NeuroNEXT Network

Standard Operating Procedure (SOP)

Creating, Verifying, Implementing, and Archiving a Randomization Sequence or Algorithm

Version 2.0

SOP NN BIO 903

Originators: NeuroNEXT CCC and DCC Personnel

Reviewed and Approved by:

Christopher S. Coffey, PhD (DCC Principal Investigator)

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)

September 21, 2016
Issue Date

October 24, 2016
Effective Date (*30 calendar days after the Issue Date*)

NN BIO 903

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR CREATING, VERIFYING, IMPLEMENTING, AND ARCHIVING A RANDOMIZATION SEQUENCE OR ALGORITHM

SOP: NN BIO 903 Version No: 2.0 Effective Date: 21Oct2016	CREATING, VERIFYING, IMPLEMENTING, AND ARCHIVING A RANDOMIZATION SEQUENCE OR ALGORITHM	Supercedes Document: Version 1.0 Effective Date: 13May2012

1. POLICY

Randomization assignment systems for all NeuroNEXT clinical trials will be developed, verified, implemented, and archived at the NeuroNEXT Data Coordinating Center (DCC). Depending on the type of trial and the requirements of the protocol, a fixed randomization sequence or adaptive randomization algorithm will be created.

The Lead Biostatistician will collaborate with the DCC PI and the Protocol Principal Investigator (PPI) to define parameters to be considered during development of the randomization sequence or algorithm. DCC Biostatisticians will then generate a brief randomization plan for the trial based on the parameters that were agreed upon during the protocol design phase. If appropriate for the project, a Biostatistician who is external to the DCC may participate in developing the assignment system and generating the randomization plan. The plan will be approved by the DCC PI, the PPI, and the External Biostatistician (if applicable) before the assignment system is created.

Clinical Study Sites (CSS) will randomize subjects through the electronic data capture (EDC) system. If the system is temporarily unavailable at the time of randomization, the CSS will follow a backup procedure that has been established and approved by the PPI and the DCC PI.

This SOP describes general procedures for:

- defining a fixed randomization strategy or adaptive randomization algorithm;
- creating, verifying, and implementing the randomization sequence;
- CSS subject randomization and access to the randomization sequence if the electronic data capture system is temporarily unavailable at the time of randomization; and
- documenting and archiving the randomization sequence.

The final randomization sequence or algorithm will be signature-approved by the DCC PI, the DCC Lead Biostatistician, and the External Biostatistician (if applicable).

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, External Biostatisticians (if applicable), or other entities associated with the NeuroNEXT Network who manage, oversee, and conduct research regulated by FDA and/or applicable review committees.

3. ROLES AND RESPONSIBILITIES

The DCC is responsible for adhering to the procedures outlined in this SOP. The DCC PI, the Lead Biostatistician, and the Information Technology Lead have general responsibility for creating, implementing, and maintaining fixed randomization sequences and adaptive randomization algorithms. The DCC Lead Biostatistician is responsible for consulting with the DCC PI, the PPI, and the External Biostatistician (if applicable) during the development of the randomization sequence or algorithm for each study.

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
NN BIO 902	Statistical Analysis Plan Development

6. ATTACHMENTS AND REFERENCES

NN BIO 903 – A	Document History
NN BIO 903 – B	Randomization Sequence Signature Page
NN BIO 903 – C	Randomization Algorithm Signature Page

Design and Analysis of Clinical Trials (Wiley Series in Probability and Statistics): Concepts and Methodologies. Chow, Shein-Chung Liu, Jen-Pei, John Wiley and Sons, Inc. 2003

Clinical Trials: A Methodologic Perspective (Wiley Series in Probability and Statistics). Piantadosi, Steven, John Wiley and Sons, Inc. 1997

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

Adaptive Randomization Sequence	A randomization sequence in which the probability of assignment of a subject to each treatment group depends either on observations made to subjects previously enrolled, or on the distribution of baseline covariates. As a result, the assignment of subjects to treatment groups cannot be defined in advance
CCC	Clinical Coordinating Center at Massachusetts General Hospital
CSS	Clinical Study Site(s)
DCC	Data Coordinating Center at The University of Iowa
DM	Data Management
DM Lead	Leader of the Data Management team at the DCC
External Biostatistician	A Biostatistician who is not a member of the DCC Biostatistics Team

Fixed Randomization Sequence	A randomization sequence in which the assignment of subjects to treatment groups can be defined in advance. This will generally be defined in the study protocol, including any blocking or stratification strategies. As subjects enroll in the study, they will be assigned to treatment group according to the randomization sequence (i.e., the first enrolled subject will be assigned to the first treatment listed on the randomization sequence, the second subject enrolled will be assigned to the second treatment listed in the randomization sequence, and so on).
IT	Information Technology
IT Lead	Leader of the Information Technology team at the DCC
Lead Biostatistician	Primary Biostatistician for a study
NINDS	National Institute of Neurological Disorders and Stroke
PPI	Protocol Principal Investigator
QA	Quality Assurance
QA Officer	Quality Assurance officer for a study
Randomization Plan	This document describes the overall plan for implementing a randomization for a protocol, and includes the plan for generating the randomization sequence for a fixed randomization, or creating and implementing rules for an adaptive randomization.
Study Biostatistician	A member of the DCC Biostatistics team. At least one Study Biostatistician will be assigned to each study, but only one Biostatistician will be assigned to prepare the randomization. The Lead Biostatistician may also act as a Study Biostatistician for a specific study.

8. SPECIFIC PROCEDURES

A. Defining the Randomization and Creating a Randomization Plan

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Lead Biostatistician	Collaborate with the PPI, DCC PI, and the External Biostatistician (if applicable) to define parameters to be incorporated into a randomization plan for the protocol.		NN BIO 901
2.	DCC Lead Biostatistician	Assign Study Biostatistician to prepare the randomization plan.		
3.	DCC Study Biostatistician	Prepare a randomization plan that includes a written description of the randomization strategy or algorithm based on the randomization procedures stated in the study protocol. For a fixed randomization sequence, the randomization plan describes: • the method that will be used to generate the random treatment assignment		

#	Who	Task	Attachment/ Reference	Related SOP
		• a back-up randomization procedure. For an adaptive randomization algorithm, the randomization plan describes: • the algorithm to be implemented • how the algorithm will be tested to ensure that it is working correctly before implementation • a back-up randomization strategy.		
4.	DCC PI, PPI, External Biostatistician (if applicable)	Review and approve the randomization plan.		NN BIO 901
5.	DCC Lead Biostatistician	After review and approval of the randomization plan, and prior to implementation, attach a version number and version date in the footer of the document.		

B. Creating, Verifying, and Implementing a Fixed Randomization Sequence

#	Who	Task	Attachment/ Reference	Related SOP
1.	DCC Lead Biostatistician	Assign Study Biostatistician to generate the randomization sequence.		
2.	DCC Study Biostatistician	Prior to enrollment of the first subject, prepare a randomized sequence of treatment assignments according to the procedure outlined in the randomization plan, the description in the study protocol, and the approved specifications. Include the following components in the randomized sequence: • an electronic file with the required randomization sequences, in a format agreed upon by the Lead Biostatistician and the leader of the information technology team; • a detailed description of the contents of the file, including column contents and all codes that were used; • a tabulation of the treatment assignment verifying that the appropriate blocking strategy has been used and an appropriate number of treatment assignments have been made in each block and for each stratum; • a listing of any computer program(s) used to generate the sequence.		
3.	DCC Lead Biostatistician	Review the electronic file visually, and by preparing appropriate tabulations, to verify that the randomization plan has been followed.		
4.	DCC Lead Biostatistician and DCC Study Biostatistician	Review together any discrepancies that are found. The Study Biostatistician resolves any deviations from the randomization plan and repeats the verification.		

#	Who	Task	Attachment/ Reference	Related SOP
5.	DCC Lead Biostatistician	Once both statisticians agree that the randomization plan has been accurately executed, forward the electronic file to the Information Technology (IT) Lead.		
6.	DCC IT Lead	Enter randomization sequences into appropriate randomization table. Print the contents of the randomization table.		
7.	DCC Lead Biostatistician	Compare original randomization table to print-out from database to validate that randomization sequences have been properly inserted into database table.		
8.	DCC PI, DCC Lead Biostatistician; External Biostatistician (if applicable)	Review and signature-approve the final randomization sequence.	NN BIO 903 - B	

C. Creating, Verifying, and Implementing an Adaptive Randomization Algorithm

#	Who	Task	Attachment/ Reference	Related SOP
1.	DCC Lead Biostatistician	Assign a Study Biostatistician to create specifications for development of an algorithm for the adaptive randomization.		
2.	DCC Study Biostatistician, DCC DM Team	Refer to the randomization plan to create specifications that include requirements for all rules that must be implemented for the adaptive randomization.		
3.	DCC Study Biostatistician, DCC DM Team	Create a testing plan to validate the algorithm that contains testing conditions for all requirements in the specifications.		
4.	DCC Study Biostatistician	Send the specifications and testing plan to the IT Lead for implementation.		
5.	DCC IT Lead	Develop and implement the randomization algorithm.		
6.	DCC Study Biostatistician	Validate the requirements according to the testing plan.		
7.	DCC PI, DCC Lead Biostatistician; External Biostatistician (if applicable)	Review and signature-approve the final randomization algorithm.	NN BIO 903 - C	
8.	DCC Lead Biostatistician	Store the electronic files containing the algorithm in a secure and restricted area on the DCC shared drive.		

D. Clinical Study Site Randomization Procedures

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	CSS	At the time of randomization of a study subject, complete the randomization process through the electronic data capture system.		
2.	Authorized CSS Personnel	If the electronic data capture system is temporarily unavailable at the time of the randomization, follow the backup procedures that have been developed and approved for the study.		
3.	Authorized CSS Personnel	Follow the procedure that has been developed regarding the final disposition of any backup randomization materials at the end of study.		

E. Documenting and Archiving the Randomization

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	DCC Un-blinded Study Biostatistician and DCC IT Lead	Access to the electronic randomization sequences will be limited to the DCC un-blinded Study Biostatistician and authorized DCC IT personnel.		
2.	DCC Lead Biostatistician, DCC IT Lead	Store the randomization plan and copies of the programs that were used to generate the randomization sequences or algorithm on a restricted area of the DCC shared drive. Access to these documents will be limited only to authorized personnel.		

Attachment NN BIO 903 - A. Document History

NeuroNEXT Network Standard Operating Procedure (SOP) Creating, Verifying, Implementing, and Archiving a Randomization Sequence or Algorithm SOP NN BIO 903				
Version	**Description of Modification**	**Reason or Justification for Modification**	**Issue Date**	**Effective Date**
1.0	New	N/A	13Apr2012	13May2012
2.0	Clarified approval process and signatories, added signature page templates as attachments, and other minor edits throughout.	Updates for version 2.0.	21Sep2016	21Oct2016