




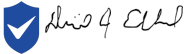
NeuroNEXT Network

Standard Operating Procedure (SOP) Validating Statistical Programs and Deliverables Version 3.0 SOP NN BIO 905

Originators: NeuroNEXT CCC and DCC Personnel

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NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR VALIDATING STATISTICAL PROGRAMS AND DELIVERABLES

1. POLICY

The purpose of this SOP is to describe the levels of validation that are required for statistical analysis programs and deliverables that are generated for the NeuroNEXT Network. NeuroNEXT Data Coordinating Center (DCC) Biostatisticians follow procedures described in a DCC internal SOP (CTSDMC SOP BIO 904) to develop programs to perform statistical analyses that are described in study-specific Statistical Analysis Plans (SAP) or that are requested by the Protocol Principal Investigator (PPI) during the course of a NeuroNEXT clinical trial.

The programs that generate statistical deliverables and perform statistical analyses are validated at one of four levels, depending on the nature and complexity of the analysis or deliverable and its relative impact on the study:

- **Level One** – Validating statistical programs used to generate critical study analyses (analyses of the primary and secondary endpoints as described in the SAP, interim analyses, and analyses for the final study report and primary manuscript).
- **Level Two** – Validating statistical programs used to generate tables and figures that are to be included in DSMB reports, study annual reports, and quarterly safety reports.
- **Level Three** – Validating statistical programs used to generate tables and figures that are included in ongoing study reports (e.g. weekly or monthly reports).
- **Level Four** – Validating statistical programs for ad hoc requests for analyses or deliverables from study investigators.

For critical study analyses, two Biostatisticians who have been assigned to the project independently write programming code to produce data sets, and perform independent analyses of those data sets (Level One validation). The results of the independent analyses are compared and any discrepancies are resolved.

Deliverables (e.g. report tables or figures) that are sent to an external group are validated similarly. For Level Two validation of deliverables, the Lead Biostatistician and Senior Leadership perform a review of the deliverables to identify any errors, inconsistencies, or unusual values. The Lead Biostatistician performs this review for Level Three validation. The contents of deliverables are checked and verified prior to their distribution outside of the DCC.

Statistical programs that are developed in response to ad hoc requests for analyses or deliverables from study investigators, are reviewed internally before they are distributed (Level Four validation).

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, 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

NeuroNEXT DCC Biostatisticians are responsible for adhering to the procedures outlined in this SOP.

The Lead Independent Biostatistician is responsible for ensuring that these procedures are followed by DCC Biostatistics Team Members (Independent Biostatisticians) who develop, document, or validate statistical analysis programs for a NeuroNEXT study.

The Lead Independent Biostatistician, in consultation with DCC Senior Leadership, is responsible for advising Independent Biostatisticians on validation strategies and the appropriate level of validation for analyses and deliverables.

Independent Biostatisticians are responsible for validating the programs developed to perform the statistical analyses and deliverables that are generated at the DCC.

4. APPLICABLE REGULATIONS AND GUIDELINES

ICH E9 Statistical Principles for Clinical Trials (September 1998)

5. REFERENCES TO OTHER APPLICABLE SOPS

NN BIO 902 Statistical Analysis Plan Development

NN BIO 904 Generation and Validation of Analysis Data Sets

DCC BIO 904 Developing, Documenting, and Storing Statistical Programs and Deliverables

NN BIO 906 Presenting Statistical Results for a Final Study Report

6. ATTACHMENTS AND REFERENCES

NN BIO 905 - A. Document History

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

CCC Clinical Coordinating Center at Massachusetts General Hospital

DCC Data Coordinating Center at The University of Iowa

Lead Independent Biostatistician The unblinded lead of the DCC Biostatistics study team (a defined position in the DCC).

Independent Biostatisticians Unblinded DCC Biostatisticians.

8. SPECIFIC PROCEDURES

A. Validating Statistical Programs

#	Who	Task	Attachment	Related SOP
1.	Lead Independent Biostatistician	Assign Independent Biostatisticians to execute and validate the programs used to perform analyses described in the SAP.		NN BIO 902 DCC SOP BIO 904
2.	Independent Biostatisticians	Determine the appropriate validation strategy and the level of validation (Level One, Level Two, Level Three, or Level Four) that is required for the deliverable or analysis, in consultation with the Lead Independent Biostatistician.		
3.	Independent Biostatisticians	Create formal documentation of the validation process for critical study analyses (Level One validation).		
4.	Independent Biostatisticians	For all other types of analyses, document the completion of the validation through email communication, and store the email with the program, report, or deliverable.		

B. Validating Level One Programs for Critical Study Analyses

#	Who	Task	Attachment	Related SOP
1.	Independent Biostatisticians	Follow procedures in DCC SOP BIO 904 to prepare the analysis results.		DCC SOP BIO 904
2.	Lead Independent Biostatistician	For critical study analyses, assign two Independent biostatisticians to independently code and generate primary and applicable secondary endpoints.		
3.	Two Independent Biostatisticians	Generate independent data sets from the raw data files.		NN BIO 904
4.	Two Independent Biostatisticians	Independently execute the data analyses described in the SAP.		
5.	Two Independent Biostatisticians	Generate the results of the independent analyses.		
6.	Two Independent Biostatisticians	Compare values for all primary and applicable secondary endpoints and identify all values where there is disagreement.		
7.	Two Independent Biostatisticians	Address any differences found in the results, and resolve any questions.		
8.	Two Independent Biostatisticians	Generate the analysis results for the report or manuscript.		
9.	Two Independent Biostatisticians	Document the code validation process, and present the analysis results and the validation documentation to the Lead Biostatistician. <ul style="list-style-type: none"> For the final study analysis, or if otherwise requested, generate a summary report that 		

#	Who	Task	Attachment	Related SOP
		describes the validation process, and include validation documentation (e.g. PROC COMPARE results).		
10.	Lead Independent Biostatistician and DCC Director	Review the report and validation of the primary and applicable secondary endpoints.		
11.	Independent Biostatisticians	Collaborate to address any inconsistencies discovered during the review.		
12.	Independent Biostatisticians	Generate the final version of the analysis results.		
13.	Independent Biostatisticians	Submit the final analysis results to the appropriate personnel for incorporation into the report or manuscript.		DCC SOP BIO 904 NN BIO 906

C. Validating Level Two Programs and Deliverables

#	Who	Task	Attachment	Related SOP
1.	Independent Biostatistician	Generate the deliverables (e.g. report tables and/or figures) according to procedures described in DCC SOP BIO 904.		DCC SOP BIO 904
2.	Independent Biostatistician	Submit deliverables to Senior Leadership and the Lead Independent Biostatistician for review.		
3.	DCC Senior Leadership and Lead Independent Biostatistician	Review the deliverables to identify errors, inconsistencies, or unusual values.		
4.	Independent Biostatisticians	Conduct a code review to determine the source of any errors, inconsistencies, or unusual values.		
5.	Independent Biostatistician	Make any necessary corrections to the code.		
6.	Independent Biostatistician	Generate the final version of the deliverables, and perform a check to ensure that all code corrections have been properly implemented.		
7.	Independent Biostatistician	Submit the validated deliverables for incorporation into the report.		DCC SOP BIO 904

D. Validating Level Three Programs and Deliverables

#	Who	Task	Attachment	Related SOP
1.	Independent Biostatistician	Generate ongoing study deliverables (e.g. tables, figures, listings) according to procedures described in DCC SOP BIO 904.		DCC SOP BIO 904

#	Who	Task	Attachment	Related SOP
2.	Independent Biostatistician	Submit the deliverables to the Lead Independent Biostatistician for review.		
3.	Lead Independent Biostatistician	Review the deliverables to identify errors, inconsistencies, or unusual values. Consult with Senior Leadership, as needed.		
4.	Independent Biostatisticians	Conduct a code review to determine the source of any errors, inconsistencies, or unusual values.		
5.	Independent Biostatisticians	Make any necessary corrections to the code.		
6.	Independent Biostatistician	Generate the final version of the deliverables, and perform a check to ensure that all code corrections have been properly implemented.		
7.	Independent Biostatistician	Submit the deliverables to the Study Team.		DCC SOP BIO 904

E. Validating Level Four Programs and Deliverables

#	Who	Task	Attachment	Related SOP
1.	Independent Biostatistician	Generate the deliverable or analysis results according to procedures described in DCC SOP BIO 904.		DCC SOP BIO 904
2.	Independent Biostatistician	Depending on the nature of the request and the level of validation required, perform a quality review of the program code used to generate the deliverable or analysis results.		
3.	Independent Biostatistician	If necessary, make any needed modifications to the code and re-generate the deliverable.		
4.	Independent Biostatistician	Submit the final version of the deliverable or analysis results to the requester.		DCC SOP BIO 904


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