-CIRB Liaison</td>
<td>NeuroNEXT Deviation Form</td>
<td>Continuing Review</td>
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<td>2. CCC-CIRB Liaison reports to CIRB</td>
<td>eIRB Continuing Review Form</td>
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<td>Version</td>
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<td>Reason or Justification for Modification</td>
<td>Completion Date</td>
<td>Issue Date</td>
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<td>2.0</td>
<td>&lt;Provide a brief but complete summary of the modifications to the SOP&gt;</td>
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