NeuroNEXT Network

Standard Operating Procedure (SOP)

Statistical Analysis Plan Development

Version 3.0

SOP NN BIO 902

Originators: NeuroNEXT CCC and DCC Personnel

Signature and Date: DocuSigned by Christopher Coffey Christopher Coffey | I approve this document 17-Feb-2023 | 3:53:39 PM PST C68AC8DD80334CF982AED1200765F147 17-Feb-2023
Name and Title: Christopher S. Coffey, PhD (DCC Principal Investigator)
Signature and Date: DocuSigned by Merit Cudkowicz Merit Cudkowicz | I approve this document 17-Feb-2023 | 8:19:51 AM EST 9F8FE4180E504C6AB0A67B835E80C644 17-Feb-2023
Name and Title: Merit E. Cudkowicz, MD MSc (CCC Principal Investigator)
Signature and Date: DocuSigned by Marianne Chase Marianne Chase | I approve this document 17-Feb-2023 | 1:33:38 PM EST 58FE690F6BCA4F2390E3DA15BCE3F578 17-Feb-2023
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17-Feb-2023

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

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22-Feb-2023 | 11:12:39 AM EST

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22-Feb-2023

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

Signature and Date:

DocuSigned by Joan Ohayon

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21-Feb-2023

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

NN BIO 902

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR STATISTICAL ANALYSIS PLAN DEVELOPMENT

1. POLICY

This SOP describes procedures for the development of a Statistical Analysis Plan (SAP) for NeuroNEXT studies. A SAP is a controlled document that accompanies the study protocol and that may include, but is not limited to, discussion of the following components:

- Primary and Secondary Objectives
- Primary and Secondary Endpoints
- Sample Size Justification
- Interim Monitoring Plan (if applicable).

Biostatisticians at the Data Coordinating Center (DCC) will serve as the primary authors of the SAP. During the development of the SAP, the DCC Independent Biostatisticians will collaborate with the DCC PI, the Protocol Principal Investigator (PPI), the Study Biostatistician, and the External Biostatistician (if applicable) to:

- broadly define the context and scope of the study;
- define a suitable study population;
- develop specific statements that describe the study's primary and secondary objectives;
- define the study treatment/intervention(s) and the dosage regimen of the investigational product (if applicable);
- determine measures taken to minimize bias, including randomization and blinding;
- establish procedures for withdrawal of subjects from the study.

The SAP will include the components described in Section 8.B of this SOP, and may include a schematic diagram of the trial design, procedures, and stages.

The finalized SAP for a U01-funded study will be versioned and signature-approved by the DCC PI, the CCC PI, and the PPI. The finalized SAP for X01-funded or SBIR-funded studies will be versioned and signature-approved by the DCC PI, the CCC PI, the Academic PI, and the Company PI.

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 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.

These policies and procedures also apply to the External Biostatistician (if applicable to the study), and any other NeuroNEXT personnel who may be involved in development of a SAP for a NeuroNEXT study.

3. ROLES AND RESPONSIBILITIES

DCC Biostatisticians are responsible for developing a SAP for each NeuroNEXT study, in collaboration with the DCC PI, the PPI, the Study Statistician and the External Biostatistician (if applicable), and for ensuring that the procedures described in this SOP are followed by NeuroNEXT personnel who are involved with SAP development.

4. APPLICABLE REGULATIONS AND GUIDELINES

ICH E6, 4.5	Compliance with Protocol
ICH E6, 4.9	Records and Reports
ICH E6, 5.1	Quality Assurance and Quality Control
ICH E6, 5.4	Trial Design
ICH E6, 5.5	Trial Management, Data Handling and Record Keeping
ICH E6, 5.23	Multicenter Trials
ICH E6, 6.0	Clinical Trial Protocol and Protocol Amendment(s)
ICH E8	General Considerations for Clinical Trials (December 1997)
ICH E9	Statistical Principles for Clinical Trials (September 1998)
ICH E10	Choice of Control Group and Related Issues in Clinical Trials (May 2001)

5. REFERENCES TO OTHER APPLICABLE SOPS

NN BIO 901	Working with an External Biostatistician

6. ATTACHMENTS AND REFERENCES

NN BIO 902 - A	Document History
NN BIO 902 – B	Statistical Analysis Plan Signature Page for U01-Funded Studies
NN BIO 902 – C	Statistical Analysis Plan Signature Page for X01-Funded and SBIR-Funded Studies

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

Academic Principal Investigator (PI)	The Principal Investigator for an SBIR-funded grant originating at an academic institution.
CCC	Clinical Coordinating Center at Massachusetts General Hospital
Company Principal Investigator (PI)	The Principal Investigator who represents the industry partner for an SBIR-funded grant.
DCC	Data Coordinating Center at The University of Iowa
External Biostatistician	A Biostatistician who is not a member of the DCC Biostatistics Team. An External Biostatistician may act as a Study Biostatistician for a study.
Independent Biostatisticians	Unblinded DCC Biostatisticians for a study. Typically, at least two Independent Biostatisticians will be assigned to each study.
Protocol Principal Investigator (PPI)	Principal Investigator of a NeuroNEXT protocol
SAP	Statistical Analysis Plan
Study Biostatistician	Blinded Biostatistician for a study.

8. SPECIFIC PROCEDURES

A. Creating a Statistical Analysis Plan

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Independent Biostatisticians	Develop the SAP.		
2.	DCC Independent Biostatisticians	Collaborate with the DCC PI, the PPI, the Study Biostatistician, and the External Biostatistician (if applicable) during SAP development.		NN BIO 901
3.	DCC Independent Biostatisticians	Include the components described in Section 8.B and take into account any protocol-specific requirements.		

B. Components of a Statistical Analysis Plan

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Independent Biostatisticians	**Overview** Broadly define the scope of the study and define the study population. Summarize measures taken to minimize bias, including randomization and blinding.		
2.	DCC Independent Biostatisticians	**Study Treatment/Intervention** Define the study treatment/intervention and the dosage regimen of the investigational product (if applicable).		
3.	DCC Independent Biostatisticians	**Primary and Secondary Objectives** Create statements that define the primary and secondary objectives of the study. • Develop specific statistical hypotheses that address the study's primary and secondary objectives. • Specify the statistical methods that are used to address secondary hypotheses and safety hypotheses.		
4.	DCC Independent Biostatisticians	**Primary and Secondary Endpoints** Define specific primary and secondary endpoints that relate directly to the statistical hypotheses developed in Step 3. Include language in the protocol that clearly defines the primary endpoint and provides rationale for its use.		
5.	DCC Independent Biostatisticians	**Hypothesis Tests** Specify statistical tests or statistical modeling used in conjunction with primary endpoint to test the primary objective.		
6.	DCC Independent Biostatisticians	**Missing Data** Specify methods for handling missing data, and clearly state whether or not the study follows the Intention to Treat (ITT) principle.		

#	Who	Task	Attachment/ Reference	Related SOP
7.	DCC Independent Biostatisticians	**Sample Size Justification** The sample size should be large enough to address the primary objective of the study. Clearly describe sample size calculations, and include the following information: • the primary endpoint; • the test statistic used to test the primary hypothesis; • the null hypothesis; • the alternative hypothesis at a chosen value of the test statistic; • Type 1 and Type 2 error levels.		
8.	DCC Independent Biostatisticians	**Safety Monitoring** Summarize how safety will be assessed throughout the life of the project, and how any interim analyses will be conducted.		
9.	DCC Independent Biostatisticians	**Study-Specific Components** Develop a plan to address any study-specific requirements that are not included in the above components.		
10.	DCC Independent Biostatisticians	**Schematic Diagram** If useful for explaining the study design, create a schematic diagram of the trial design, procedures, and stages.		

C. Approval and Sign-Off

#	Who	Task	Attachment/ Reference	Related SOP
1.	DCC PI, CCC PI, and PPI	For a U01-funded study, signature-approve the Statistical Analysis Plan.	NN BIO 902 – B	NN BIO 901
2.	DCC PI, CCC PI, Academic PI, and Company PI	For SBIR-funded studies, signature-approve the Statistical Analysis Plan.	NN BIO 902 – C	NN BIO 901

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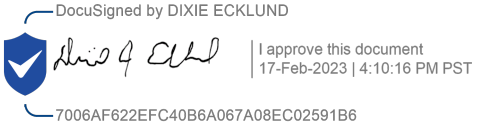
DIXIE ECKLUND dixie-ecklund@uiowa.edu Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Drawn on Device Signature ID: 7006AF62-2EFC-40B6-A067-A08EC02591B6 Using IP Address: 128.255.112.230 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/17/2023 8:16:57 AM Viewed: 2/17/2023 7:09:53 PM Signed: 2/17/2023 7:10:19 PM
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Joan Ohayon ohayonj@ninds.nih.gov Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 72C6AAFD-8CC4-4855-82AC-A0700072901A Using IP Address: 156.40.137.188 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/17/2023 8:16:58 AM Resent: 2/21/2023 8:25:46 AM Viewed: 2/21/2023 9:41:00 AM Signed: 2/21/2023 9:41:15 AM
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Marianne Chase MCHASE@mgh.harvard.edu Sr Director, Clinical Trial Operations Insight OBO The Massachusetts General Hospital Security Level: Email, Account Authentication (Required), Logged in	 Signature Adoption: Pre-selected Style Signature ID: 58FE690F-6BCA-4F23-90E3-DA15BCE3F578 Using IP Address: 73.114.253.109 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/17/2023 8:16:57 AM Viewed: 2/17/2023 1:33:10 PM Signed: 2/17/2023 1:33:46 PM
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Merit Cudkowicz cudkowicz.merit@mgh.harvard.edu Chief of Neurology Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 9F8FE418-0E50-4C6A-B0A6-7B835E80C644 Using IP Address: 68.239.56.73 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/17/2023 8:16:57 AM Viewed: 2/17/2023 8:19:41 AM Signed: 2/17/2023 8:19:54 AM
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Stacey Grabert sgrabert@mgh.harvard.edu Director QA Stacey Grabert Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 60CC52B0-747A-44E6-B220-8D8D880698C0 Using IP Address: 132.183.56.49 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/17/2023 8:16:58 AM Resent: 2/21/2023 8:25:46 AM Viewed: 2/22/2023 11:12:24 AM Signed: 2/22/2023 11:12:41 AM
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