National Institute of Neurological Disorders and Stroke

NINDS Standard Operating Procedure

NINDS SOP 18

SOP Title: Data Management in NINDS

Version: 1.2

Approval Signature: L. Nath Digitally signed by Nath, Avindra (NIH/NINDS) [E] Date: 2022.08.02 21:54:54 -04'00'

NINDS Clinical Director

Date of Approval: see above

Date of Implementation: 8/1/2022

Previous Versions: N/A

Table of Contents

Table of Contents

1. PURPOSE

The purpose of this SOP is to outline the NINDS Clinical Trials Unit (CTU) requirements for standardized research data collection and management for all protocols within the NINDS Intramural Clinical Neuroscience Program (CNP).

2. POLICY

The CTU multidisciplinary Data Management team provides support to research teams for the development of comprehensive data management plans to address database design, data collection, data entry, CRF creation and data storage from inception through completion of the study. The CTU Data Management team is also available to assist teams in developing a Quality Control (QC) plan to ensure that the requirements for trial-related activities have been fulfilled and the quality and integrity of the trial data are accurate and have been protected.

This policy is consistent with:

- Good Clinical Practice (GCP) Guidelines. (https://www.fda.gov/files/drugs/published/E6%28R2%29-Good-Clinical-Practice--Integrated-Addendum-to-ICH-E6%28R1%29.pdf).
- 21 CFR parts:
  - 11: (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11),
  - 312: (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312).
  - 812: (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=812)
- Human Subjects Protection regulations - 45 CFR 46
- NIH Policies

3. APPLICABILITY

All research protocols conducted in the NINDS intramural CNP, including FDA regulated and non-FDA regulated studies, interventional and observational protocols, are expected to be conducted in a manner which ensures that all data collection practices adhere to ALCOA-C principles, i.e., the data are attributable, legible, documented contemporaneously, original, accurate, and complete (ALCOA-C) (See Appendix A).

4. ROLES AND RESPONSIBILITIES

4.1. Principal Investigator Responsibilities

- Ensure adequate delegation of authority of research responsibilities to members of the research team, including collection, documentation and verification of obtained clinical and research data.
- Ensure all members of the research team are informed about their responsibilities pertaining to the protocol and data management.
- In collaboration with the Data Management Team, create a Data Management Plan (DMP), including the selection of a data management system that complies with requirements and standards.
- Update the DMP and submit to the data manager, whenever changes to the data capture process, (e.g., new CRF, new storage location of data, change in location of source data), have been planned and developed.

- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and 21 CFR 812.140, and to make those records available for inspection in accordance with 21 CFR 312.68 and 21 CFR 812.145.
- Comply with NIH policies on data sharing and responding to data inquiries from entities providing oversight.
- Assume responsibility for all activities delegated to the Research Team.

4.2. Research Team Responsibilities

- Produce and maintain accurate and complete source documentation.
- Ensure that all source data is documented in the Medical Record/Research Record following ALCOA-C guidelines.
- Ensure the overall quality of the research data is verifiable and acceptable and in compliance with sponsor requirements.
- Review data discrepancy/clarification resolutions for accuracy, consistency, and timely response.
- Develop, implement, and maintain a Quality Control (QC) plan:
  - Establish a schedule of QC activities
  - Perform QC of source documentation, data abstraction, CRF completion
  - Perform QC of data entered into the electronic database
- Develop a quality improvement plan, as needed.
- Review quality assurance (QA) queries and requests for clarification.

4.3 Data Manager Responsibilities

- Assist Principal Investigator (PI)/Associate Investigator (AI) or delegated study team member, with the development and implementation of the Data Management Plan (DMP) and assist study team to ensure compliance with the DMP throughout the protocol life cycle (study design to database lock and publication).
- Serve as a liaison between the PI/Research team and Electronic Data Capture (eDC) Team, e.g., CiSTAR.
- Work with the study team for the development of a protocol specific CiSTAR database, as applicable.
- May assist study team in the development of protocol specific Case Report Forms (CRF).
- May advise study team in developing a QC plan for each stage of data handling.
  - To ensure accurate and complete source data documentation
  - To ensure accurate and complete CRF documentation
  - To resolve discrepancies in data
  - Utilize database report tools to assist with QC activities

5 PROCEDURES

5.1 Development of a Data Management Plan

5.1.2 Data Management Planning Meeting

Development of a NINDS DMP should begin during the protocol development phase. The NINDS CTU data management team is available for consultation during the development phase, as needed. Refer to Appendix B (DM and CiSTAR flowchart) and Appendix C (CiSTAR User Agreement) for a description of the process employed for the development of a database in CiSTAR.

5.1.3 At time of Scientific Review Committee (SRC) Submission

- The PI will complete and submit the Phase 1 DMP document (Included with the SRC packet). See Appendix D.
- The CTU Lead, QA and Data Management Office will review the submitted Phase 1 DMP document and assign the protocol to the appropriate data management staff member.

5.1.4 Following SRC Approval

- The assigned Data Manager will contact the PI/Study team to schedule a DM Planning Meeting.
- DM Meeting attendees should include:
    - Principal Investigator and/or Lead Associate Investigator
    - Study team member or members who will be providing the PI with data management support
    - CTU, Lead QA and Data Management Office
    - Assigned CTU Data Manager
    - CTU Statistician
- During the DM meeting, the Phase 2 DMP document (see Appendix E) will be completed, which identifies:
    - The origin of all source data, including each eligibility criterion, adverse event data elements, all applicable research data collected during the study, and the type and location of source documentation (mapping the data)
    - The data to be captured in the electronic database, e.g., CiSTAR
    - The electronic Case Report Forms (eCRFs) to be used for data capture and any necessary rules, e.g., calculations, hiding elements, assigned to the eCRF to optimize data collection
- The NIH Library may be contacted by the data manager and/or study team to assist with identifying the current version of tests and questionnaires being utilized in the study and to determine if copyright approval is required.
- Study team must obtain all applicable licenses and copyright approvals, in advance of eCRF development and completion.
- The PI must complete the PI questionnaire which identifies all investigators requiring access to the electronic database and their respective role(s).

5.1.5 After Study Initiation

- The Phase 2 DMP document must be updated with any changes to the protocol that result in a modification to data collection.
- The PI questionnaire must be updated with any change to investigator responsibility pertaining to data collection.

5.2 Elements of a Data Management Plan

The DMP includes information about the source data to be collected, captured and stored, the method of data collection, the location and storage of the source data and the planned sharing of data. The DMP will also identify which data, when not captured directly into a protocol electronic database, will be transferred to an electronic database via direct data pull from another electronic system or transcribed from the source data. In addition, the DMP will identify the QC procedures which the study team will employ to ensure reliable data.

In addition to the source data, the study team should consider the storage location of data and documents pertaining to the statistical analysis plan, relevant processed data including data from interim analyses, key data processing steps, data dictionaries and relevant study-logs. Information pertaining to data processing should be considered at the time of developing a DMP to ensure consistent methodology during data analysis and may be needed to comply with requirements for data sharing and to enhance reproducibility of results.

5.2.1 Source Data

The DMP should describe the origin of the data to be collected, (e.g., subject response via a participant questionnaire, EMG recordings during TMS procedure, records of subject performance on physiological tests (e.g., 25 ft walk test) or behavioral tests (e.g., MOCA test)). Minimum data captured for most trials conducted at NINDS include:

- Demographics and Baseline Characteristics
    - History and Physical Exam Findings
    - Baseline labs
    - Baseline physiologic and behavior measures
- Data to support the primary and secondary outcomes measures
- All research related study procedures
- Safety Events/Adverse Events/Adverse Device Effects
    - Adverse event data must be captured in the medical record (CRIS) as well as the research record
- Non-compliance events
- Source documentation of each eligibility criterion
- Documentation of informed consent and informed consent process

5.2.2. Case Report Forms

Case report forms (CRFs) can be printed, optical, or electronic documents designed to record all the protocol required information to be reported to the sponsor on each trial subject (ICH E6, 1.11). The primary objective of a CRF is to preserve and maintain quality and reliable data for analysis.

A CRF may contain source data or may include data that is transcribed from the source. When the latter is employed, it is typically used to capture important study data that will be analyzed in support of the primary and secondary outcome measures.

The use of CRFs facilitates the collection of data in a standardized format consistent with:

- The protocol and
- Regulatory requirements

In addition, the CRF will contribute to efficient and complete data collection and facilitate efficient data analysis.

The NINDS CNP encourages the standardization of documentation and data collection across all research protocols to adhere to data standards in the scientific community. Standardization allows for systematic aggregate reporting, facilitates data sharing, and joint data analyses with outside partners adhering to similar data standards.

The NINDS Common Data Elements (CDEs) website serves as a repository and dissemination tool for all NINDS CDEs for Investigators to utilize for trials being planned, and ongoing research. NINDS strongly encourages that researchers who receive funding from the Institute ensure their data collection is compatible with these CDEs.

When considering CDEs or CRFs, the NINDS CDE website (https://www.commondataelements.ninds.nih.gov) can be used to search the libraries for both standardized CDEs and CRFs. When CRFs are used, they should be used in their entirety when possible. If the data elements in a CRF must be modified (either adding or subtracting elements) then a Unique Data Element/Form will be created.

Investigators are responsible for ensuring that the use of copyright protected forms or questionnaires are approved by the authors, and fees paid when required. Confirmation of copyright approval, when required, should be included on the PI questionnaire.

5.2.3. Biospecimen tracking and management

A DMP should include a description of the collection or receipt of biospecimens as well as the labeling, storage and tracking of biospecimens. Biospecimens may include, but are not limited to, saliva, urine, blood, CSF, and skin/muscle/organ tissue. NINDS currently supports investigators using STAMS, *Samples Tracking and Management System*, developed by NINDS IT as an electronic biospecimen storage and tracking system. A samples tracking and management system should include the following information:

a. Origin: the origin and type of each biospecimen should be recorded in the database.

b. Labeling: each specimen should include a label with a unique identifier, e.g., barcode, which should not reflect its identity, but rather should be coded with the information to identify the sample, e.g., participant identifier, date and/or time point of sample collection, sample type, location of the stored sample. The label should be readable by an electronic data tracking system as well as to the individual pulling the sample.

c. Storage: the storage location should be identified prior to the start of the study to ensure necessary conditions for the sample storage can be maintained and adequate space is identified. If temperature or humidity conditions are required, then the storage system should be capable of recording and storing a log of these conditions. In addition, the system should notify the investigator of any excursions requiring attention. Allowable excursions should be pre-specified in the laboratory manual. The storage location should be secure and only accessible by those authorized to have access.

d. Tracking: an electronic tracking system should be capable of tracking the biospecimen throughout the life of the specimen from collection, through freezing/thawing, processing, storage, distribution, and destruction, if applicable. The biospecimen database should be updated each time a biospecimen or sample is moved within or out of the biospecimen storage location, and the database should be able to track the location changes of the sample. The database must be able to identify each position in storage (i.e., the position in the storage box, rack/shelf, and freezer). The electronic tracking system should permit queries to locate an individual sample stored in the location identified. The biospecimen database should provide an audit trail to track all changes made to the data, including but not limited to all specimen data, system metadata, and clinical data. The computer-generated and automatic reports should include: original data and new data;

date and time changed; how the change was made; who made the changes; and why the changes were made.

5.2.4. Method of Data Collection

Data collection may be accomplished by using electronic or paper documentation methods.

DMPs for data collected using paper may include processes for data transfer into an electronic system, as well as storage of the source data and source documentation. According to OMB M-19-21, *Transition to Electronic Records*, all Federal agencies are directed to ensure that all Federal records are created, retained, and managed in electronic formats with appropriate metadata by December 31, 2022.

NINDS requires all NINDS sponsored FDA regulated studies use a 21 CFR part 11 compliant data capture system for all electronic data captured and stored. The NINDS eDC system, CiSTAR, meets the requirements of 21 CFR part 11. For non-FDA regulated studies, investigators are encouraged to use CiSTAR or another eDC system for electronically captured source data. Electronically captured data improves data quality by:

- Eliminating unnecessary duplication of data entry
- Reducing the possibility for transcription errors
- Allowing direct data entry of source data during a subject's visit, when appropriate
- Reducing or eliminating the need to transcribe source data
- Facilitates remote monitoring of data
- Promotes real-time access for data review
- Facilitates the collection of accurate and complete data

Databases that are not 21 CFR part 11 compliant do not have the system requirements for data integrity integrated into the system. When the investigator is using such a system, the DMP will document the steps to be taken that would otherwise automatically be performed.

All modes of data collection must ensure that the data are complete, consistent, accurate, trustworthy, and reliable for the life of the study.

5.2.5 Data Storage and Protection

Proper storage and preservation of data is important to:

- Ensure that data can be retrieved by the study team and other researchers
- Meet legal and institutional requirements for sharing and retention
- Allow for verification and replication of study results

Data may be stored electronically, in paper format, or in a combination of both electronic and paper format.

Data collected or entered electronically (including physiological, imaging, genomic, etc.) must be stored in a secure manner and be password protected, consistent with 21 CFR Part 11. Original paper documents should be stored in a secure (locked) room or file cabinet.

The DMP will document all storage locations.

5.2.6 Data Access

The review of source data is important to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the research data. Authorized representatives of the sponsor(s) (including site monitors), NINDS Clinical Director (CD) or designee, and regulatory agencies must have access to examine electronic records or certified copies of clinical research records for the purposes of QA reviews, audits, and evaluation of the study safety and progress.

The records must be accessible for inspection and copying at reasonable times and in a reasonable manner.

Data access permissions are determined by the PI and recorded in the DMP. Permissions should specify who has access to the data, to what data the individual is permitted to access, and the level of access, i.e., data entry, viewing data only, and/or modifying data.

5.2.7. Quality Control Review

Quality control (QC) processes entail contemporaneous review of data to verify the accuracy and validity of the collected and recorded data by the study staff involved in the research. QC processes should occur close in time to the point of data collection to ensure the validity of the data. Reviewing the data in real-time assures internal consistency by conducting operational checks of the data at every stage of data collection and data handling while verifying compliance with the protocol and the reliability of the data. QC activities in a clinical trial:

- Ensures that the trial is conducted in compliance with the protocol, applicable policies and Good Clinical Practice
- Resolve systemic problems in real-time and before the end of the trial
- Help to minimize data queries by external auditors and inspectors
- Assures the credibility and reliability of the data
- Ensures that the data entered at all stages of the trial is consistent and accurate

QC measures should be incorporated into the DMP, thus measures should be developed prospectively to ensure the integrity and reliability of the data from the start of data collection rather than in response to data inaccuracies discovered during the course of the trial.

QC measures may include, but are not limited to:

1. Data Validation tools: Data validation specifications should be incorporated into the data collection process. Examples of validation checks in an eDC system includes methods to ensure that all possible data fields are completed prior to allowing the form to be locked or building data fields with data ranges whereby an alert appears when data is entered outside of the range.

2. Scheduled visit tools: In an electronic database, required procedures (with forms to be completed) can be assigned to visit timepoints during the database build, ensuring that all procedures are completed during each visit.

3. Data entry validation: Double data entry methods, which include a source data entry person followed by second person who verifies the accuracy of the data. Two person data entry methods may include verification of source data and/or verification of data entered onto a CRF.

4. Batch data: Consider developing a plan for validating batched data or complex data sets that are entered electronically from the source.

5. Timing of QC procedures: QC procedures should occur on a pre-determined schedule and should be completed on a regular basis from study start through study completion and data locking.

5.2.8 Data Protections and Data Sharing

Personally Identifiable Information (PII) must be protected and stored in a secure manner. PII should be stored on a secure server with a key to personal identifying information. According to Office of Human Subjects Research Protections (OHSRP) Policy 107, Privacy and Confidentiality, the NIH follows federal law provided by the Privacy Act of 1974 (5 U.S.C. 552a). This Act includes procedures for: 1) Protecting records that can be retrieved by personal identifiers such as a name, social security number, or other identifying number or symbol, and 2) Persons accessing identifiable records and requesting correction(s) of these records. Investigators are responsible for following the plan described in the protocol for protecting the confidentiality of information and data provided by research subjects.

NIH has issued a new Final NIH Policy for Data Management and Sharing (DMS), which will require NIH funded researchers to prospectively submit a plan outlining how scientific data from their research will be managed and shared. On January 25, 2023, the new policy will come into effect and replace the 2003 NIH Data Sharing Policy currently in effect. The DMS Policy applies to all research, funded or conducted in whole or in part by NIH, that results in the generation of scientific data. This includes research funded or conducted by extramural grants, contracts, Intramural Research Projects, or other funding agreements regardless of NIH funding level or funding mechanism. The DMS Policy does not apply to research and other activities that do not generate scientific data, including training, infrastructure development, and non-research activities.

5.2.9 Data Reporting

The Final Rule which became effective on January 18, 2017, details the requirements for submitting registration and summary results information to ClinicalTrials.gov. The requirements apply to the responsible party (sponsor or PI) for certain clinical trials of drug products (including biological products) and device products that are regulated by the Food and Drug Administration (FDA) and for pediatric postmarket surveillances of a device product that are ordered by FDA.

The NIH Policy complements the Final Rule in that the NIH Policy applies to all clinical trials funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the Final Rule. The responsible parties for such applicable clinical trials are required to submit clinical trial results information specified in § 11.48 by the earlier of 1 year after the completion date or 30 calendar days after the date of initial FDA approval, licensure, or clearance (79 FR 69594).

Data collected throughout the study should provide all data elements necessary for reporting to ClinicalTrials.gov. The requirements are outlined in the Final Rule, §11.48—*"What constitutes clinical trial results information?"* via the following link: https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission

The PI or the study sponsor is responsible for reporting results of applicable clinical trials to the ClinicalTrials.gov website.

5.2.10 Data Retention and Destruction

Research related records should be retained according to the NIH Records Management Schedule (NIH Manual Chapter 1743-3000 Records Retention).

NIH records may not be destroyed unless consistent with applicable regulations and the NIH policies governing record maintenance and retention.

The NIH Intramural Record Retention Schedule provides guidance for records related to the planning, development, oversight and execution of biomedical research projects and programs performed by NIH research staff, contractors or under collaborative research and development agreements (CRADAs).

These records span the project lifecycle and include documents which:

- Facilitate data analysis, publication, collaboration, and peer review;
- Demonstrate compliance with accepted policies and standards for the conduct of good science;
- Validate and reproduce research outcomes;
- Support intellectual property claims; and
- Defend against allegations of research misconduct and malpractice.

6. APPENDICES

APPENDIX A

ALCOA-C

Source data should adhere to the regulatory requirements for recordkeeping and comply with ALCOA-C guidelines. The Acronym ALCOA-C represents the following elements:

Attributable

When documenting data on paper, every written element needs to be traced back to the authorized individual who is responsible for recording it. This requires:

- A signature or initials of the data author.
- Date of data collection.
- An identifier to a subject visit.
- Changes to a record need to be initialed, dated, and an explanation for the change.

Legible

- Information should be easily understood, and permanently recorded.
- Extraneous information on source documents should be avoided.
- On paper, everything written must be easy to read and recorded in a permanent medium. Handwriting must be clear to reduce the likelihood of transcription errors and allow a study to be accurately re-created.
- The risk of illegibility is reduced by using electronic source records as data and information are presented in a clean and standardized format.

Contemporaneous

- Information should be recorded in a timely manner and should be complete. An acceptable delay should be defined and justified. Errors occur when attempting to reconstruct a subject visit after it occurred.
- Data should be recorded, signed, and dated at the time of trial conduct, rather than risk an individual recalling the wrong information from memory.
- On paper, data needs to be documented in real-time and dated with the current date (no predating or postdating).
- Automatic date and time stamps support this every time clinical data is entered, edited, or modified in an electronic system that has the appropriate controls in place to fully support compliance with 21 CFR Part 11.

Original

- Source information should be preserved in its original form.
- Source documents are part of the permanent research records and should not be destroyed.
- The source is the earliest record – the first place that data is documented. If corrections or revisions are required, changes should not obscure prior entries.
- Paper source documents should be preserved and kept in their original form. When the first record is electronic, an audit trail can track any and all subsequent queries and changes.

Accurate

- Accurate documentation is a record of the information, consistent with the protocol, made without error.
- The document and data should be accurate, real, and represent the facts. There should be a high level of honesty and accuracy in reporting, and documents should be double checked for accuracy.

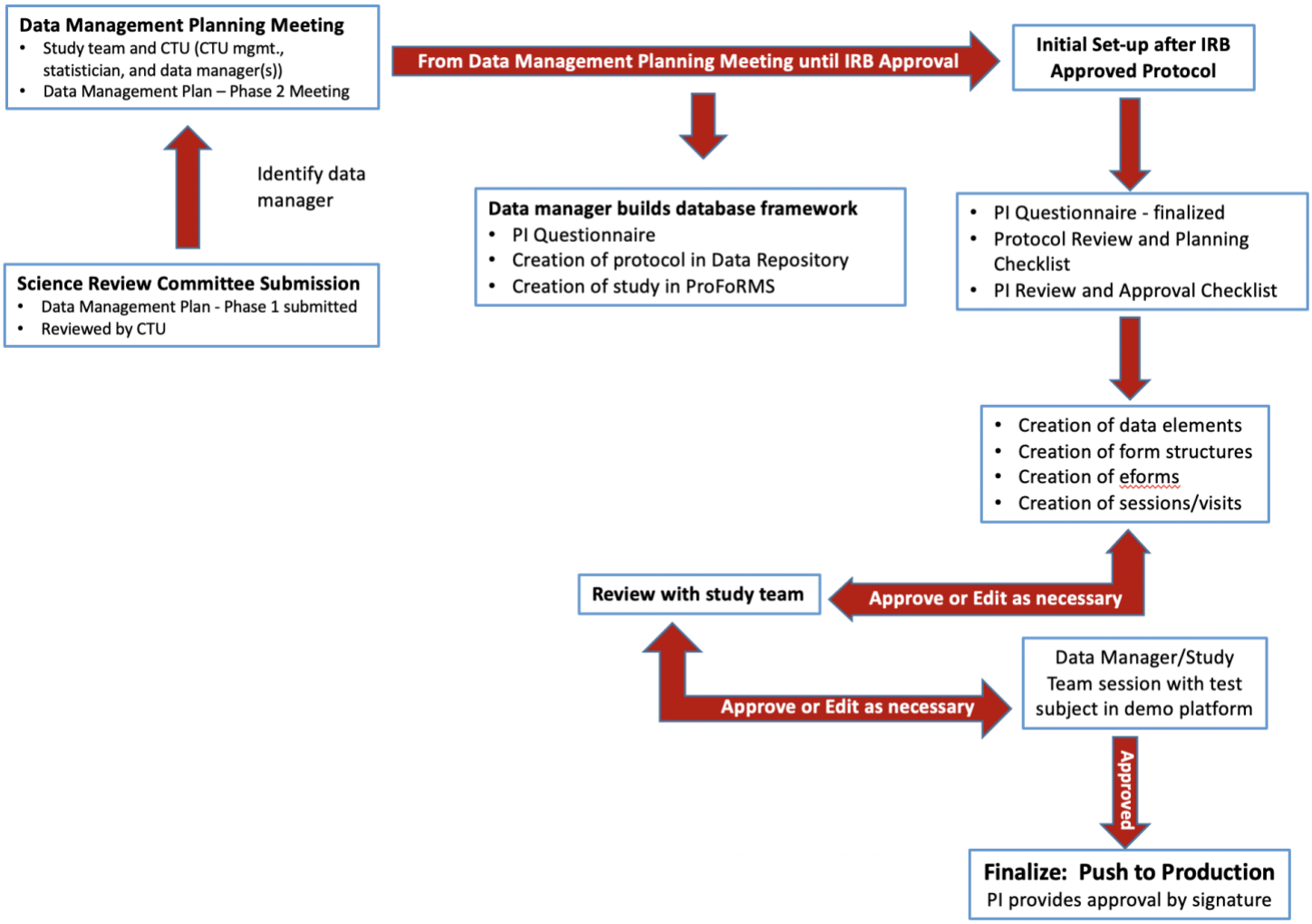
- If errors are discovered, they should be corrected using the guidelines in the "Guidance for Industry Electronic Source Data in Clinical Investigations".
- Source documentation should completely reflect the true observations in an honest, accurate, and thorough representation of facts describing the conduct of the study.
- There will be times when source documents are incomplete, inconsistent, or wrong. If changes are required, modifying a paper record always need to be done in a compliant manner.
- When the source is electronic, audit trails can provide transparency to prevent data from being altered in a way that is difficult to detect.
- Additionally, automatic edit checks can immediately alert when missing data points or out-of-range data are entered.

Complete

- The data recorded should be complete to the point in time.

APPENDIX B

DATA MANAGEMENT AND CISTAR FLOW CHART



APPENDIX C

CISTAR USER AGREEMENT TEMPLATE

CLICK HERE FOR THE CURRENT VERSION OF THE CISTAR DATA MANAGEMENT AGREEMENT

CiSTAR Data Management Agreement

Agreement between the Principal Investigator and
CTU Data Manager

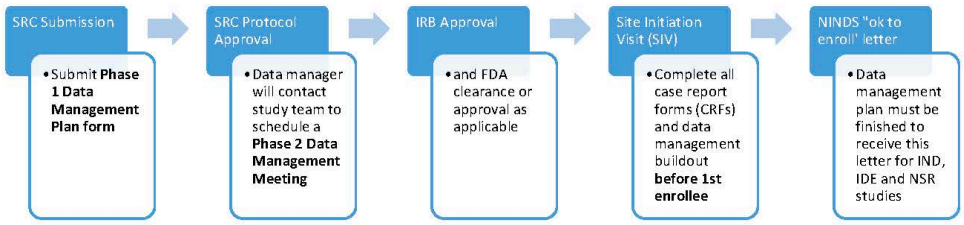
IRB #:

PI:

Protocol title:

Introduction: Utilization of the CiSTAR electronic data capture system requires the Principal Investigator and all members of the study team acknowledge that they have read the CTU Data Management SOP and have read and acknowledged receipt of the CiSTAR Data Management Agreement. It is the responsibility of the protocol Principal Investigator to ensure compliance with the agreement, of each individual study team member. Failure to adhere to the policies and procedures of use of the CiSTAR system will result in delay in implementation of the database and could compromise the integrity of the data.

Timeline of Data Management Events for NINDS Protocols:



Part 1: Database Set-Up in CiSTAR

A. Initial Set-Up - Overview

Following the Phase 2 data management planning meeting and after receipt of the paper CRFs, the CiSTAR Data Manager will provide the study team with the projected date of completion of the database in the CiSTAR Demo site. The projected date considers the study team's anticipated start date as well as the number and complexity of the requested case report forms (CRFs). Complexity is determined by the number and type of data elements, form design, and number of rules applied to the form.

The database will initially be built in the CiSTAR ProForms Demo platform. The study team will be able to review and test all forms, in the demo platform. Once the demo database is approved by the study team, all forms and functionality will be moved to the CiSTAR ProForms Production platform for data collection.

B. Review Process in CiSTAR Demo

1. The PI and study team will be notified by email, when the protocol has been completed in the CiSTAR demo platform.

V 1.0; 27Jul22

2. The PI and study team will have up to **10 business days** to test and document any changes/revisions to the electronic Case Report Forms (eCRFs) and protocol set up in the CiSTAR demo platform.
3. All change requests should be submitted by email to the CiSTAR Data Manager.
4. An estimate of time to completion will be provided by the CTU Data Manager to the PI and study team following receipt of requested revisions. Depending on the extent of revisions requested, a **30-day lead time**, is required each time revisions need to be applied.
5. It is the PI's and study team's responsibility to factor this revision time into their research process.

C. Revision Options in CiSTAR

1. Revisions in Demo
   A. The PI and study team will be permitted up to **2 revision** requests to the existing electronic Case Report Forms (eCRFs) and protocol set up in the CiSTAR system.
   B. Any additional revisions beyond the 2 complimentary revisions, will need review and approval from the CTU Lead, QA and Data Management Office.
   C. Additional revisions exceeding the 2 complimentary revisions may also be subject to review and written approval from the NINDS Clinical Director.
   D. All revisions and changes may be submitted using track changes on paper versions of the CRFs, to allow the Data Manager to easily identify requested changes from the original.
2. Revisions in Production
   a. The addition of new elements to the protocol, such as new eCRFs and visits, will need review and approval by the CTU Data Manager and may be subject to review and written approval from the CTU Lead, QA and Data Management Office.
   b. All additional new eCRFs and visit types **must have** documented IRB approval, if applicable.
   c. An estimate of time to completion will be provided by the CTU Data manager to the PI and study team. On average, a **30-day lead time** for new elements to be implemented and finalized should be expected.
   d. It is the PI's and study team's responsibility to factor this revision time into their research process.
   e. Changes or edits to the eCRFs, visits or protocol parameters in CiSTAR after the site initiation visit and official study start date will require review by the Lead, QA and Data Management Office.
   f. Once data is entered on a form in production, the data elements associated with the form requiring a change, will not be able to be modified. A new form will be built in the database and the original form will be archived. Data entered on the original form, prior to the change request will be available in ProForms or Data repository.

D. Pre-Site Initiation Visit (SIV)

1. All changes and edits to the CiSTAR database and/or CRFs need to be finalized prior to the site initiation visit and study start date.
2. No recruiting, data collection or analysis may be performed prior to the site initiation visit.

Part 2: Study Initiation through Study Closure

A. CiSTAR Investigator Training

1. The PI has the authority to determine which individuals have access to the CiSTAR database and the individual's role, e.g., ability to enter, change or view data.
2. The PI questionnaire which lists all investigators requiring access to the database and their respective roles must be submitted to the data manager in order for access and role(s) to be assigned.
3. The Data Manager is available to conduct a CiSTAR investigator training for all investigators with access to the database. This training should be scheduled prior to the SIV meeting.
4. In addition to providing study teams with Quick Start manuals developed for CiSTAR users, the data manager is available to provide investigator training. Training topics may include:
   i. How to request an account in CiSTAR
   ii. Overall review of protocol set-up (CiSTAR overview)

iii. How to add a subject to your protocol in CiSTAR
iv. How to create a GUID (Globally Unique Identifier)
v. How to create or schedule a visit in CiSTAR
vi. Overview of the Dashboard
vii. How to set up a PSR (Patient Self-Report) token email
viii. How to save data in CiSTAR
ix. How to export data from ProForms to an excel or csv file
x. How to export data from Data Repository using the Query tool
xi. How to request Tech support for CiSTAR

B. Site Initiation Visit (SIV)

1. Prior to participant enrollment, a Site Initiation Visit (SIV) will be scheduled and conducted by CTU staff or a Contract Research Organization (which may include CTU QA team, CTU data manager, statistician, protocol navigator)
2. All members of the research team, including the PI are required to attend.
3. The SIV will consist of protocol review, good clinical practice, good documentation practice, data management, data collection, including a review of all eCRFs and may include instruction on how to enter data and use the database (CiSTAR), if a separate CiSTAR Investigator Training has not been scheduled.

C. During the study

1. Assistance from the CTU Data managers will be provided for technical questions or issues, as needed.
2. Once the study has commenced, the PI must approve and notify the data manager of any new study team members needing access to the CiSTAR database. An updated PI questionnaire must be submitted to the data manager, when new users are added.
3. New AIs will undergo database training, by the assigned data manager, prior to being granted access to the CiSTAR database.
4. The PI has the authority to determine which data sets are to be shared with collaborators.

D. Study completion

1. Following the final data entry in the database, the cleaning and verification of the data (Quality Control Review) should be completed by the study team in preparation for the quality assurance close-out visit.
2. The PI will notify the Lead, QA and Data Management Office at time of study completion to schedule a close-out visit, at which time select data in the CiSTAR database will be reviewed by the auditor/monitor.

E. Study close out

3. All action items identified during the close-out visit should be resolved prior to the CiSTAR ProForms database being locked.
4. Study data will be de-identified and transferred to the CiSTAR Repository database after the study is closed and all eCRFs have been locked.

Part 3: Migrating data

A. Migrating data from closed protocol

1. For protocols in which data was collected in another electronic data capture system, the principal investigator may wish to migrate data into CiSTAR.
2. Data must be presented to the data manager in either an excel or csv format.
3. The study team is responsible for cleaning all data prior to data migration.
4. The Data Manager will build the repository database according to the fields identified in the received spreadsheet.
5. Previously collected data will be migrated and stored in the CiSTAR Repository database.

B. Migrating data from open protocol

1. The PI/study team will need to determine if:
   a. a new direct data capture system will be built in CiSTAR ProForms and implemented on an established date with only newly enrolled patient data being captured in the CiSTAR ProForms database and previously collected data being migrated and stored in the CiSTAR Repository database or
   b. a new direct data capture system will be built in CiSTAR ProForms and implemented on an established date for collection of new participant data; while previously collected data will be migrated into the new data capture system, combining old and new data in CiSTAR ProForms.
2. In the instance that there will be data migration: Quality Control Review will be required by the study team before and after migration.

Part 4: Communication with CiSTAR team

A. While database is being built in Demo platform

Study team Point of Contact (POC), should communicate directly with the data manager using the communication method agreed upon, e.g., Email, Microsoft Teams, Telephone, or other mechanism

B. After database has been built in Production platform

Once the database has been built in the Production platform, the Study team POC should communicate directly with the Data Manager communication with the CiSTAR team should be initiated through the CiSTAR-ops (cistar-ops@mail.nih.gov) email address.

Part 5: CiSTAR use and data management practices

A. User access

1. At no time will any user share their password.
2. Individual study team member access is to be determined by the PI in writing and is at the discretion of the PI.

B. Data Collection

1. Data collection can occur by:
   a. Direct data entry
   b. Patient self-report
   c. Offline capture using portable/mobile devices
2. Each data entry once complete is subjected to the following data locking process:
   a. Form saved – content is saved but form is not completed; content can be edited with all changes captured in audit trail
   b. Form completed – content is saved, and all required fields completed; content can be edited with all changes captured in audit trail
   c. Form locked – content is saved, and form is locked. Prior to locking, user should verify data entered and enter password to lock the form.

   All entries and changes to any form at all phases (saved, completed and locked) are recorded (original data and new data; date and time changed; who made the changes; why the changes were made) and logged. If changes are made after a form is locked, the user will be prompted to enter username and password, and reason for change.
3. If data is being collected on paper CRFs, all data should be entered in the CiSTAR database as soon as possible but not later than **30 business days** from the start of data collection.
4. All original or source data collected on paper CRFs must be stored in a secure location with restricted access as detailed in the IRB approved protocol document.

C. The use of PII

1. The CiSTAR system can be used to collect and store Person Identifying Information (PII).

2. When absolutely needed and approved, the sharing of PII can occur within the CiSTAR system for approved users who are on the IRB approved protocol and have written permission from the PI. This is the recommended method of sharing.
3. At no time should PII be downloaded by the PI or study team or stored anywhere else, outside of the CiSTAR system, unless explicitly written in the study protocol and approved by the IRB.

_____ _____

Principal Investigator Date

_____ _____

CiSTAR Data Manager Date

_____ _____

CTU Lead, QA and Data Management Office Date

APPENDIX D

PHASE 1 DATA MANAGEMENT PLAN

Protocol #:
Protocol Title:
Principal Investigator:
Lead Associate Investigator:
Date:

Note: FDA regulated studies are required to utilize a 21 CRF Part 11 compliant clinical trial database. The NINDS supported electronic database, CiSTAR, is a 21 CFR 11 compliant database. NINDS highly recommends investigators utilize CiSTAR to collect and store clinical research data.

1. Will you be utilizing an electronic database to collect and/or store data for this study? Yes No

2. If utilizing an electronic database, please specify the system you plan to utilize:
   _____

3. Is the proposed study an FDA regulated study, i.e., utilizing an investigational drug or device? Yes No

4. Does your study include a device (Significant Risk or Non-Significant Risk)? Yes No

5. Is this study a clinical trial? Yes No
   Per NIH definition, a clinical trial is "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

6. Is this a multi-site study? Yes No

7. Does this study involve an outside sponsor? Yes No

8. Does this study involve a non-NIH or non-NINDS collaborator? Yes No

9. Is the coordinating site, sponsor, or collaborator providing a database for this study? Yes No

10. If yes to question 6, 7 or 8 and the primary data is collected in a non-NINDS database, is it possible that you will also be collecting data that will need to be stored in a database outside of the coordinating or collaborator's database? Yes No N/A

APPENDIX E

PHASE 2 DATA MANAGEMENT PLAN

DATA MANAGEMENT PLAN Phase 2
Project or Protocol #:
Protocol Title:
Principal Investigator:
Lead Associate Investigator:
Date:

Study Start:

1. Anticipated date to commence enrollment? _____

Regulatory Binder:

2. How/Where will you maintain your regulatory binder documents?
   Paper Regulatory Binder _____
   Electronic Regulatory Binder (Server)_____ CiSTAR _____
   Other *(please specific)*
   _____

3. Who will be primary contact for managing the Regulatory Binder?
   _____

4. Where will you maintain your investigator qualification documents (CVs, licenses, training certificates)?
   _____

Documentation:

5. Will you utilize a biospecimen storing and tracking system? Yes____ No____

   If yes, specify method used:
   _____

6. Will you be using an electronic data capture system (eDC)? Yes____ No____. If yes, which eDC system will be utilized for collecting and/or storing research data?
   _____

   a. Who will be responsible for entering the data into CiSTAR (for training purposes)?
      _____

   b. If utilizing a database other than CiSTAR, who will be responsible for entering data?
      _____

The tables below will be utilized to map all source data (which may be captured in your ECD system) and CRFs you plan to utilize in your study. This plan will provide a map of all data collected in your protocol.

- In Table 1, please specify the source data and the collection and/or storage location of the source data.
- In Table 2, please identify the source location for each inclusion and exclusion criterion.
- In Table 3, please identify the source location for each adverse event data element
- In Table 4, please specify the CRFs to be utilized in this protocol.

List all and indicate by placing an X. Only one source document (except consent) should be identified in Tables 1, 2 and 3, as this represents the 1st place this data is documented. More than one X is allowed in the CRF table. (See tables below).

Note: Protocols which meet the definition of a clinical trial are considered "applicable trials" and the PI or Sponsor is required to report results on the CT.gov website within one year of collecting the primary outcome measure for the last participant. All primary and secondary outcome measures and safety data must be reported. It is suggested that these data be captured in an electronic database to facilitate timely reporting of results.

Table 1: Source Data: Identify all data to be collected during the study

Date	Source (Choose ONLY 1 source location)				
	Paper recorded form, e.g., source questionnaire	Electronic Database, e.g., source entered directly into CiSTAR	CRIS/Medical Record, e.g., labs, ECG, Physical Exam	Password Protected Server**, e.g., EMG, MRI image	Notes
*Protocol Consent					
*Inclusion/exclusion criteria (see Table 2)					
*Demographics/Baseline Characteristics (race, ethnicity, age and gender/sex)					
*History and Physical					
*Neurological Exam					

*mandatory **document location pathway in the notes section

Table 2: Eligibility Source: List each inclusion/exclusion criterion and the source location

Inclusion/Exclusion Criteria	Source (Choose ONLY 1 source location)					
	Patient verbal report: source	Paper recorded	Electronic database,	CRIS/Medical Record, e.g.,	Password Protected	Other

	documented on Inc/Exc Checklist	form, e.g., source questionnaire	e.g., source entered into CiSTAR	labs, ECG, Physical Exam	Server**, e.g., EMG, MRI image	

**document location pathway in the notes section

Table 3: Adverse Event Source: Determine the source location for each AE element

Indicate which Adverse Event Coding System will be used (e.g., CTCAE v5): _____

AE element	Source (Choose ONLY 1 source location)		
	CRIS	CiSTAR AE Form	Other
Description of Adverse Event			
Adverse Event Term (MeDRA code)			
System Organ Class			
Date study team notified			
Start Date			
End Date			
Determination of Seriousness			
Determination of Relatedness to the drug/device/research			
Determination of Expectedness			
Action Taken			
Grade			
Outcome			
Resolution			

Table 4: Database/CRFs: Identify all CRFs to be used to collect data for study. Below is a sample list, please complete according to your protocol needs.

Data	Case Report Forms or Data Document				
	Paper Form	Electronic Database, e.g., CiSTAR	Password Protected Server**	Location	Notes
Inclusion/Exclusion Checklist					
Demographics, e.g., race, ethnicity, age, gender/sex					

Medications					
Adverse Events					
Baseline Characteristics					
CRF to capture Primary Endpoint					
CRF to capture Secondary Endpoint					

Resource links

21CFR part 11
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry
https://www.fda.gov/media/93884/download

OHSRP Policy 3014-300 – Investigator responsibilities
https://policymanual.nih.gov/3014-300

21 CFR parts 50
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

21 CFR parts 312
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312

45 CFR 46
http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/

NIH Intramural Research Program Human Data Sharing Policy
https://policymanual.nih.gov/3016

NIH Genomic Data Sharing Policy
https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing/