Guidance for Data Coordinating Centers (DCCs) Management of NIDDK Clinical Cooperative Agreements

1.0 PURPOSE:

This document provides guidance on the management of NIDDK-funded clinical cooperative agreements that are managed by a Data Coordinating Center (DCC)[1]. It serves as a tool for identifying and communicating specific needs and requirements for the successful conduct of NIDDK extramural clinical studies and also ensures consistent standards and expectations in the management of these studies.

This guidance document may be used to assist NIDDK staff when developing Funding Opportunity Announcements (FOAs) for DCCs and may also be useful in assisting stakeholders understand NIDDK's general expectations associated with DCCs supporting large clinical studies that are funded by NIDDK.

In addition, this guidance document may be used by NIDDK staff to facilitate discussions with stakeholders prior to launching a large clinical study program and to evaluate a DCC's infrastructure and function during site visits.

It should be noted that this is a guidance document. This document does not specifically apply to any given award nor does this document supersede or limit the official terms and conditions of any award or other agreements entered with NIDDK or other components of NIH.

2.0 SCOPE:

This guidance document applies to NIDDK extramural staff involved in the planning and management of NIDDK-funded studies conducted under a clinical cooperative agreement where a DCC will manage any aspect of the study.

This guidance document may also be used as a tool for NIDDK extramural investigators working to identify a DCC for an investigator-initiated clinical trial/study.

3.0 BACKGROUND:

NIDDK serves as sponsor for many of the extramural clinical trials/studies conducted by the Institute. For extramural studies, DCCs aid in regulatory and clinical study support. DCCs supporting NIDDK-funded clinical studies receive funding from NIDDK and operate as partners with NIDDK in the conduct of clinical trials/studies. DCCs have the delegated responsibility for many of the sponsor responsibilities, such as the collection of site regulatory records and financial disclosure forms, managing Serious Adverse Event (SAE) information to and from the clinical

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sites, SAE evaluation and reporting, and monitoring of the study/trial to promote compliance at the clinical site. DCCs also provide expert assistance in protocol design, protocol implementation, Institutional Review Board (IRB) approvals, data management, statistical analysis, and in facilitating scientific publications. In addition, DCCs provide significant administrative and organizational support to NIDDK by coordinating and leading study team meetings and managing and coordinating payment to clinical sites and ancillary facilities, such as laboratories, pharmacies, and drug distribution centers.

For studies involving donated study drug as part of a contractual agreement (e.g., Cooperative Research and Development Agreement, CRADA; Clinical Trail Agreement, CTA), DCCs manage certain interactions with the pharmaceutical manufacturers who provide the test material (with or without matched placebo). These duties include tasks such as providing pharmaceutical partners with copies of regulatory submissions, exchanging safety information, and coordinating drug shipments and distribution to clinical sites. Some DCCs also serve in the capacity of managing repository samples from clinical trials/studies. Because DCCs manage a multitude of clinical study responsibilities for NIDDK, clear expectations regarding needs and responsibilities are vital to the NIDDK-DCC partnership.

Below are functional categories often delegated to DCCs that should apply to most extramural studies. It is recognized that there may be functional categories/delegated activities not listed in this document that are required for a specific clinical study. These special requirements should be addressed in the FOA for that study.

The guidance below should be considered in broad context. In some cases, the guidance focuses on planning, infrastructure, and other considerations needed to support appropriate operations and outcomes. In other cases, the guidance focuses more on operational and outcome expectations. Taken as a whole, the guidance frames considerations and expectations for DCC establishment and appropriate operations once established.

4.0 FUNCTIONAL AREAS:

DCC EXPERTISE, TRAINING, AND PERSONNEL MANAGEMENT:

1. Identify available DCC staff and/or committed collaborators with specific expertise in subject matter, feasibility assessments, protocol design, clinical trial methodology, statistical analysis, and Information Technology (IT) support, and define their roles for the protocol and/or consortium.
2. Provide ongoing training of appropriate DCC staff and external collaborators in protocol certification, Good Clinical Practices (GCP), human subjects protection training, ethics training, IT security, and data capture. Include documentation of proficiency, which may include existing expertise and previous training. Provide appropriate DCC staff with training in Food and Drug

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Administration (FDA) regulations to support the management of Investigational New Drug/New Device Exemption (IND/IDE) studies.
3. Ensure the training of clinical site personnel that are managed by the DCC relative to study responsibilities delegated to them.
4. Have written procedures for training staff (DCC and external collaborators). Establish a tracking system and timelines/triggers for retraining at appropriate intervals.

STUDY ADMINISTRATION AND FINANCIAL MANAGEMENT:

1. Identify the space, staff, and equipment to be used for the project and ensure that they are suitable for the project's activities.
2. Solicit budgets and project enrollment from potential participating clinical sites. Develop a plan that outlines how to administer appropriate payments to sites and other units as appropriate that will foster compliance with study objectives.
3. Identify fixed and variable costs and establish procedures for negotiation of third-party agreements or selection of subawards/subcontractors (i.e., clinical sites, clinical pharmacies, clinical laboratories, drug distribution centers, biospecimen repository, etc.) and develop processes to efficiently administer and manage same throughout the project. Have a process for evaluating qualifications and standards of clinical pharmacies, clinical laboratories, drug distribution centers, and biospecimen repositories.
4. Develop procedures to require study investigators and others associated with the study to identify financial and other conflicts of interest on a routine basis, at least annually, and share this information with the NIDDK Program staff.

PROTOCOL ADMINISTRATION AND DATA MANAGEMENT:

1. Have a plan to monitor recruitment and retention. Coordinate with Steering Committee and NIDDK to assess protocol feasibility and demonstrate that recruitment goals are realistic using available data on the target population from registries or prior studies to the extent possible.
2. Manage protocol registration and appropriate updates on clinicaltrials.gov. Manage posting of clinical trial consent forms on clinicaltrials.gov.
3. Have a plan for assuring version control of study-related documents (e.g., protocol, consent, CRFs, MOPs, etc.) and for tracking approvals of these documents. Ensure that properly-versioned documents and approval correspondence electronically available to study stakeholders.
4. Establish processes for tracking ancillary studies and changes/approvals by the Protocol Review Committee (or other scientific review body), Data and Safety Monitoring Board (DSMB), Observational Study Monitoring Boards (OSMBs), and Institutional Review Boards (IRBs).
5. Establish a mechanism to process requests for ancillary analyses not addressed in the study protocol analysis plan, to include specific plans for documenting scientific review and feedback by study personnel alongside requestor proposals/responses.

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6. Develop a system to track participant consent for biospecimens per protocol to ensure proper and ethical use of biospecimens during and post-study.
7. Develop a system to track biospecimens at local laboratories, central laboratories, and repositories, when appropriate, and maintain the link between the biospecimens and the study data incorporating appropriate QC samples. Develop and implement a biospecimen tracking tool for central laboratories and/or biorepositories, as appropriate.
8. Have processes that cover study management, data handling/data systems, and recordkeeping for compliance with GCP guidelines. Ensure electronic data systems are validated, per GCP guidelines, to ensure the integrity of the data. Develop a plan and assign responsibilities for Information Technology (IT) security at each site or core lab and secure data transfer protocols for data transferred between study locations.
9. Have a procedure for establishing the randomization system, giving preference to real-time data-interactive allocation. This process may also include restricted access, flexibility for data-dependent randomization procedures, and electronic eligibility checks capability, and a locally secured record for each unit's allocation.
10. Ensure data management systems comply with privacy and accessibility regulatory requirements and/or Public Laws.
11. Have a process to identify steps taken for the Statistical Analysis Plan (SAP) and Data Management Plan to assure rigor and transparency throughout.
12. Establish a Statistical Analysis Plan (SAP), both within the protocol and as a separate document. The latter should be more detailed and should be finalized before the start of data analysis, with version control and subsequent modifications clearly documented. Have a process to assure that the SAP informs data management, validation, and repository archiving/curation plans.
13. Establish a Data Monitoring Plan that includes safety, efficacy, futility, and stopping rules/guidelines and any internal pilot(s) to assess adequacy of design. Have a plan for Interim Analyses. Have a process to assess impact of interim analyses on Data Monitoring Plan.
14. Utilize data dictionaries (meta data) that describe the formatting and descriptive contents of uploaded data for all systems (including clinical site systems) and provide appropriate expertise for disseminating these data in a rigorous and transparent manner that supports reproducibility.
15. Have a process that will test, validate, and optimize data capture systems to provide immediate feedback on user errors, logic errors, and out-of-range data, including across-form consistency designed to yield data adequate to meet study objectives by following specified analysis plan(s).
16. Have a plan for ensuring accurate and reliable data analyses which are detailed in protocol documents external to those reviewed by IRBs and are in line with emerging standards of rigor and transparency in research.
17. Have a Quality Assurance plan to prepare study database for "lock" prior to each pivotal (OSMB/DSMB-reviewed or published) analysis and to assure data analysis software (including in-house programming code) has been validated as carrying out the SAP in a reproducible manner.

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18. Have a process to assure emerging standards in data curation (e.g., CDISC or BRIDG data models), data analysis (e.g., benchmarking for reproducibility), and data dissemination (e.g., CONSORT and other reporting standards) have been considered in developing above plans.
19. Develop and document a data security plan with appropriate security processes and procedures (regardless of data capture approach).
20. Develop a plan for disaster recovery of data and repository samples that meets project needs for availability, confidentiality, and data/application location.

COMMUNICATION AND COORDINATION WITH STAKEHOLDERS

1. Develop a plan that describes communication methods and access privileges/passwords to conference calls, SharePoint, websites, email, paper records, and newsletters for project teams, Steering Committees, OSMBs/DSMBs, NIDDK staff, and DCC staff. Make project documents accessible to appropriate study staff and other stakeholders.
2. Establish a process for communicating with pharmaceutical partners and ensuring documentation/verification of transactions for regulatory documents, study drug materials, and/or study data as described in the study contractual agreement.
3. Ensure that a public website remains current and includes an adequate description of the study or studies and process for applying for ancillary studies (e.g., list of clinical sites, contact information, procedures to apply to ancillary study, links to clinicaltrials.gov, and ancillary study application), as appropriate.
4. In conjunction with the Steering Committee and NIDDK, develop a plan that would facilitate interactions with all stakeholders to facilitate setting realistic goals and sharing study management ideas and strategies.
5. Facilitate and arrange logistics for in-person meetings and conference calls and identify staff responsible for meeting coordination (e.g., planning, note taking, tracking completion of action items, and distribution of minutes and reports for meetings).
6. Establish a plan to meet NIDDK guidelines for OSMB/DSMB meeting support (e.g., report preparation, coordination with clinical investigators and NIDDK staff for OSMB/DSMB participation, OSMB/DSMB member payments, etc.).
7. Collaborate with clinicians and committees to design and develop appropriate reports and establish reporting frequency, including reporting by site, when appropriate. Collaborate with NIDDK staff to develop and generate appropriate reports for the OSMB/DSMB, Steering Committee, and others.

QUALITY ASSURANCE AND SITE MONITORING:

1. Identify DCC staff to ensure quality assurance and quality control for responsibilities delegated to the DCC as well as those delegated to study collaborators managed by the DCC.
2. Establish required NIDDK processes for quality assurance and oversight as outlined in the NIDDK Policy for Oversight of Sponsor Responsibilities Delegated to DCCs Managing NIDDK Funded Extramural Clinical Cooperative Agreements.

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3. Establish a quality management plan at the start of the program, which focuses on key variables and potential vulnerable areas (risk-based approach). Have processes documented for establishing and reviewing DCC Standard Operating Procedures, checklists, and tools.
4. Conduct process reviews during the study to ensure that the study is implemented appropriately at study sites and procedures at DCC are robust. Establish a plan for testing key protocol processes and procedures (simulating study visits, forms completion with sham data, etc.).
5. Establish a plan to validate statistical programming which will ensure reproducibility and accuracy of results, and prospectively archive data 'snapshots' with accompanying code.
6. Have a procedure for identifying, correcting, and documenting possible data errors. Have a procedure for quantifying measurement errors in key variables.
7. Have well-described site monitoring plans. Establish assessment tools and metrics for clinic site evaluations (e.g., protocol deviations/violations, late forms, recruitment and retention rates, missing data, data entry accuracy, etc.).
8. Provide timely feedback to sites including real-time reporting on items like enrollment eligibility (inclusion/exclusion), forms completion, missed visits, data entry issues and point-in-time reporting on items like performance reports and comparisons among sites. Employ statistical monitoring to examine aggregate data and identify potential site variations.
9. Have a procedure for documenting and handling protocol deviations/violations. Have a plan that outlines how to address and document responses and corrections to identified problems. Provide reports for clinical sites on items such as upcoming site visits and unresolved protocol deviations and other deficiencies.

SAFETY, REGULATORY, AND DOCUMENT MANAGEMENT:

1. Establish a randomization system with a process that permits rapid identification of product(s) in case of a medical emergency but does not permit undetectable breaks of the blinding.
2. Develop a well-defined reporting process for adverse events (AE), serious adverse events (SAEs), and unanticipated problems (as defined by OHRP) that is defined precisely and is in compliance with local IRB requirements, 21 CFR 312.32 for Investigational New Drugs (IND), 21 CFR 812.150 for Investigational Device Exemptions (IDE), and International Conference on Harmonization Regulations E2A, as applicable.
3. Ensure training of study staff on SAE and unanticipated problems (UP) regulations
4. In conjunction with the OSMB/DSMB, develop a plan to report safety analyses and report AEs to the OSMB/DSMB in a format that highlights trends or signals.
5. Have a clear process for SAE communication and reconciliation with clinical sites and SAE and Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting to NIDDK
6. Verify center(s) Federal-wide Assurance status when the DCC is responsible for site selection.
7. Collaborate with investigators to create and distribute the consent document template(s).
8. Review consent documents for signatures and use of the appropriate IRB date stamped form during site visits. Verify that the IRB-approved informed consent forms at clinical sites have required

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elements and are factually correct. If translation (to languages other than English) and back-translation (to English) of site consent is needed, facilitate process to ensure IRB approval.

9. As appropriate, develop an online regulatory documents library that accepts site submissions and produces reports and email alerts about outstanding or expired documents, specifically IRB annual approvals.
10. Support human subjects data, biospecimen repository, and regulatory activities, as appropriate. For programs collecting, processing, assaying, storing or distributing biospecimens, ensure that systems are in place to maintain subject confidentiality and to track subject informed consent.
11. Verify compliance with GCP guidelines for the handling of investigational products, such as labelling to protect the blind, proper handling and storage according to manufacturer's labeling.
12. Establish process for drug distribution, shipment of study drug to clinical sites, and drug accountability during study.
13. Establish a clinical site activation process to include essential document collection. Maintain essential documents on file per ICH E6 (GCP), Section 8.
14. Establish process for maintaining regulatory records (FDA) and essential documents (GCP) and plan for access/inspection of records by NIDDK or FDA.
15. Establish a process for preparing and managing IND/IDE annual reports and other required regulatory documents/reports to NIDDK.
16. Ensure regulatory compliance for computerized systems used in clinical investigations. Establish processes to ensure compliance with 21 CFR Part 11 and FDA regulations regarding the management of clinical records, source documents, and computerized systems. Ensure compliance with ICH E6 (GCP) for computerized systems and electronic documents.
17. Establish processes for the transmission of electronic source data/clinical study data from clinical sites and electronic records/clinical study data to NIDDK.

POST-STUDY MANAGEMENT AND CLOSE-OUT ACTIVITIES:

1. Establish, document, and follow processes for manuscripts and presentations tracking, preparation, review, communication, and submission (including interaction with pharmaceutical and device collaborators as appropriate).
2. Provide leadership in coordination of and analysis for publications and presentations including establishing timelines for preparation and submission of primary and secondary manuscripts that adhere to reporting standards, in parallel to processes for rigor and transparency: providing results to study registries and archiving data "snapshots" and code to support reproducibility.
3. Ensure compliance with NIDDK repository policy for public use of data and biospecimens. Ensure compliance with entry of final data in clinicaltrials.gov
4. Establish a plan for disposition and access to study records and data/biospecimens at completion of study. Regulatory records should be available for inspection by FDA or NIDDK.
5. Establish a process(es) for accountability and return/destruction of study drug upon study termination.

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6. Establish a plan for providing any final study records and/or data to pharmaceutical partners per contractual agreements and ensuring documentation/verification of these transactions

5.0 RELATED NIDDK DOCUMENTS

Related NIDDK policies and checklists are available for NIDDK staff. Please consult the Office of Clinical Research Support (OCRS).

6.0 INQUIRIES

Questions and comments regarding this Guidance document may be directed to the NIDDK Regulatory Program Specialist, Office of Clinical Research Support (OCRS).

7.0 AVAILABILITY

This guidance document is available electronically on the NIDDK Extramural Intranet.
https://www.niddk.nih.gov/research-funding/human-subjects-research/policies-clinical-researchers

8.0 APPROVAL

Dr. Gregory Germino, Deputy Director, Office of the Director, NIDDK

9.0 VERSION CONTROL

Version 1.1: Dated February 22, 2019

Changes made to Version 1.0 include editorial and administrative revisions due to an internal review. Revised sections include: Purpose, Scope, Background, Availability, and Related NIDDK Documents.

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