**GENERAL INFORMATION ABOUT THE**

**NeuroNEXT NETWORK PROTOCOL TEMPLATE**

The attached document is a template that may be used by the NeuroNEXT Protocol Principal Investigator (PPI) and their staff to develop the clinical protocol for their study. It is based on the NINDS protocol template.

**Below are some guidelines/suggestions for using the template:**

1. All drafts and final versions should be version controlled (see NN GA 103 SOP) . Please label all draft versions as decimals (e.g. v0.1, v0.2, etc.). When a version is final and all changes are accepted, the clean final version is labeled as a whole number (e.g. v1.0, 2.0, etc.). Drafts between final versions should also be labeled as decimals (e.g. 1.1, 1.2, etc.).
2. The version date (for draft and final document) should be updated with the current date along with the version numbers as each draft of the document is created.
3. Numbered headers in the document are linked to the Table of Contents (TOC). The TOC may be updated by right clicking the TOC and selecting “Update Field”.
4. The text highlighted in the gray boxes is guidance language and must be deleted in the draft/final protocol document. NOTE: it is not necessary/required to bullet items in the protocol as they appear in the guidance language.
5. Italicized text must be updated by the author. The italicized text should then be deleted and the updated language should not be italicized.
6. Language that is in the template and is not highlighted in gray or italicized is template language from the NeuroNEXT CCC and/or DCC and should not be changed. Please direct any questions or suggestions for revised language in these sections to the CCC Project Manager.
7. Please be sure to check the entire document carefully to ensure that all gray highlighted and italicized text has been deleted/changed as appropriate.
8. Depending upon the study design, not all sections listed in the template may be needed.
9. This page, “General Information about the NeuroNEXT Network Protocol Template”, must be deleted from the protocol document. Once this page is deleted the page numbering will self-correct.
10. Protocol Amendments: Any modification to the protocol should be listed in a Summary of Changes document that may be included as an appendix to the protocol. The document should include the following:
	1. The exact words that are changed
	2. The location in the protocol
	3. The date the modification was approved by the steering committee
	4. The date the modifications became effective

**Full Protocol Title**

* Insert full protocol title

**Protocol Version:** *(e.g. 1.0, 2.0, etc.)*

**Protocol Date:** *(MM/DD/YYYY)*

**SHORT PROTOCOL TITLE**

* Not required but may be helpful

**Protocol Principal Investigator (PPI);**

* Name, degree, title, and institution

**Supported by:**

**The National Institute of Neurological Disorders and Stroke (NINDS)**

* Include application or grant number(s) when available

**Study Intervention Provided by:**

* Name of pharmaceutical company or device manufacturer, if any, providing study drug or device

**Sponsor of IND/IDE:**

* List official IND/IDE holder if study requires IND or IDE: name (individual or company)
* Include IND/IDE # if available

The information contained herein is confidential and proprietary in nature, and will not be disclosed to any third party without written approval of authorized designee. This document may be disclosed to the appropriate institutional review boards or to duly authorized representatives of the US Food and Drug Administration or a national regulatory authority under the condition that they maintain confidentiality.

**TABLE OF CONTENTS**

[INVESTIGATOR AGREEMENT 3](#_Toc336511161)

[1 STUDY OBJECTIVES 3](#_Toc336511162)

[1.1 Primary Objectives 3](#_Toc336511163)

[1.2 Secondary Objectives 3](#_Toc336511164)

[2 BACKGROUND 3](#_Toc336511165)

[2.1 Rationale 3](#_Toc336511166)

[2.2 Supporting Data 3](#_Toc336511167)

[3 STUDY DESIGN 3](#_Toc336511168)

[4 SELECTION AND ENROLLMENT OF SUBJECTS 3](#_Toc336511169)

[4.1 Inclusion Criteria 3](#_Toc336511170)

[4.2 Exclusion Criteria 3](#_Toc336511171)

[4.3 Subject Withdrawal Criteria 3](#_Toc336511172)

[4.4 Study Enrollment Procedures 3](#_Toc336511173)

[4.4.1 Subject Recruitment and Retention 3](#_Toc336511174)

[4.4.2 Screening Logs 3](#_Toc336511175)

[4.4.3 Informed Consent 3](#_Toc336511176)

[4.4.4 Assent 3](#_Toc336511177)

[4.4.5 Randomization/Treatment Assignment 3](#_Toc336511178)

[5 STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG OR DEVICE 3](#_Toc336511179)

[5.1 Study Medications/Interventions, Administration, and Duration 3](#_Toc336511180)

[5.2 Handling of Study Medications/Interventions 3](#_Toc336511181)

[5.3 Concomitant Interventions 3](#_Toc336511182)

[5.3.1 Required Concomitant Medications/Interventions 3](#_Toc336511183)

[5.3.2 Prohibited Medications/Interventions 3](#_Toc336511184)

[5.3.3 Precautionary Medications/Interventions 3](#_Toc336511185)

[5.4 Subject compliance 3](#_Toc336511186)

[6 CLINICAL AND LABORATORY EVALUATIONS/STUDY PROCEDURES 3](#_Toc336511187)

[6.1 Schedule of Activities 3](#_Toc336511188)

[Schedule of Activities 3](#_Toc336511189)

[6.2 Timing of Study Activities 3](#_Toc336511190)

[6.2.1 Screening/Pre-Randomization Evaluations/procedures 3](#_Toc336511191)

[6.2.2 On-Study/On-Interventions Evaluations/procedures 3](#_Toc336511192)

[6.2.3 Study Medication/Intervention Discontinuation Evaluations/procedures 3](#_Toc336511193)

[6.2.4 On Study/Off-Intervention Evaluations 3](#_Toc336511194)

[6.2.5 Final On-Study Evaluations 3](#_Toc336511195)

[6.2.6 Off-Study Requirements 3](#_Toc336511196)

[6.2.7 Pregnancy (Optional) 3](#_Toc336511197)

[6.3 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS 3](#_Toc336511198)

[6.3.1 Informed Consent 3](#_Toc336511199)

[6.3.2 Protocol Violations 3](#_Toc336511200)

[6.3.3 Documentation of [specify the Disease/Disorder under study] 3](#_Toc336511201)

[6.3.4 Medical History 3](#_Toc336511202)

[6.3.5 Treatment History 3](#_Toc336511203)

[6.3.6 Concomitant Medications/Treatments 3](#_Toc336511204)

[6.3.7 Protocol Amendments and Study Termination 3](#_Toc336511205)

[6.3.8 Clinical Assessments 3](#_Toc336511206)

[6.3.9 Laboratory Evaluations 3](#_Toc336511207)

[6.3.10 Pharmacokinetic Studies 3](#_Toc336511208)

[6.3.11 Other Laboratory Studies 3](#_Toc336511209)

[6.3.12 Questionnaires 3](#_Toc336511210)

[6.3.13 Subject Adherence Assessments 3](#_Toc336511211)

[6.3.14 Additional Evaluations 3](#_Toc336511212)

[7 MANAGEMENT OF ADVERSE EXPERIENCES 3](#_Toc336511213)

[8 CRITERIA FOR INTERVENTION DISCONTINUATION 3](#_Toc336511214)

[9 STATISTICAL CONSIDERATIONS 3](#_Toc336511215)

[9.1 General Design Issues 3](#_Toc336511216)

[9.2 Outcomes 3](#_Toc336511217)

[9.2.1 Primary Outcome (including definition) 3](#_Toc336511218)

[9.2.2 Secondary Outcome(s) 3](#_Toc336511219)

[9.3 Sample Size and Accrual 3](#_Toc336511220)

[9.4 Data Monitoring 3](#_Toc336511221)

[9.5 Data Analyses 3](#_Toc336511222)

[10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING 3](#_Toc336511223)

[10.1 Data Management 3](#_Toc336511224)

[10.1.1 Registration 3](#_Toc336511225)

[10.1.2 Data Entry 3](#_Toc336511226)

[10.2 Role of Data Management 3](#_Toc336511227)

[10.3 Quality Assurance 3](#_Toc336511228)

[10.3.1 Development of Monitoring Plan 3](#_Toc336511229)

[10.3.2 Site Monitoring Visits 3](#_Toc336511230)

[10.3.3 Laboratory Data Flow 3](#_Toc336511231)

[10.4 Adverse Experience Reporting 3](#_Toc336511232)

[10.4.1 Definitions of Adverse Events, Suspected Adverse Drug Reactions & Serious Adverse Events 3](#_Toc336511233)

[11 HUMAN SUBJECTS 3](#_Toc336511234)

[11.1 Institutional Review Board (IRB) Review and Informed Consent 3](#_Toc336511235)

[11.2 Subject Confidentiality 3](#_Toc336511236)

[11.3 Study Modification/Discontinuation 3](#_Toc336511237)

[12 PUBLICATION OF RESEARCH FINDINGS 3](#_Toc336511238)

[13 REFERENCES 3](#_Toc336511239)

[Appendix A: Model Informed Consent Form 3](#_Toc336511240)

# INVESTIGATOR AGREEMENT

I have read the foregoing protocol *[INSERT VERSION NUMBER AND DATE]* and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by the NeuroNEXT Network in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by the NeuroNEXT Network will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

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**Investigator Signature Date**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Print Investigator’s Name**

**SIGNATURE PAGE**

**Study Number:**

* Insert Study Number (This number will be provided by the DCC, after funding is awarded)

Principal Investigator Approval:

 Signature: Date:

|  |  |  |  |
| --- | --- | --- | --- |
|  Name: | *Insert PPI Name* |  |  |

NeuroNEXT Clinical Coordinating Center Approval:

Signature: Date:

|  |  |  |  |
| --- | --- | --- | --- |
|  Name: | Merit Cudkowicz, MD |  |  |

NeuroNEXT Data Coordinating Center Approval:

Signature: Date:

|  |  |  |  |
| --- | --- | --- | --- |
| Name: | Christopher Coffey, PhD |  |  |

**LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS**

AE Adverse Event

CCC Clinical Coordination Center

CDE Common Data Elements

CFR Code of Federal Regulations

CIRB Central Institutional Review Board

CRF Case report form

CS Clinically Significant

CSS PI Clinical Study Site PI

DCC Data Coordination Center

DM Data Management

DSMB Data Safety Monitoring Board

eCRF Electronic Case Report Form

EDC Electronic data capture

FDA Food and Drug Administration

GCP Good Clinical Practice

HIPAA Health Insurance Portability and Accountability Act

ICH International Conference on Harmonization

IMM Independent Medical Monitor

MedDRA Medical Dictionary for Regulatory Activities

NINDS National Institute of Neurological Disorders and Stroke

PPI Protocol Principal Investigator

PSC Protocol Steering Committee

SAE Serious adverse event

SOA Schedule of Activities

*(ADD AS NEEDED)***SYNOPSIS**

* This Synopsis should provide a bare-bones outline of the study, approximately 1-2 pages

Study Title

* List full title and short title if there is one

Objectives

* Specify objectives and hypotheses to be tested

Design and Outcomes

* A brief description of the study design (e.g. multicenter, randomized, double-blind, Phase)
* Include the outcome variables for the primary and if applicable, secondary objectives
* A brief overview diagram may be used here. (Complex diagrams may be included in Section 3, Study Design)

Interventions and Duration

* Briefly describe the interventions to be used/compared
* Include mode of administration, if applicable
* Indicate the total length of time each subject will be on study (intervention period + additional follow-up off intervention or cross-over plans, as applicable)
* Include an estimate for duration on enrollment if available
* A brief statement about the schedule and type of evaluations to be performed during the study may also be included

Sample Size and Population

* Briefly describe the number and type (patient population) of subjects to be studied
* List inclusion and exclusion criteria

\*If the study will be using a randomization schema that will be stratified, list the stratification factors. If there will be separate objectives and outcome variables for the strata, list these in the appropriate sections above.

# STUDY OBJECTIVES

## Primary Objectives

* + The primary objective should always be to address a specific hypothesis.
	+ State the hypothesis in quantifiable terms: e.g., “the experimental treatment will result in 12 months of additional survival compared to the control treatment.”
	+ For statistical purposes, it may be worthwhile to state both the null and the alternative hypotheses
	+ This primary objective must match the one used in section 9, Statistical Design

## Secondary Objectives

* Secondary objectives may or may not be hypothesis-driven, may include secondary outcomes, and may include more general non-experimental objectives (e.g. to develop a registry, to collect natural history data)

# BACKGROUND

## Rationale

* Provide historical background
* Describe the patient population to be studied and justify any restrictions on the population
* Provide rationale behind the proposed research, and potential benefits to patients and/or society
* Name and describe the intervention regimens, and justify why these particular interventions have been chosen
* Describe and justify the route of administration, dosage, intervention period, etc.
* Spell out the need, relevance and priority for the study

## Supporting Data

* Describe previous pre-clinical or clinical studies leading up to, and supporting the proposed research
* Provide the scientific and medical data (e.g. results of Phase I and II studies) that justify the study, its design, and the intervention groups
* Summarize the known and potential risks of the interventions
* For drug studies, package insert information can be referred to, but does not need to be included unless there is a new, significant change
* Justify any aspects of the study not FDA-approved (e.g. different dosing schedule, new combination of drugs, new drug formulation)

# STUDY DESIGN

* Briefly describe the study design and indicate, in general terms, how the design will fulfill the intent of the study
* Use diagrams to explain design complexities

# SELECTION AND ENROLLMENT OF SUBJECTS

## Inclusion Criteria

* List all inclusion criteria
* It is recommended that criteria be numbered
* Each number should describe on specific criterion
* Criterion should be written so that a positive answer results in inclusion

## Exclusion Criteria

* List all exclusion criteria
* It is recommended that criteria be numbered
* Criterion should be written so that a negative answer results in exclusion

## Subject Withdrawal Criteria

* When and how to withdraw subjects from the trial/investigational product
* The type and timing of the data to be collected for withdrawn subjects
* Whether and how subjects are to be replaced
* The follow up for subjects withdrawn from investigational project treatment/trial treatment

## Study Enrollment Procedures

* Methods of enrollment, including procedures for patient registration and/or randomization if applicable
* Procedures for obtaining informed consent (including timing, who may consent subjects, and documentation of the consent process)
* Treatment assignment, and randomization, if applicable

### Subject Recruitment and Retention

* Describe in detail the methods for identifying and recruiting candidates for the trial

Participants will be recruited from clinics at participating NeuroNEXT Network sites. Postings will be placed on *[Insert website address(es)]* website. Flyers about the study will be sent to community neurologists at NeuroNEXT clinical sites. Webinars will be conducted for participant recruitment as needed. Interested participants will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the patients can provide their contact information. We will use the NeuroNEXT Recruitment and Retention Committee to identify recruitment strategies.

*Add additional text here as appropriate*

### Screening Logs

* Describe procedures (e.g. maintaining a screening log at each clinical site) for documenting how subjects learned of the trial, which referred them to the trial, reasons for ineligibility, and reasons for nonparticipation of eligible subjects
* Describe how this information will be collected centrally and used to enhance subject recruitment efforts

Screening logs to document reasons for ineligibility and reasons for nonparticipation of eligible subjects will be stored centrally at the NeuroNEXT Data Coordination Center.

*Add additional text here as appropriate*

### Informed Consent

* Describe consent procedures, including who at CSS is allowed to complete consenting process
* Include procedures for proxy consent or if subject is unable to read or is physically unable to sign the informed consent form, if applicable
* Include consent documentation requirements

Written informed consent will be obtained from each study participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant’s willingness to participate in the study will be documented in writing in a consent form approved by the NeuroNEXT Central Institutional Review Board (CIRB), which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and a copy will be given to the participant. It will also be explained to the participant that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

### Assent

* Describe assent procedures, if applicable

### Randomization/Treatment Assignment

* Describe the procedure for obtaining intervention group assignment if needed, if applicable

# STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG OR DEVICE

## Study Medications/Interventions, Administration, and Duration

* Indicate each study intervention/medication, including:
	+ How it is administered
	+ The schedule for administration
	+ Potential side effects
* Indicate where the subject will be treated (e.g. intensive care unit, out patient clinic)
* State guidelines for use of appropriate supportive care medications or treatments

## Handling of Study Medications/Interventions

* Describe how the interventions are to be acquired by the participating clinical sites
* Describe how interventions will be stored, prepared, labeled, and dispensed, including when study medication will be dispensed
* Describe requirements of site pharmacies / pharmacists for preparing, storing and dispensing IP
* If applicable, describe the disposition of unused study products (e.g. materials to be returned to the NeuroNEXT Central Pharmacy, destroyed per institutional SOP)
* Describe procedures for documenting study intervention accountability
* If appropriate, reference the study’s Manual of Operations for detailed instructions about these issues
* Note mechanisms, if any, for masking (i.e. blinding) study interventions (e.g. if a placebo is being used in a drug trial, note whether it has a similar color, taste, etc. as the active drug)
* Include information on dose changes, if applicable
* Include information about code break procedures, if applicable

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount received from the central pharmacy, and the amount destroyed upon completion of the study. An investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. *[if a designated unblnded pharmacist is to be utilized describe the procedures and responsibilities e.g.The designated unblinded pharmacist must keep drug inventory and accountability logs].* The inventory will include details of *[insert name of study medication/device]* received and dispensed to subjects, batch, and ID numbers. All unused *[insert vial, tablets, etc]* must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site will be instructed by the CCC or designee to either destroy the remaining study medication/device or return it to the Central Pharmacy or manufacturer. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of [*insert name of study drug]* received and dispensed drug must be reconciled.

## Concomitant Interventions

* Required, prohibited and precautionary interventions (e.g. medications) will depend upon the interventions and the outcomes of the study
* Interventions not listed in sections 5.3.2 – 5.3.3 are permitted

### Required Concomitant Medications/Interventions

* List any concomitant medications or interventions required per protocol
* If applicable, Indicate whether or not the NeuroNEXT Central Pharmacy will be providing the concomitant medications

### Prohibited Medications/Interventions

* List all concomitant intervention(s) that are prohibited during study participation
* Describe procedure for handling situation(s) when subject uses prohibited intervention during study participation. This may also be detailed in section 8: Criteria for Intervention Discontinuation

### Precautionary Medications/Interventions

* Include instructions for modifications to the study interventions, if appropriate

## Subject compliance

* Indicate whether compliance of subjects with the study intervention is to be assessed
* Provide details as to how compliance will be assessed (e.g. pill counts, electronic monitoring devices, adherence questionnaires)
* In section 9.5 Data Analyses, describe how subject compliance information will be incorporated into the analysis of the study results

# CLINICAL AND LABORATORY EVALUATIONS/STUDY PROCEDURES

## Schedule of Activities

* The Schedule of Activities (SOA) in section 6.1 should include all study evaluations
* Use “X” in a cell to indicate that a particular evaluation is to be performed at a particular study visit
* The definitions for the Schedule of Activities included in section 6.2 define the evaluations, provide timelines, visit windows, and include special considerations or instructions for evaluations
	+ Special considerations or exceptions may be noted by using a footnote to the SOA
* The activities and their order in the template table in section 6.1 are examples only
* The activities should be specific for the particular protocol and should be arranged for clearest presentation
* Additional columns may be needed to specify activities at intervention failure, at premature discontinuation of study interventions, or at other special timepoints that require a different set of evaluations.
* In complicated studies with multiple study steps or multiple randomization points, it may be useful to include in the table the time of each step/randomization and the time that the study medication/intervention is given to the subject.
* It may also be useful to include footnotes with fuller explanations of specific procedures or timepoints

Schedule of Activities*(update evaluation as well as visit name per protocol. Also provide visit windows if appropriate. Use footers as needed to provide additional detail (e.g. listing of lab tests to be done, etc.)*

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Evaluation* | *Screening**(-XX days)* | *Pre-Randomization/Pre-Baseline**(-XX days)* | *Randomization/Baseline/Day 1/Day 0* | *4 wk* | *8* | *12* | *16* | *20* | *24* | *32* | *40* | *48* |
| *Written Informed Consent* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Inclusion/Exclusion Review* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Documentation of Disease/Disorder* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Medical History/Demographics* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Vital Signs/Weight/Height* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Physical Examination* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Neurological Examination* |  |  |  |  |  |  |  |  |  |  |  |  |
| *\*Add additional clinical assessments as necessary* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Concomitant Medication Review*  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Safety Labs*1 |  |  |  |  |  |  |  |  |  |  |  |  |
| *Research Labs* |  |  |  |  |  |  |  |  |  |  |  |  |
| *Urinalysis*  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Randomization*  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Dispense Study Drug*  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Drug Accountability/ Compliance*  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Adverse Event Review*  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Questionnaires* |  |  |  |  |  |  |  |  |  |  |  |  |

## Timing of Study Activities

* This section should include definitions of the column headings in the SOA as well as any special instructions

### Screening/Pre-Randomization Evaluations/procedures

* These evaluations/procedures occur prior to the subject receiving any study interventions
* Screening:
	+ Specify allowable range of time prior to study entry during which all screening evaluations to determine eligibility must be completed
	+ Indicate whether screening and pre-study entry/baseline/randomization activities must be separated by a certain number of days or hours or whether the activities may occur concurrently
	+ If screening involves performing procedures that are not part of routine patient management, indicate the procedure to obtain informed consent for screening
* Pre-Randomization/Pre-Baseline:
	+ For subjects who have successfully been screened for eligibility and are slated to be randomized into the study, specify allowable windows for pre-randomization/baseline activities relative to screening activities and study entry.
* Randomization/Baseline:
	+ Specify time window for;
		- Study entry (i.e. randomization, baseline) relative to completion of pre-randomization/baseline activities
		- Initiation of study medication/intervention relative to randomization/baseline
* If baseline activities are to be completed after randomization, the column should be moved under On-Study Evaluations

### On-Study/On-Interventions Evaluations/procedures

* Indicate schedule of activities occurring after randomization/baseline while the subject is on-study and on (or about to start) study medication/intervention
* Include the allowable time window in which study visits may take place, e.g. study visits must be scheduled on the weeks indicated in the SOA ± 7 days
* Include the allowable time window for each activity, if appropriate, e.g. vital signs are to be collected at 60 minute intervals ± 5 minutes

### Study Medication/Intervention Discontinuation Evaluations/procedures

* Define “study medication/intervention discontinuation” (e.g. completion of study, premature/early discontinuation)
* Define “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial
* Specify activities needed for subjects at the time of discontinuation of study medication/intervention
* Specify activities needed for subjects who prematurely discontinue vs. subjects who completed the full treatment course expected under the protocol
* Specify whether dosage reductions, temporary suspensions and rechallenges, or ‘drug holidays’ will be allowed, and how they will be managed

### On Study/Off-Intervention Evaluations

* For trials following an intention-to-treat design, subjects who discontinue intervention should continue to be followed and evaluated on study
	+ Describe efforts to be made to retain subjects being followed as intent-to-treat and, when practical, to encourage them to resume study medication/intervention
* Indicate the schedule of activities to be completed with the subject is “off study medication/intervention/on study”, i.e., no longer on study medication/intervention but still being followed for outcomes, if possible
* Indicate evaluations needed for subjects who complete scheduled study intervention and for subjects who prematurely discontinue from study medication/intervention, if applicable

### Final On-Study Evaluations

* Indicate the schedule of activities to be completed at the subject’s final visit on study

### Off-Study Requirements

* Specify any requirements for follow-up on subjects once they have completed the protocol-specified period no study intervention
	+ For example, it may be appropriate to ask the subject to return to the site two weeks or so after the subject goes off study in order to evaluate the subject for any adverse events and to provide further information about options for future clinical care

### Pregnancy (Optional)

* Specify instructions for women who become pregnant while on-study.
* If a pregnant woman is allowed to remain on study, specify whether they must sign a pregnancy consent form (refer to appropriate appendix) and whether additional evaluations are needed

## SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

* Explain the rows of the table of the Schedule of Activities from top to bottom. Specify the data items that must be included in the source document

### Informed Consent

* + Include any special consent issues (e.g. surrogate consent)
	+ Specify who is authorized to obtain consent (i.e. Principal Investigator only or IRB approved designee)

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant’s willingness to participate in the study will be documented in writing in a consent form, approved by the NeuroNEXT CIRB, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

### Protocol Violations

* Define what will be considered protocol violations
* Describe reporting procedures for protocol violations

### Documentation of [specify the Disease/Disorder under study]

* Include clinical, laboratory, radiological or other recognized methods of documenting the disease or disorder from the subject’s source document

### Medical History

### Treatment History

* Include any prior treatment of the disease/disorder to be obtained from the subjects source document that may be relevant to the study

### Concomitant Medications/Treatments

* Clarify which concomitant medications/treatments that are to be documented from the subject’s source (e.g. all concomitant medications, only certain classifications of medications)

### Protocol Amendments and Study Termination

* Include information about requirements for re-consenting subjects to protocol amendments, if applicable.

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the CIRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the CIRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

The Sponsor and NeuroNEXT Network reserve the right to discontinue the study at a clinical study site(s) for safety or administrative reasons at any time. Should the study be terminated and/or the clinical study site closed for any reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

### Clinical Assessments

* Define which clinical parameters are measured and when
* If a physical exam is required, specify extent of the physical exam needed
* Specify which clinical events should be recorded on the CRFs.
* The NeuroNEXT DCC/CCC utilize the NINDS Common Data Elements in developing the CRF’s whenever possible (see http://www.commondataelements.ninds.nih.gov/)

### Laboratory Evaluations

* Specify recording instructions. For example:
	+ The Investigator must review, sign and date all lab reports
	+ Investigator must indicate if out of range lab value is Clinically Significant “CS” or Not Clinically Significant “NCS” on the lab report
* Specify the grading system to be used, if any (e.g. CTCAE version 4.0)

### Pharmacokinetic Studies

* This section is applicable for studies involving drugs as study interventions when pharmacokinetics are being performed.
* Pertinent additional information can be included in this section or in an appendix (e.g. sample collection, processing, shipment)

### Other Laboratory Studies

* Other laboratory studies (e.g., metabolic studies) and special tests should be explained here

### Questionnaires

* Include information about subject and caretaker interviews regarding quality of life, etc. For example:
	+ What the questionnaire will measure
	+ How the questionnaire will be completed (e.g. by subject, administered by study staff, online)
* Actual questionnaire forms may be included as an appendix, but should be referenced here.

### Subject Adherence Assessments

* Steps to track and document subject compliance may be included here

### Additional Evaluations

# MANAGEMENT OF ADVERSE EXPERIENCES

* Include:
	+ A list of expected adverse experiences for each study medication/intervention
	+ Criteria for subject management and modification of the study intervention regimen
	+ Procedures for modification (forms, additional labs, and change in regimen)
	+ List alphabetically by adverse experience or group by body system
* For investigational drug studies, the Protocol Principal Investigator (PPI) should work closely with the appropriate party (e.g. pharmaceutical company representative) to ensure that toxicities that have been seen in previous studies are identified, and that a plan for management and documentation of these toxicities is developed

*Pregnancy:*

*Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug*

*may have interfered with the effectiveness of a contraceptive medication. However, the*

*outcome of all pregnancies that occur during paternal or maternal exposure to study drug (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject has been withdrawn from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the [insert reporting structure].*

# CRITERIA FOR INTERVENTION DISCONTINUATION

* List criteria for discontinuing study medication/intervention and methods for determining when criteria are met
* Include procedures for maintaining subject participation in follow-up activities

# STATISTICAL CONSIDERATIONS

The NeuroNEXT Data Coordinating Center has developed a statistical analysis plan, in collaboration with the protocol principal investigator and protocol steering committee.

* *Insert statistical analysis plan*

## General Design Issues

* Describe general design issues including:
	+ Primary and secondary hypotheses and how they relate to choice of primary and secondary outcome measures;
	+ The validity and reliability of the primary and secondary outcome measures;
	+ Whether the documentation of an outcome will be reviewed and adjudicated by a committee, how quickly the committee will perform the adjudication, and whether the committee will be masked to the subject’s intervention group assignment;
	+ Choice of study design (e.g., parallel groups, crossover, immediate versus deferred intervention, factorial, large simple trial, equivalency or non-inferiority trial);
	+ Details of why certain design features were chosen (e.g., for a crossover trial, how the length of the washout period was chosen);
	+ What factors (if any) will be used to stratify the randomization;
	+ If each subject is to be followed for a fixed follow-up period (e.g., to 24 months) rather than to a common closeout date (e.g., 24 months following enrollment of the last subject), clarify why the particular fixed time period was chosen.
* Statisticians sometimes use computer simulations to investigate the operating characteristics of complex clinical trial designs (such as adaptive designs), to choose between alternative outcome measures, or to determine sample size, taking into account the impact of such factors as noncompliance, losses to follow-up, missing data, and subject eligibility criteria (risk profile).  If simulations were performed to aid in the design of this clinical trial, sufficient details about the simulations should be provided (possibly in an appendix to the trial protocol) to assure that the simulations were performed and analyzed in a valid manner.  See the article, “The design of simulation studies in medical statistics”, by Burton et al., Statist. Med. 2006: **25**:4279-4292 for guidance on how to document a simulation study.  It is particularly important to discuss the range of conditions that were considered in the simulation, why this range was considered appropriate, how robust the findings were across the range of conditions considered, and how the study will adjust for any design deficiencies (e.g., bias, loss of power) the simulations reveal.

## Outcomes

### Primary Outcome (including definition)

### Secondary Outcome(s)

## Sample Size and Accrual

* Describe the statistical and clinical bases for the sample size calculation
* State the assumptions made regarding accrual rate, event rate, noncompliance rate, loss-to-follow up rate and Type I and II errors
* Describe the plan for compensating for failures in these assumptions
* Describe what the power will be for assessing secondary outcomes
* If the randomization will be stratified, indicate whether (and why) there is a sample size goal for each stratum

## Data Monitoring

All aspects of the study will be monitored by qualified individuals designated by the sponsor. Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study subjects, and, if requested, agrees to assist the monitors.

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include contemporaneous assessment of serious adverse events.

The monitoring of subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. A Data and Safety Monitoring Board (DSMB) appointed by the NIH/NINDS will meet at six-month intervals (or as determined by the NINDS) to review partially unblinded study data provided by the study statistician. This committee will monitor rates of adverse events and endpoints in the trial and will monitor the performance of the trial. The frequency and format of DSMB meetings, reports, and guidelines for interim analysis will be agreed upon prior to study subject enrollment.

The Protocol PI will appoint an Independent Medical Monitor (IMM) to review all adverse events, in a blinded fashion, on a periodic basis. In addition the IMM will review all events that meet the regulatory definition of a Serious Adverse Event, upon receipt of notification via the Electronic Data Capture (EDC) system.

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. FDA, Office of Human Research Protection (OHRP), and NeuroNEXT CIRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. At that point, all ongoing AEs will be followed to resolution, but no new AEs will be recorded. The IMM/DSMB will review cumulative AEs; the frequency of this review will be determined by the IMM/DSMB in conjunction with the Protocol PI.

Each Clinical Study Site Investigator and research team (co-Investigators, research nurse, clinical trial coordinator) are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures. Aggregate reports blinded by treatment group, detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures, will be available from the DCC for review by the IMM. A separate report detailing protocol compliance will also be available monthly from the DCC for review by the Protocol PI, who will provide feedback to individual sites as needed. The Protocol Steering Committee (PSC) will advise the Protocol PI as to whether the protocol or informed consent document requires revision based on these reports.

## Data Analyses

# DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

## Data Management

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the study sites, the CCC, and at the DCC.

The general NINDS Common Data Elements (CDE) will be used to construct data collection forms. All study data will be collected via systems created in collaboration with the DCC and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

### Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical study site will attest to the participant’s eligibility as per protocol criteria and obtain appropriate informed consent. NeuroNEXT CIRB approval for the protocol must be on file at the DCC before accrual can occur from the clinical study site.

The DCC will use a system of coded identifiers to protect participant confidentiality.  When the participant is registered to participate in the study using the DCC-provided web-based registration, the system will assign a participant ID number. The unique ID code will include a protocol ID, a site ID, and a unique participant ID. To confirm the correct participant ID, the data entry system will require a second entry of the unique participant ID and compare for consistency. In this fashion, no personal identifiers would be accessible to the DCC and the data will be collected on the correctly identified subject.

### Data Entry

Data entry will occur at the enrolling clinical study sites. Data quality assurance and analyses will be performed by the DCC. The DCC, located at the University of Iowa, will coordinate all data and statistical services for the study, as well as on-site monitoring for all participating clinical study sites.

Data collection for this study will be accomplished with online electronic case report forms.  Using encrypted communication links, online forms will be developed that contain the requisite data fields.

## Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with NeuroNEXT policies, and applicable Sponsor and regulatory requirements. The DCC will instruct site personnel to collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the clinical study sites (CSS), the CCC, and at the DCC.

The DCC is responsible for all aspects of clinical data management, and for properly instructing key study personnel (including the CCC, the CSS, and DCC staff) on how to collect, transcribe, correct and transmit the data onto CRFs or other data collection forms and logs.

The DCC is responsible for establishing procedures to ensure that clinical data management activities occur as required at the CCC, the CSS, and at the DCC.

## Quality Assurance

By signing this protocol, the Sponsor and Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

### Development of Monitoring Plan

Onsite monitoring visits will be conducted by DCC monitors according to a pre-defined Monitoring Plan. The monitoring plan will detail the frequency of on-site visits, the study data to be monitored, the review of any regulatory files, drug and supplies accountability (if applicable), documentation of the on-site visit, and the resolution process for data errors that are discovered during the visits. All participating clinical study sites will be monitored at least once after a study initiation visit and all sites will have a close-out visit for each protocol. One on-site monitoring visit is anticipated for each clinical study site per year. All subjects will be monitored for inclusion and exclusion criteria, informed consent procedures, and adverse events. A certain percentage of data is also monitored/ source data verified against the data entered into the study database. The monitoring plan will include flexibility to revise the frequency of visits or data monitored depending on clinical study site or study related issues.

### Site Monitoring Visits

On-site monitoring visits will be conducted by DCC monitors according to a pre-defined monitoring plan for each protocol. The goal of on-site monitoring is to analyze (review) the data as it is collected, to check the validity and integrity of the data, to verify source documentation, to ensure protection of human subjects, and to ensure protocol compliance with federal regulations. During the monitoring visit, the monitor 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. The monitor also conducts a CRF review that includes checks of all adverse event documentation, verifies the presence of all critical correspondence and records related to investigational products and clinical supplies (if applicable), and determines if protocol violations have occurred and are documented properly. After the monitoring visit, the monitor documents the results of the monitoring visit and completes a post-visit monitoring letter that conveys any issues discovered during the visit and the need for data corrections, if appropriate. Drug and supplies accountability may also be monitored during the site visit. The DCC will work closely with the CCC to monitor and document drug distribution from the manufacturers to the clinical study sites (CSS). Each CSS will be provided with a drug accountability log which will be reviewed by the DCC monitors and reconciled with distribution logs. At the study closeout visit, the monitors confirm that appropriate data have been reviewed, source documentation has been verified, and all required documents are present in the Study Regulatory File.

### Laboratory Data Flow

*Safety Monitoring Labs*: The DCC will provide laboratories with online forms and/or electronic data exchange mechanisms - depending on their capabilities and needs - to enter, update and obtain relevant data. When a blood or urine sample has been obtained, the clinical study site study coordinator will send the sample (participant ID, site ID, and protocol ID numbers will be used) to the University of Rochester central laboratory. Results will be sent via a secure system to University of Rochester laboratory with no individual-identifying information on the report. The laboratory will electronically communicate the test results to the respective clinical study sites in a secure manner.  The laboratory will also transfer test results electronically to the DCC.

## Adverse Experience Reporting

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The Site Investigator will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Each clinical study site’s Principal Investigator and research team are responsible for identifying adverse events and reporting them through the DCC Online Adverse Event Reporting System. Investigators are also responsible for complying with NeuroNEXT CIRB’s reporting requirements for all safety reports. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator’s study file.

An adverse event is defined as: “…an unfavorable and unintended sign, symptom, or disease associated with a participant’s participation in this research trial.”

Serious adverse events include those events that: “result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects.”

Unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks described in the protocol.

Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study.

***On-line Adverse Event Reporting System***

Upon entry of a serious adverse event by a site investigator, the DCC Online Adverse Event Reporting System will immediately notify the Independent Medical Monitor (IMM).

* Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE) Investigators must report all other AEs within **5 working days/7 calendar days** (of learning of the event).

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. The IMM may determine that the Serious Adverse Event requires expedited reporting to the FDA. The DCC will prepare a Medwatch safety report for submission to the FDA. If warranted, the IMM will notify the DSMB chair. The DSMB may suggest changes to the protocol or consent form to the Study Chair as a consequence of adverse events.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DCC in a timely fashion (within 5 working days). The events will be presented in tabular form and given to the IMM on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious, expected/unexpected and relationship to study drug) for the IMM and the DSMB on a quarterly basis or as requested. In addition, all adverse events will be coded using the MedDRA system. A separate report detailing protocol compliance will also be available from the DCC for DSMB and/or site review monthly or as requested. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

### Definitions of Adverse Events, Suspected Adverse Drug Reactions & Serious Adverse Events

#### Adverse Event and Suspected Adverse Drug Reactions

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical 🡪 symptoms reported by the subject or signs detected on examination.

Ancillary Tests 🡪 abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures: the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Site Investigator.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigators Brochure or package insert or described in the protocol. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

#### Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
	1. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
	1. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
	1. This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the subject’s ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an *adverse* experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the Site Investigator or Sponsor, suggests a reasonable possibility that the investigational product caused the event.

The Site Investigator is responsible for classifying adverse events as serious or non-serious.

#### Assessment and Recording of Adverse Events

This study will utilize the CTCAE version 4.0 coding system for adverse event recording. Adverse events reported using CTCAE will be recoded into MedDRA terms by the DCC.

**Assessment of Adverse Events**

At each visit (including telephone interviews), the subject will be asked “Have you had any problems or symptoms since your last visit?” in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

**Relatedness of Adverse Event to Investigational Product**

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject’s clinical state or by other modes of therapy administered to the subject. (suspected ADR)
4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject’s clinical state. (suspected ADR)
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

**Recording of Adverse Events**

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject’s study binder. The site should fill out the AE Log and enter the AE information into the online Adverse Event Reporting System within 5 working days of the site learning of a new AE or receiving an update on an existing AE.

Please Note: Serious Adverse Events (SAEs) must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site learning of the SAE.

Entries on the AE Log (and into the online Adverse Event Reporting System) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

**Adverse Events and Serious Adverse Events - Reportable Events**

The following are considered reportable events and must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site being notified of the event.

* All events that meet the above criteria for Serious Adverse Events (SAEs)

All occurrences of Serious Adverse Events (SAEs) must be reported within 24 hours of discovery of the event. All other Adverse Events (AEs) must be reported within *insert timeline for reporting* (of discovery of the event).

**Adverse Event Data Management System (AEDAMS)**

Upon entry of a serious adverse event by a clinical site, the DCC Online Adverse Event Reporting System will immediately notify the IMM. If warranted, the IMM will notify the DSMB chair.

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The DSMB may suggest changes to the protocol or consent form to the Project PI as a consequence of adverse events. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DCC within 5 working days. The events will be presented in tabular form and given to the IMM on a monthly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB.

# HUMAN SUBJECTS

Documented approval from the NeuroNEXT CIRB will be obtained for all participating centers prior to clinical trial start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for each CSS PI and co-investigator.

## Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the NeuroNEXT CIRB responsible for oversight of the study. A signed consent form, approved by the NeuroNEXT CIRB, will be obtained from the subject. For subjects who cannot provide consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject’s record.

## Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by CIRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor’s designee.

## Study Modification/Discontinuation

The study may be modified or discontinued at any time by the CIRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

# PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies of the NeuroNEXT Network and procedures developed by the NeuroNEXT Data Sharing and Publication Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

# REFERENCES

* Provide the citations for all publications and presentations referenced in the text of the protocol

# Appendix A: Model Informed Consent Form