NeuroNEXT Network

Standard Operating Procedure (SOP)

Quality Assurance Audits

Version 3.0

SOP NN QA 801

Originators: NeuroNEXT CCC and DCC Personnel

Reviewed and Approved by:

Signature and Date: DocuSigned by Christopher Coffey Christopher Coffey | I approve this document 16-Feb-2023 | 11:02:27 AM PST C68AC8DD80334CF982AED1200765F147 16-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 | 9:32:47 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 | 1:39:02 PM EST 58FE690F6BCA4F2390E3DA15BCE3F578 17-Feb-2023
Name and Title: Marianne Chase, MS (DCC Quality Assurance Manager)

Name and Title: Marianne Chase, BA (CCC Senior Director of Clinical Trials Operations)
Signature and Date: DocuSigned by DIXIE ECKLUND I approve this document 17-Feb-2023 | 4:04:55 PM PST 7006AF622EFC40B6A067A08EC02591B6 17-Feb-2023
Name and Title: Dixie J. Ecklund, RN MSN MBA (DCC Associate Director)
Signature and Date: DocuSigned by Stacey Grabert I approve this document 22-Feb-2023 | 11:14:35 AM EST 60CC52B0747A44E6B2208D8D880698C0 22-Feb-2023
Name and Title: Stacey Grabert, Pharm.D, MS, (CCC Director of Quality Assurance)
Signature and Date: DocuSigned by Joan Ohayon I approve this document 21-Feb-2023 | 6:42:20 AM PST 72C6AAFD8CC4485582ACA0700072901A 21-Feb-2023
Name and Title: Joan Ohayon, RN, MSN, CRNP, MSCN (NINDS, NeuroNEXT Program Official)

NEURONEXT NETWORK STANDARD OPERATING PROCEDURE FOR QUALITY ASSURANCE AUDITS

1. POLICY

The Data Coordinating Center (DCC) and/or the Clinical Coordinating Center (CCC) may arrange for periodic audits of ongoing and completed research for the NeuroNEXT Network at Clinical Study Sites (CSS), as required per protocol. The CCC and, when applicable, the DCC will act on findings of concern with immediate corrective actions, as well as long-range process improvements.

Audits of CSS will not be performed by personnel responsible for conducting site monitoring visits. Auditors may use procedures outlined in NeuroNEXT SOPs or other mutually agreed-upon procedures, working papers, or tools provided by the auditor to conduct and document the audit.

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 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.

3. ROLES AND RESPONSIBILITIES

As required by a NeuroNEXT protocol, the Sponsor, the DCC, and/or the CCC may conduct audit-related activities such as:

- Determining if audits of the CSS are needed, according to the protocol and in conjunction with the PPI and/or Sponsor
- Identifying a trained and qualified auditor to conduct the program audit; this individual may be either a DCC or CCC employee, or an outside contractor
- Ensuring that the auditor is informed of the requirements for the audit, and his/her/their responsibilities in performing the audit
- Providing access to all relevant documentation necessary for carrying out a thorough audit, as determined by the PPI and/or Sponsor, DCC and CCC Leadership, as well as the CCC Quality Assurance (QA) team
- Ensuring that audits are scheduled and completed if appropriate funding is available
- Fully cooperating with QA audits by any authorized third party
- Developing and implementing Corrective Action and Preventative Action (CAPA) plans for any issues identified by an auditor.

As required by a NeuroNEXT protocol, a CSS auditor may be responsible for audit activities that include, but are not limited to, the following:

- Preparing for a CSS audit (as applicable)
- Conducting the audit according to applicable NeuroNEXT SOPs and regulatory requirements
- Reviewing preliminary audit observations with the PPI and the DCC and CCC Leadership
- Documenting observations in an audit report
- Submitting the final audit report to the PPI and/or Sponsor, the DCC PI, the CCC PI, and other applicable entities that may be designated by the DCC PI and the CCC PI.

As required by a NeuroNEXT protocol and if applicable to a study, the DCC and/or CCC is/are responsible for maintaining audit reports, and for maintaining a list of audit dates (to present to an FDA inspector).

Appropriate personnel from the CSS, DCC and CCC are responsible for developing and maintaining CAPA plans for any issues that are identified during a CSS audit.

The Study Team is responsible for following up on all corrective actions to ensure resolution.

The responsibility to conduct any or all of these activities may be delegated at the discretion of the PPI/Sponsor to the DCC and/or CCC, or to subcontractors of the DCC or CCC. Those individuals and entities also take on responsibility for meeting regulatory requirements on behalf of the PPI/Sponsor, but the PPI/Sponsor has the ultimate responsibility, and must therefore supervise those delegated activities effectively.

4. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.54	General Responsibilities of Sponsors
ICH E6, 2.13	The Principles of ICH GCP
ICH E6, 5.1	Quality Assurance and Quality Control
ICH E6, 5.19	Audit
ICH E6, 5.20	Noncompliance
FDA	Compliance Policy Guide 7151.02

5. REFERENCES TO OTHER APPLICABLE SOPS

NN GA 105	Vendor Selection and Agreements
NN RA 202	Trial Master File Maintenance
NN RA 203	Site Regulatory Binder Maintenance
NN SS 402	Site Initiation Visits and Site Training
NN SS 403	Routine Monitoring
NN SS 404	Site Performance Monitoring
NN SS 406	Suspension or Early Termination of a Study or a Clinical Site
NN QA 802	Quality Management

6. ATTACHMENTS AND REFERENCES

NN QA 801 – A	Document History

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

CAPA	Corrective and Preventive Action
CCC	Clinical Coordinating Center at Massachusetts General Hospital
Clinical Study Site (CSS)	Clinical site that conducts research for a NeuroNEXT protocol
DCC	Data Coordinating Center at The University of Iowa
FDA	US Food and Drug Administration
PPI	Protocol Principal Investigator
RMF	Regulatory Master File
QA	Quality Assurance

8. SPECIFIC PROCEDURES

A. Auditing a Clinical Study Site (CSS)

#	*Who*	*Task*	*Attachment/ Reference*	*Related SOP*
1.	Study Team	If it is determined that a CSS audit is necessary, confirm that funding is available prior to scheduling the audit.		
2.	Sponsor	Select an in-house auditor, an external auditor, or delegate responsibility to the CCC and/or DCC per contract to conduct the audit on behalf of the Sponsor.		
3.	CCC and DCC	Work with the auditor and the clinical site to schedule the audit.		
4.	Study Team	If an external auditor is used, and as applicable to the firm, review the firm's SOPs, audit report process, and/or a Scope of Work document to ensure that they are adequate. Alternatively, require the auditor to follow the NeuroNEXT SOP for conducting investigative site audits.		NN GA 105 NN SS 403
5.	DCC / CCC Personnel	Instruct the auditor to meet with the investigator (and staff) to review the purpose and scope of the audit and sign a site monitoring log to document the visit.		
6.	DCC / CCC Personnel	After the audit is complete, request that the auditor provide a report and a completed checklist to the CCC and DCC, and review any significant findings and applicable evidence with the DCC/CCC Leadership and/or other appropriate staff.		
7.	CCC	File the reviewed and approved checklist in the TMF, if applicable.		NN RA 202
8.	Study Team	After reviewing the audit results, determine and document follow-up actions (e.g. no action indicated, data disqualification, study site termination).		NN SS 404 NN SS 406

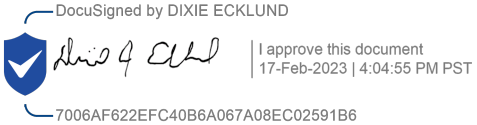
DocuSign

Certificate Of Completion

Envelope Id: 79E0BF104CF74584BCA39F15C8A099DD
Status: Completed
Subject: Complete with DocuSign: NN QA 801 Quality Assurance Audits v3.0.docx
Source Envelope:
Document Pages: 5
Signatures: 6
Envelope Originator:
Certificate Pages: 6
Initials: 0
Tania Leeder
AutoNav: Enabled
TLEEDER@PARTNERS.ORG
EnvelopeId Stamping: Disabled
IP Address: 24.62.91.235
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
2/16/2023 9:17:27 AM
Holder: Tania Leeder
TLEEDER@PARTNERS.ORG
Location: DocuSign

Signer Events	Signature	Timestamp
Christopher Coffey christopher-coffey@uiowa.edu Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Pre-selected Style Signature ID: C68AC8DD-8033-4CF9-82AE-D1200765F147 Using IP Address: 128.255.113.139 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/16/2023 9:23:03 AM Viewed: 2/16/2023 2:02:17 PM Signed: 2/16/2023 2:02:29 PM
Electronic Record and Signature Disclosure: Accepted: 2/16/2023 2:02:17 PM ID: dfe302f7-295e-4a59-98a6-a62a358720b1		
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: 2/16/2023 9:23:04 AM Viewed: 2/17/2023 7:04:30 PM Signed: 2/17/2023 7:04:57 PM
Electronic Record and Signature Disclosure: Accepted: 2/17/2023 7:04:30 PM ID: 5af64ed9-3fef-4b1d-a629-1e4c8f34ff5f		

Signer Events	Signature	Timestamp
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: 2/16/2023 9:23:05 AM Resent: 2/21/2023 8:26:09 AM Viewed: 2/21/2023 9:42:08 AM Signed: 2/21/2023 9:42:23 AM
Electronic Record and Signature Disclosure: Accepted: 2/13/2023 2:03:22 PM ID: 385a0a53-0f0c-4395-88f6-d5700c36e050		
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: 2/16/2023 9:23:04 AM Viewed: 2/17/2023 1:38:42 PM Signed: 2/17/2023 1:39:06 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Merit Cudkowicz cudkowicz.merit@mgh.harvard.edu Chief of Neurology Security Level: Email, Account Authentication (Required), Logged in	 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: 2/16/2023 9:23:03 AM Viewed: 2/17/2023 9:32:38 AM Signed: 2/17/2023 9:32:49 AM
Electronic Record and Signature Disclosure: Accepted: 2/17/2023 9:32:38 AM ID: 604ad891-9bec-44b2-947c-18044e8f8545		

Signer Events	Signature	Timestamp
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: 2/16/2023 9:23:04 AM Resent: 2/21/2023 8:26:10 AM Viewed: 2/22/2023 11:14:23 AM Signed: 2/22/2023 11:14:37 AM
Electronic Record and Signature Disclosure: Accepted: 7/20/2020 8:50:14 AM ID: 5ebadf74-e399-40fd-be82-9c7ca902061b		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	2/16/2023 9:23:05 AM
Certified Delivered	Security Checked	2/22/2023 11:14:23 AM
Signing Complete	Security Checked	2/22/2023 11:14:37 AM
Completed	Security Checked	2/22/2023 11:14:37 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Insight OBO The Massachusetts General Hospital (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Insight OBO The Massachusetts General Hospital:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: jhenrique@mgh.harvard.edu

To advise Insight OBO The Massachusetts General Hospital of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at jhenrique@mgh.harvard.edu and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Insight OBO The Massachusetts General Hospital

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to jhenrique@mgh.harvard.edu and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Insight OBO The Massachusetts General Hospital

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to jhenrique@mgh.harvard.edu and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Insight OBO The Massachusetts General Hospital as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Insight OBO The Massachusetts General Hospital during the course of your relationship with Insight OBO The Massachusetts General Hospital.