

# NeuroNEXT Network

## Standard Operating Procedure (SOP)

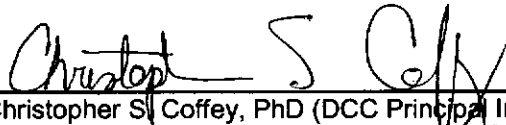
### Statistical Analysis Plan Development

Version 2.0

SOP NN BIO 902

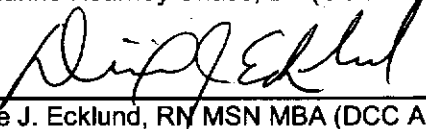
Originators: NeuroNEXT CCC and DCC Personnel


Reviewed and Approved by:

  
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Christopher S. Coffey, PhD (DCC Principal Investigator)

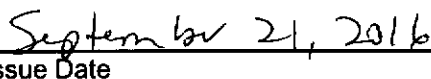
  
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Merit E. Cudkowicz, MD MSc (CCC Principal Investigator)

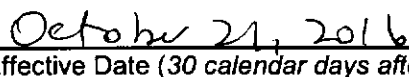
  
\_\_\_\_\_  
Marianne Kearney Chase, BA (CCC Director of Clinical Operations)

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

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

  
\_\_\_\_\_  
Janice Cordell, RN MPH (NINDS, NeuroNEXT Program Official)

  
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Issue Date

  
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Effective Date (30 calendar days after the Issue Date)

## NN BIO 902

### NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR STATISTICAL ANALYSIS PLAN DEVELOPMENT

SOP: NN BIO 902 Version No: 2.0 Effective Date: 21Oct2016	STATISTICAL ANALYSIS PLAN DEVELOPMENT	Supersedes Document: Version 1.0 Effective Date: 13May2012
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#### 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

Biostatisticians at the Data Coordinating Center (DCC) will serve as the primary authors of the SAP. During the development of the SAP, the DCC Study Biostatistician will collaborate with the DCC PI, the Protocol Principal Investigator (PPI), 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 required 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 1996 ICH E6 Consolidated Guidance. 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, 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
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### 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 X01-funded or 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 X01-funded or 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.
Lead Biostatistician	The primary Biostatistician for a study
Protocol Principal Investigator (PPI)	Principal Investigator of a NeuroNEXT protocol

SAP

Statistical Analysis Plan

Study Biostatistician

A member of the DCC Biostatistics team. At least one Study Biostatistician will be assigned to each NeuroNEXT study. The Lead Biostatistician may also act as a Study Biostatistician for a specific study.

## 8. SPECIFIC PROCEDURES

### A. Creating a Statistical Analysis Plan

#	Who	Task	Attachment/Reference	Related SOP
1.	DCC Lead Biostatistician	Assign Study Biostatistician(s) to develop the SAP.		
2.	DCC Study Biostatistician	Collaborate with the DCC PI, the PPI, and the External Biostatistician (if applicable) during the development of the SAP.		NN BIO 901
3.	DCC Study Biostatistician	Create the SAP, including the required components described in Section 8.B, and taking into account any protocol-specific requirements.		

### B. Required Components for a Statistical Analysis Plan

#	Who	Task	Attachment/Reference	Related SOP
1.	DCC Study Biostatistician	<p><b>Overview</b></p> <p>Broadly define the scope of the study and define the study population. Summarize measures taken to minimize bias, including randomization and blinding.</p>		
2.	DCC Study Biostatistician	<p><b>Study Treatment/Intervention</b></p> <p>Define the study treatment/intervention and the dosage regimen of the investigational product (if applicable).</p>		
3.	DCC Study Biostatistician	<p><b>Primary and Secondary Objectives</b></p> <p>Create statements that define the primary and secondary objectives of the study.</p> <ul style="list-style-type: none"> <li>Develop specific statistical hypotheses that address the study's primary and secondary objectives.</li> <li>Specify the statistical methods that are used to address secondary hypotheses and safety hypotheses.</li> </ul>		
4.	DCC Study Biostatistician	<p><b>Primary and Secondary Endpoints</b></p> <p>Define specific primary and secondary endpoints that relate directly to the statistical hypotheses developed in Step 3.</p> <p>Include language in the protocol that clearly defines the primary endpoint and provides rationale for its use.</p>		
5.	DCC Study Biostatistician	<p><b>Hypothesis Tests</b></p> <p>Specify statistical tests or statistical modeling used in conjunction with primary endpoint to test the primary objective.</p>		

#	Who	Task	Attachment/ Reference	Related SOP
6.	DCC Study Biostatistician	<b>Missing Data</b> Specify methods for handling missing data, and clearly state whether or not the study follows the Intention to Treat (ITT) principle.		
7.	DCC Study Biostatistician	<b>Sample Size Justification</b> 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: <ul style="list-style-type: none"> <li>the primary endpoint;</li> <li>the test statistic used to test the primary hypothesis;</li> <li>the null hypothesis;</li> <li>the alternative hypothesis at a chosen value of the test statistic;</li> <li>Type 1 and Type 2 error levels.</li> </ul>		
8.	DCC Study Biostatistician	<b>Safety Monitoring Plan</b> Develop a safety monitoring plan that describes how safety will be assessed throughout the life of the project, and how any interim analyses will be conducted.		
9.	DCC Study Biostatistician	<b>Study-Specific Components</b> Develop a plan to address any study-specific requirements that are not included in the above components.		
10.	DCC Study Biostatistician	<b>Schematic Diagram</b> 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, approve the final Statistical Analysis Plan by signing and dating the Statistical Analysis Plan Signature Page.	NN BIO 902 – B	NN BIO 901
2.	DCC PI, CCC PI, Academic PI, and Company PI	For X01-funded or SBIR-funded studies, approve the final Statistical Analysis Plan by signing and dating the Statistical Analysis Plan Signature Page.	NN BIO 902 – C	NN BIO 901

**Attachment NN BIO 902 - A. Document History**

<b>NeuroNEXT Network Standard Operating Procedure (SOP)</b> <b>Statistical Analysis Plan Development</b> <b>SOP NN BIO 902</b>				
<b>Version</b>	<b>Description of Modification</b>	<b>Reason or Justification for Modification</b>	<b>Issue Date</b>	<b>Effective Date</b>
1.0	New	N/A	13Apr2012	13May2012
2.0	Updated Policy section and required components of a SAP (Section 8.B), and removed references to Protocol Steering Committee participation in the SAP development process. Modified signatories for the SAP, and differentiated between the signatories for a U01-funded grant and signatories for X01-funded and SBIR-funded grants.	Updates for version 2.0 to align with revised DCC SOP and to include references for X01-funded and SBIR-funded grants.	21Sep2016	21Oct2016