**Tool Summary Sheet**

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| **Tool:** | Guideline: Study Start-up through Site Initiation Visit and Site Activation for Extramural Studies Requiring Additional NIDCR Oversight |
| **Purpose:** | To clarify the Extramural study start-up process from protocol development through site initiation and activation. Explicitly included are studies requiring additional NIDCR oversight. |
| **Audience/User:** | Lead Investigators and study team members of Extramural studies supported by the NIDCR, the Clinical Research Operations and Management Support team (CROMS), and Program Officials of the NIDCR |
| **Details:** | This document identifies prerequisites for a) the scheduling of a site initiation visit and b) site activation (i.e., the authorization to begin subject recruitment). Also discussed are other study start-up recommendations. Useful tools are referenced. |
| **Best Practice Recommendations:** | * This guidance should be reviewed early in the protocol development process. * Tools referenced in the guidance document should be reviewed early in the start-up process to determine those which are most useful and appropriate. Most tools are accompanied by a summary sheet that details the purpose of the tool, the audience for the tool, and best practices associated with the tool. * Referenced tools are bolded, for convenience, and can be found on the CROMS website in the Clinical Tool Box section. Many are also located on the NIDCR’s Toolkit for Clinical Researchers website. * Clinical research tasks must be conducted in accordance with Good Clinical Practice (GCP) in order to ensure human subject safety and data integrity. |

**Tool Revision History:**

|  |  |  |
| --- | --- | --- |
| **Version** | |  |
| **Number** | **Date** | **Summary of Revisions Made:** |
| 1.0 | 23FEB2012 | Approved version |
| 2.0 | 19DEC2013 | Updated to reflect current risk/oversight process and policy, and revised/added definitions and references to existing tools and templates. |

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# ABBREVIATIONS AND TERMINOLOGY

|  |  |
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| Ancillary Clinical Site (or Ancillary Clinical Study Site) | Physical site or location that may be an extension from the Clinical Site / Clinical Study Site (e.g., homes, schools, public locations) where subjects are seen for study purposes. Study personnel travel from a Clinical Site / Clinical Study Site to this ancillary site in order to perform some or all study procedures on subjects. Study personnel are not affiliated with or located at the ancillary site, but are affiliated with the Clinical Site / Clinical Study Site. Study documents, study product, and study materials are not maintained at the ancillary site; these usually travel with the study personnel and are maintained at the Clinical Site / Clinical Study Site. |
| CD | Consent document |
| Clinical Site (or Clinical Study Site) | Physical site or location where participant/subject records are maintained; often this is the location where participants/subjects are seen by study staff for study purposes and study procedures are performed, where study product or materials are maintained, and where data and regulatory records are stored. Study personnel are affiliated with the Clinical Site and operate in and from this location. (The term “Clinical Study Site” may be preferred for studies which include a dental or medical clinic and the use of the word “clinic” requires further definition.) |
| CRA | Clinical Research Associate. Monitor; person who monitors the progress of the investigation as well as sites participating in a clinical study and who is responsible for assessing study conduct in adherence with protocol requirements. |
| CRF | Case Report Form (term used to describe the set of data collection instruments of clinical trials). The term “data collection forms” is a common term for other clinical research, such as behavioral interventions, specimen collection studies, and observational studies. |
| Clinical Research | Patient-oriented research, including epidemiologic and behavioral studies, outcomes research, and health services research. Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which a researcher directly interacts with human subjects. It includes research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies, but does not include in vitro studies using human tissues not linked to a living individual. Studies falling under [45 CFR 46.101(b) (4)](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101) are not considered clinical research for purposes of this definition. |
| Clinical Trial evaluating a drug, device or biologic | A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices [<http://www.hhs.gov/ohrp/archive/irb/irb_chapter5.htm>]. Drugs include any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or abnormal conditions. Testing of drugs in humans proceeds through different phases:  Phase I: Testing in a small number of subjects (e.g., 20-80) to evaluate its safety, determine a safe dosage range, and identify side effects.  Phase II: Study in a larger group of people (no more than several hundred) to determine preliminary efficacy for a particular indication and further evaluate safety by determining the common short-term side effects and risks associated with the drug.  Phase III: Study in a larger number of subjects (from several hundred to several thousand) to confirm a drug’s efficacy, to determine its safety, and to compare the intervention to commonly used treatments.  Phase IV: Studies done after the drug has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread and long-term use.  Devices encompass a broad range of medical products and product development stages may vary according to device. If NIDCR support is sought, discussion should begin with program and OCTOM at an early stage to outline NIDCR expectations.  See Appendix D for details on behavioral interventions. |
| Clinical Trial evaluating a behavioral Intervention | A controlled study involving human subjects, designed to test a well-characterized behavioral intervention and evaluate prospectively the efficacy or effectiveness of the behavioral or psychosocial intervention on behavioral or social targets relevant to public health. “Behavioral intervention” is a broad term that describes an approach to preventing, maintaining or changing behavior of individuals or groups through the use of non-medical or non-pharmaceutical techniques. Behavioral intervention clinical trials proceed through different phases, typically called “stages” to distinguish them from drug or device trials:  Stage I(a): Define the clinical problem of interest, and define the rationale for why the intervention is expected to address the problem, including identifying proposed mediators and moderators. The main product of this stage is a draft behavioral intervention that is described in sufficient detail – typically in an intervention manual – so that it can be delivered as intended.  Stage I(b): Test the intervention for acceptability to the target population and to the intended interventionists, and test the feasibility of conducting an efficacy trial in subsequent stages.  Stage II: Test the efficacy of an intervention, and further clarify variables that mediate and moderate the intervention’s effects.  Stage III: Prepare and/or adapt an efficacious intervention to be delivered in community (non-research) settings by the end-user interventionists in a sustainable way. Stage III is not meant to be a return to “black box” intervention research, but rather a systematic study of how an intervention can be delivered in a “real world” setting. Rigorous measurement of deviations from intervention fidelity, and of variables that might affect intervention delivery are expected in this stage. |
| CROMS | Clinical Research Operations and Management Support services. The term CROMS is used to identify the NIDCR contractor who provides operational and research services to Intramural and Extramural supported studies and infrastructure support to the Office of Clinical Trials Operations and Management (OCTOM). |
| CSOC | Clinical Study Oversight Committee. The CSOC is an independent group of experts that makes recommendations to NIDCR, and through NIDCR to the study investigators on clinical studies not involving an intervention. Such clinical research studies may be complex, involve risk or vulnerable populations, and may be observational, specimen collection, epidemiology or surveillance studies. The responsibilities of the CSOC are to 1) monitor human subject safety by reviewing and evaluating the accumulated study data, 2) evaluate study conduct and progress, and 3) make recommendations to NIDCR concerning the continuation, modification, or termination of the study. The CSOC considers study-specific data as well as relevant background information about the disease, procedures and progress of the study. |
| CToA | Clinical Terms of Award. A term and condition of grant/cooperative agreement awards, the purpose of which is to ensure that all clinical research and trials involving [human subjects](http://grants.nih.gov/grants/policy/hs/) and conducted under grants and cooperative agreements supported by NIDCR are well designed, conducted with rigor, monitored commensurate with risk and complexity, and that the Institute is kept informed of study progress through reporting. |
| DCC | Data Coordinating Center (This may be CROMS or another group.) Synonym: data management center (DMC). |
| Device | An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--  (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,  (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or  (3) intended to affect the structure or any function of the body of man or other animals, and  which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. |
| Drug | (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C). |
| DSMB | Data and Safety Monitoring Board. The DSMB is an independent group of experts that makes recommendations to NIDCR, and through NIDCR to the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to NIDCR concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice. From the International Conference on Harmonisation (ICH) guidance, GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. |
| ICH | International Conference on Harmonisation |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug application |
| IRB1 | Institutional Review Board. An administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the organization with which it is affiliated. The Institutional Review Board has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction. |
| ISM | Independent Safety Monitor. An ISM is a qualified clinician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by evaluation of adverse events, immediately after they occur, with follow-up through resolution or stabilization. The ISM evaluates individual and cumulative participant safety data when making recommendations regarding continuation of the study. An ISM could be the sole independent monitor for the study or may perform this role as a member of a DSMB. An ISM is appropriate as the sole independent safety monitor for small, early phase studies of short duration. DSMBs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events rather than all adverse events. |
| MOP | Manual of Procedures. A Manual of Procedures (MOP) is a handbook that guides a study’s conduct and operations. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. |
| OCTOM | NIDCR Office of Clinical Trials Operations and Management |
| PI | Principal Investigator. The lead investigator of the study. This PI may also be a site PI. This position may also be termed the “Study Director.” |
| QMP | Quality Management Plan. The quality management plan describes the process designed to ensure compliance with human subject safety, quality and integrity of the data, and compliance with the protocol. |
| Site Activation | The point in time when all initial requirements have been satisfied and a site may begin to enroll subjects into the study. The NIDCR Program Official, assisted by CROMS and OCTOM, issues the approval for site activation. |
| Site Initiation Visit (SIV) | The on-site meeting designed to prepare the study team for conducting the study. The meeting includes (at a minimum) the PI, other investigators, site study coordinator, other site staff assuming study responsibilities, and data management representative. The Site Initiation Visit may also include NIDCR Program Official or representative, OCTOM representative, and a clinical monitor. |
| Site PI | Convenience term used to identify the lead principal investigator at a site. This term is created to differentiate the role of lead investigators at each clinical site (i.e., the Site PI) from the lead investigator of the study (i.e., the PI). One of the site PIs may also be the PI or Study Director of the study. |
| TMF | Trial Master File; the file that contains all of the key documents relating to a clinical study, usually maintained by the sponsor or sponsor representative (e.g., a Contract Research Organization [CRO]). This file contains “Essential Documents,” defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. Example of some content: IRB-approved protocols, consents, assents, advertisements; investigator curriculum vitae or list of qualifications; study team training log/documentation. |

1 verbatim definition from [NIH Glossary of Terms](http://grants.nih.gov/grants/glossary.htm#A)

# INTRODUCTION

Implementation and conduct of a clinical study can be a complex process that involves a team from various disciplines and multiple steps that are dependent on one another. This document offers guidance for navigating the clinical research study start-up and activation process. This guide is for NIDCR Extramural clinical research studies that are determined to require additional oversight by the NIDCR Medical Monitor. Studies may require additional oversight because they are more than minimal risk to human subjects or have other characteristics that indicate a need for additional NIDCR oversight, (e.g., complex study design, vulnerable population, large sample size, high NIDCR profile, multi-center, large NIDCR investment of funds).

NIDCR receives clinical research study plans within a grant proposal. Clinical Terms of Award requires the clinical research study plan to be documented in a consolidated format to include applicable elements of a clinical protocol in accordance with the International Conference on Harmonisation’s Guideline for Good Clinical Practice - ICH GCP E6, Section 6. NIDCR recommends the investigator use the relevant NIDCR protocol template to ensure all applicable elements of ICH are included in the protocol document.

The start-up and activation process begins with the development of a clinical research study plan in the form a protocol. Other study documents such as consent and assent documents, data collection or case report forms, Manual of Procedures, checklists and logs will be helpful, if not already required, to implement a clinical study. To meet Human Subject Protections regulatory requirements and other applicable regulatory requirements, other documents including Institutional Review Board (IRB) approvals are required in accordance with ICH E6 Section 8. In order to have standardization of procedures across the study, adequate documentation is necessary. This guide will identify which documents and steps need to be completed to begin conduct of clinical research in compliance with Good Clinical Practice.

Figure 1 depicts both a simple and a more complex graphic of the components of Extramural clinical research study implementation and oversight, including the process for site initiation, CToA, and site activation.

Figure 1. Components of Extramural Clinical Research Study Implementation and Oversight

NIDCR Components of Clinical Research Study Implementation and Oversight
Protocol & Related Documents and Study Administration, Regulatory Requirements, Subject Safety Oversight, Data & Quality Management, Specimen Management, and Clinical Site Monitoring

Part 1 - High Level Overview of Processes:

1. Concept, Pre-application reviewed by NIDCR Program Officer (e.g., R34/U01)

2. Protocol Development and Study Preparation
(Protocol includes all required template elements. Grant or Protocol may have IRB approval before funding. Full protocol with NIDCR review. [Important: A minimum of 3 months is needed for review and harmonization across all documents and processes. Begin work on components of Clinical Trials Implementation as early in the protocol development process as possible. Allow for time to address comments. At least 3 months are needed for document review and implementation.]  May need to be resubmitted to IRB before subject enrollment.)

3. Concurrent development of processes for:
• Protocol-related and Study Administration Documents and Processes
• Regulatory Requirements Human Subjects Protections (46 CFR Part 46: All NIH funded studies are governed by 45 CFR Part 46. If a study is under IND or IDE, additional regulations will apply [see OCTOM for guidance].) 
• Subject Safety Oversight
• Data & Quality Management
• Specimen Management
• Clinical Site Monitoring

4. Site Initiation and Activation Process:
a. IRB approval of protocol, consent/assent documents, and other applicable study materials
b. Clinical Terms of Award (CToA) met by site, site funding released
c. Site meets remaining activation requirements
d. Site Activated
e. Site Enrollment Begins


Part 2 - Detail of Processes:

1. Concept, Pre-application reviewed by NIDCR Program Officer (e.g., R34/U01)

2. Protocol Development and Study Preparation
(Protocol includes all required template elements. Grant or Protocol may have IRB approval before funding. Full protocol with NIDCR review [Important: A minimum of 3 months is needed for review and harmonization across all documents and processes. Begin work on components of Clinical Trials Implementation as early in the protocol development process as possible. Allow for time to address comments. At least 3 months are needed for document review and implementation.]  May need to be resubmitted to IRB before subject enrollment.)

3. Concurrent development of processes for:
• Protocol-related and Study Administration Documents and Processes
- Documents: Protocol and consent document (other materials-e.g., advertisements) Guided by HS & GCP [PI and staff, Data Coordinating Center (DCC), Program Officer (PO),OCTOM, Medical Monitor (MM)]
- Documents: Study plan, timeline, communication plan, and documentation of meeting agendas/minutes [PI and staff, DCC]
- Process: Study planning meetings and other administrative activities [PIs and staff, DCC, PO]
- Document: Manual of Procedures [PI and staff, DCC, PO, OCTOM]
• Regulatory Requirements Human Subjects Protections (45 CFR Part 46: All NIH funded studies are governed by 45 CFR Part 46. If a study is under IND or IDE, additional regulations will apply [see OCTOM for guidance].) 
- Process: IRB Review, Feedback, Material Update, and IRB Approval of protocol, consent document, and other materials
- Process: Only if applicable: Certificate of Confidentiality, IND/IDE, Registry in Clinicaltrials.gov [PI and staff]
- Process: Essential Regulatory Document Collection [PI and staff, DCC]
• Subject Safety Oversight
- Document: Safety Monitoring Plan (Prepared by PI or CROMS and reviewed by Safety Oversight Committee [CSOC, DSMB, ISM] as indicated.)
- Process: Scheduling and Facilitating Safety Oversight Meetings [CROMS, OCTOM]
- Process: Serious Adverse Event and Unanticipated Problem Reporting [CROMS & OCTOM]
• Data & Quality Management
- Process: Data Collection Tools, Case Report Form (Data Collection Form) Development [DCC, PI, Statistician]
- Documents: Data Management Plan, Case Report Forms, CRF Completion Guidelines [PI and Staff, DCC]
- Document: Quality Management Plan [PI and staff, DCC]
• Specimen Management
- Document: Specimen Handling Plan (may be part of MOP) [PI and staff, DCC]
- Process: Preparation of specimen materials: tubes, labels, barcoding [PI and staff, DCC]
- Process: Tracking system: Shipping, handling, disposition logs & Training on Specimen Handling [PI and staff, DCC]
- Process: Preparation of other study materials (e.g., brochures)
• Clinical Site Monitoring [CROMS monitors consent eligibility, AEs, data collection as directed]
- Document: Site Assessment Questionnaire [CROMS and Clinical Sites]
- Document: Clinical Monitoring Plan [CROMS]
- Process: Site Initiation Visit [PIs and staff, PO, DCC, CROMS, OCTOM] (preferably scheduled to occur after IRB approvals received – item 4a below)

4. Site Initiation and Activation Process:
a. IRB approval of protocol, consent/assent documents, and other applicable study materials (SIV preferably scheduled to occur after these approvals received)
b. Clinical Terms of Award (CToA) met by site, site funding released
c. Site meets remaining activation requirements
d. Site Activated
e. Site Enrollment Begins

5. Reports generated:
• Accrual Reports [DCC]
• Protocol Deviation Reports
• Clinical Site Monitoring Visit Reports [CROMS]
• Safety Data Reports: SAE Reporting, Safety Updates [CROMS or other DCC]

# PROTOCOL-RELATED AND STUDY ADMINISTRATION DOCUMENTS AND PROCESSES

## Protocol and Consent/Assent Document Development, Review, and Internal Team Review and Approval

### Protocol

For studies that include an intervention, prepare the protocol using the NIDCR Extramural **Clinical Trial (Interventional) Protocol Template.** For studies without an intervention, prepare the protocol using the NIDCR Extramural **Clinical Study (Observational) Protocol Template**. These templates provide thorough guidance on the required content.

Once the draft protocol has been written, it should be distributed to the study team for review and comment. The draft protocol review team should include one or more individuals in each of the following categories: NIDCR Program Official; Principal Investigator (PI); site study coordinator with logistical expertise; NIDCR Medical Monitor; Data Coordinating Center (DCC) study coordinator; statistician; data manager; and a representative from the Office of Clinical Trials Operations and Management (OCTOM).

The process for review and update of the protocol during this development stage should be specified early on. Identify the person(s) responsible for delivery of protocol drafts, for integration of comments from multiple sources into one version, and for version control; identify the process for distributing documents and reviewer comments; identify who and how decisions about protocol changes will be made; develop a communication plan that may include convening regularly scheduled meetings (e.g., teleconferences) with protocol reviewers to discuss proposed changes prior to implementation. Minutes from such meetings are critical to the update process.

Please refer to the **Version Control Guidelines** for the NIDCR prescribed version control process. In brief, draft documents should include both a version date and a version number. Versions prior to approval will begin with 0.1 and the number will be incremented with each new draft; dates will be updated with the new issuance date. Please ensure that all document headers and footers are updated for each new draft.

To document the approval of all required reviewers for a protocol draft version to become final and ready for IRB submission, the study PI or team leader may initiate use of the **Extramural Clinical Protocol Approval Form**.

A separate process for authoring, tracking, and approving protocol amendments should also be established during study start-up. The Extramural Clinical Protocol Approval Form may also be used to approve amended protocols prior to IRB submission.

All tools referenced in this section (3.1.1) can be found in the Protocol section of the Clinical Tool Box.

### Consent Documents (CD) and Assent Documents

Because the consent and assent documents are highly dependent on the content of the protocol, their development will begin in earnest as soon as the protocol procedures and study-associated risks are well described. The consent document (CD) should be prepared using both the [Office of Human Research Protections (OHRP) guidance](http://www.hhs.gov/ohrp/policy/#informed) and local IRB requirements.

The CD review team is likely to be a subset of the protocol review team. At a minimum, the PI, site study coordinator, and DCC study coordinator or lead-site study coordinator should review the CD. Additionally, NIDCR staff will review the document and will communicate comments from NIDCR to the PI.

For multi-center studies, the PI may choose to distribute his/her CD to be used as a sample/starting point for other participating sites. Often individual IRBs have unique requirements for CDs, and it is likely that significant modifications of the initial CD template may be required. If there is any CD language that may not be modified, that language should be designated as such in the sample CD. In addition to the site review team, the CD should be reviewed by the Program Official and by the DCC or lead-site study coordinator who will ensure, among other things, that any required language has not been modified.

The **Consent Document Review Checklist** can be used to conduct a quality review of the CD; it will ensure that all required elements are included and that the CD is consistent with the protocol. See the Consent Documents folder of Clinical Tool Box.

Assent documents for minors and other subjects not able to provide consent will also be developed and reviewed as needed.

## Other Reviews and Approvals of Protocol and Consent/Assent Documents

### Scientific or Local Research Committee, Radiation or Other Therapeutic Review Committee

A clinical institution may require that the protocol and CD be reviewed by a scientific or other local research committee and/or a radiation or other therapeutic review committee. Often this review is conducted prior to the IRB and DSMB review.

### NIDCR Safety Oversight Review

The purpose of the NIDCR safety oversight review is to independently assess the safety data (e.g., adverse events and unanticipated problems) as well as study progress (e.g., recruitment and enrollment), study conduct (e.g., protocol deviations), and key data elements determined on an individual study basis. All studies are assessed to determine the level of data and safety oversight required. Studies requiring additional oversight may be assigned to safety oversight committees (i.e., Data and Safety Monitoring Board [DSMB][[1]](#footnote-1) or Clinical Study Oversight Committee [CSOC]) or to the Medical Monitor for both an initial protocol review and for ongoing reviews during the data collection portion of the studies.

Protocol and CD review should be completed by the designated DSMB/CSOC/Medical Monitor after the protocol team has completed their review and prior to site activation. The Program Official (PO) will provide the oversight-review-ready protocol and CD to OCTOM and the Medical Monitor. For protocols requiring committee review, an OCTOM representative will ensure that the protocol is added to the designated safety oversight committee docket for review at an upcoming meeting. Each DSMB or CSOC will be guided by a written charter.

It is best practice to submit the protocol and CD for a Safety Oversight review prior to submitting to the Institutional Review Board (IRB). In this way, any recommended changes can be implemented prior to submission of the documents to the IRB, thus reducing the likelihood of an extra IRB update cycle.

In addition to an initial review of the protocol and CD, the study will be scheduled for regular reviews (e.g., yearly) by the DSMB/CSOC/Medical Monitor. Following each review, the DSMB/CSOC/Medical Monitor will recommend to the NIDCR that the study either (1) continue as presented, (2) continue with modifications that the oversight committee will supply, or (3) be terminated for cause, with the cause specified. These recommendations are communicated in writing to NIDCR. NIDCR will convey accepted recommendations to the PI usually within one month.

### IRB Review

Follow local IRB guidelines for creation and submission of materials.

For multi-site studies, it is conceivable that a site IRB, other than that of the lead-site, may recommend changes to the protocol that are not consistent with the protocol that has been accepted at other sites. In some instances, IRBs have asked that the protocol be put into the local IRB’s template. It is not feasible or good practice to have different protocols at different sites for the same study; such cases will require further discussion with the study team. If the IRB continues to require a particular protocol change, then it will likely be necessary to amend the protocol at the other participating sites as well.

The protocol, CD, and other relevant study related materials must be approved by the site’s IRB before that site is initiated.

## Study Plan, Timeline, and Communication Plan

It is very important to establish a study plan that identifies all of the required activities that must be completed during the start-up process. The plan should also identify dependencies between various activities so that the study team understands the impact of one set of activities on another.

### Identify all Parties who will be Participating in the Study and Clarify the Responsibilities

Ensure that all study start-up activities are explicitly assigned. The **Task Distribution Checklist** can be used to support this goal (see the Project Management folder of Clinical Tool Box and the NIDCR’s Toolkit for Clinical Researchers website). This spreadsheet includes a comprehensive list of research activities and a means to identify the relevant group responsible for each. It also affords the ability to differentiate subtask responsibilities (e.g., author vs. reviewer vs. approver).

In certain cases of an Investigational New Drug application (IND), the IND sponsor may wish to officially transfer some of the sponsor obligations. This requires that the transferred obligations are documented, the document is signed, and it is provided to the Food and Drug Administration (FDA) as part of the IND.

The **Delegation of Responsibilities Log** is used by a clinical site to specify the names of individuals who will be responsible for implementing specified protocol activities (see the Essential Documents section in the Clinical Tool Box and the NIDCR Toolkit). This document will be completed prior to site initiation.

### Prepare Timeline or Start-up Tracking Tool

Once the full set of study activities is identified and the owner of each activity is established, a study start-up timeline or tracking tool should be prepared. There are several options for tools to support this effort. The **Countdown to Enrollment** is an Excel file that lists all of the study specific start-up activities along with the responsible parties and whether or not the activity is required a) before the first subject can be enrolled in the study; b) before the first subject can be enrolled at a specific site; or c) before an individual is permitted to engage in an activity (e.g., completion of randomization system training may be required prior to authorizing an individual to be able to use the randomization system to enroll a subject). The document also captures projected and actual dates of activity completion and denotes via comment the other activities that are required prior to the completion of other activities. This tool is available in the Project Management folder of the Clinical Tool Box.

There are project management software programs available that support the development of a start-up timeline and Gantt chart including Microsoft Project. Other project management applications may also be used.

The study **Start-up Timeline Calculator** takes advantage of more widely available software (i.e., MS Excel) while simultaneously providing the opportunity to model activity dependencies. There is a simple version of this calculator that can be used to get a rough estimate of when enrollment can begin and a more complex calculator that can be used to create a detailed start-up timeline with dependencies. This tool is available in the Project Management folder of Clinical Tool Box and in the NIDCR Toolkit.

### Conduct Regular Meetings during Start-up

Regular meetings with study staff, the PI, and the site PIs will facilitate study organization, communication, and tracking of progress toward initiation and activation. An OCTOM representative may participate in these meetings as well. The **Running Agenda and Meeting Minutes** **(RAMM)** document is an MS Excel file with multiple spreadsheets (see the Project Management folder of Clinical Tool Box and the NIDCR Toolkit). The document acts both as minutes from previous meetings and an agenda for the upcoming meeting. Additional pages of the spreadsheet capture study announcements, action items, and decisions. This one document retains items from all previous meetings, so that the one file is a complete archive for meeting minutes.

Regardless of the choice of start-up tracking tool (see Section 3.3.2), it is strongly recommended that the tool is prepared early in the start-up process, maintained vigorously during the process, and discussed regularly at team meetings, so that implications of missed target dates can be illuminated.

## Manual of Procedures (MOP) or Other Study Process Documentation

A Manual of Procedures (MOP) is a handbook that guides a study’s conduct and operations. It supplements the study protocol by detailing a study’s organization, operational data definitions, recruitment, screening, enrollment, randomization, intervention procedures and follow-up procedures, data collection methods, data flow, Case Report Forms (CRFs), and quality control procedures. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Procedures in the MOP should be followed with the same degree of vigor as those documented in the protocol. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

A MOP or set of study-specific Standard Operating Procedures (SOPs) and other procedural documents should be prepared prior to site initiation. See the **Manual of Procedures Template** (in the Project Management folder of Clinical Tool Box and in the NIDCR Toolkit) for a template that includes detailed guidance for the content.

# REGULATORY REQUIREMENTS

## Institutional Review Board (IRB)

Each site will submit the final protocol, consent/assent documents, and other applicable materials to the governing IRB. IRB approval of materials is required for a) release of grant funds, via the Clinical Terms of Award process and b) site activation for enrollment. See Section 3.2.3 for additional details regarding IRB review.

## Submission of Other Applications/Request /Information

### Certificate of Confidentiality

Protocols that collect sensitive data may benefit from a certificate of confidentiality (see <http://grants.nih.gov/grants/policy/coc/>). According to the website, “Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants.” Applications for a Certificate of Confidentiality are submitted to the NIDCR Certificate of Confidentiality Coordinator. The IRB approved CD must include a description of the protections and limitations of the Certificate of Confidentiality, including the circumstances in which the investigators plan to disclose voluntarily identifying information about research participants. Certificates from NIDCR generally take several weeks to be issued.

### Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)

If an IND or IDE is anticipated, early communication with the NIDCR Program Official, Medical Monitor, and OCTOM is highly recommended. The **IND Applicability Checklist** can be used to determine if an IND is needed (see the Regulatory folder of Clinical Tool Box and the NIDCR Toolkit).

For guidance on the IND application process, see: <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm>.

Once an IND application has been submitted, you must plan for a minimum of 30 days before beginning the study. Often the FDA will require additional information after the initial review, which can further impact study start-up timelines.

### ClinicalTrials.gov

The PI is responsible for registering applicable clinical trials into ClinicalTrials.gov prior to enrolling the first subject in the study. For more information see <http://clinicaltrials.gov/>.

## Essential Documents

Per Good Clinical Practice (GCP), essential documents are those documents that “individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.” Some essential documents should be filed only at the study site, others only in the sponsor (e.g., the IND holder, when applicable) files; the rest (the majority) should be maintained ultimately in both locations.

The **Essential Document Management Tool** clarifies the collection of these documents (see the Essential Documents folder of Clinical Tool Box). It provides both a recommended filing structure and references to relevant regulations and guidelines. Certain documents must be in place prior to site initiation and are identified in this tool.

Clinical sites can also use the **Extramural Essential Document Binder Tabs** to help organize the site files and clarify the required content of those files. (Synonyms for this binder include: Investigator Binder, Regulatory Binder, Investigational Site File (ISF) or Study Binder.) Two versions of these binder tabs are posted within the Essential Documents tab of Clinical Tool Box - one set that includes the instructions and sample documents, and one set that does not, for ease of printing.

Many of the site essential documents have corresponding templates available on the Clinical Tool Box page of the CROMS website and in the NIDCR Toolkit. These include, but are not limited to: **Site Screening and Enrollment Log**, **Training Log**, **Delegation of Responsibilities Log**, and a link to the **FDA 1572**. Please peruse these websites for the full list of available templates.

The site essential documents will either be reviewed prior to the site initiation visit, if CROMS is responsible for maintaining the Trial Master File, or they will be reviewed by CROMS and/or OCTOM during the site initiation visit. Files must be deemed complete by the DCC or CROMS prior to site activation.

# SUBJECT SAFETY OVERSIGHT

## Safety Monitoring Plan (SMP)

Clinical research studies must be monitored for safety and potential risk to the subject. Monitoring of participant/subject safety may be described in the protocol. A safety monitoring plan will be prepared by the PI’s designee or by CROMS, when appropriate. This plan must be reviewed and approved by the NIDCR Medical Monitor prior to site activation.

See Section 3.2.2 for further details of the Safety Oversight process.

In addition to Adverse Event (AE)/Serious Adverse Event (SAE) monitoring, the protocol and SMP should detail the process for monitoring and reporting Unanticipated Problems.

# DATA AND QUALITY MANAGEMENT

## Data Collection Tools

Study data must be initially captured using one or more of the following methods: on paper source documents, in electronic medical records or other electronic databases (e.g., central laboratory database), and/or in Electronic Data Capture (EDC) systems. Please note that GCP requires that the protocol describes instances when the EDC acts as the source document.

If paper CRFs are used, the DCC may provide support for initial data capture by providing source document templates. These are tools the site can use to create an initial data record that is able to be easily matched to the data collection instrument. Often these templates are created from the CRF. IMPORTANT NOTE: templates of this nature should only be used as the initial data record. If the data are captured elsewhere, they MUST NOT be transcribed onto source document templates. Each transcription increases the likelihood of a data error.

The Case Report Form will be designed to collect study related data in a manner that is practical and able to be easily rendered into an electronic database. Forms will be developed using Good Data Management Practices (GDMP), as established by the Society for Clinical Data Management, or using other best data management practices. The method for committing data to an electronic database should be determined during the start-up phase. Some studies may choose to use paper CRFs and to have a DCC enter the data into the database. Many EDCs permit immediate feedback of potential data errors, so they can be resolved in real time.

Sites that wish to create their own clinical database, or use support from a DCC, should use the **Data Management Considerations** document to confirm that they or the DCC have sufficient experience, adequate expertise, and appropriately validated software (see the Data Management section of Clinical Tool Box and the NIDCR Toolkit). OCTOM can assist sites in determining experience, expertise, and appropriate software for the study. The CRF and data collection system should be in place prior to site initiation but must be in place prior to site activation.

## Clinical Data Management Plan

A Clinical Data Management Plan (CDMP) is the document that summarizes the study’s approach to handling the data. A CDMP includes, but is not limited to: a) a description of the system being used to handle the clinical data; b) a description of the validation plan (i.e., methods for confirming that data are correct, such as range checks, valid value checks, and data cross-checks); c) a description of how external data will be reviewed and integrated with the clinical database; and d) documentation of the resultant clinical database that will be available for analysis. All studies are required to prepare a CDMP. See the Data Management section of Clinical Tool Box and the NIDCR Toolkit for a **Clinical Data Management Plan Template**.

## Statistical Analysis Planning

The protocol will contain sufficient statistical detail to describe the statistical analyses and the basis for any sample size and power calculations. A statistical analysis plan (SAP) may ultimately be prepared to elaborate on those protocol specifications. The SAP is not required prior to study start-up, but should be completed well in advance of database lock.

Statistical review of the CRF is another form of statistical planning. Review of the CRF by the study statistician ensures collection of the data that are necessary to support the protocol specified analyses. A statistical review of the protocol and CRF is necessary to ensure the study is appropriately designed and powered to meet its objectives.

## Quality Management Plan (QMP)

Quality management is a process of checking clinical research records for completion, accuracy and logic. It is performed by clinical research site staff to identify and resolve problems found in the conduct of their clinical research. This review and documentation of their findings and their plans to resolve and prevent problems is called a corrective and preventive action plan.

The quality management plan describes the process designed to ensure compliance with human subject safety, quality and integrity of the data, and compliance with the protocol. The NIDCR requests that a quality management plan be submitted to NIDCR for review and comment. OCTOM and CROMS can provide the site assistance with developing a quality management plan that is appropriate for the study design.

Quality Management tools are available in the Quality Management section of Clinical Tool Box and in the NIDCR Toolkit. Items include:

|  |  |
| --- | --- |
| An Introduction to Site-Level Quality Management within the Clinical Research Process | A slide presentation, providing an overview of quality management (QM) and of these QM tools |
| Clinical Quality Management Plan (CQMP)Template | A template, including instructional and sample text, to be used to document the study/site specific approach to quality management |
| Quality Management of Clinical Research – Brief Overview | An overview of QM term definitions, activity examples, and available tools and templates |
| Quality Management Subject/Participant Data Review Tool | A checklist that can be used to conduct reviews of subject level data and processes |
| Quality Management Study-wide Review Tool | A checklist of study-level quality review activities |
| Quality Management Summary Report Template | A template to support the regular reporting of the quality review activities, as specified in the CQMP |

# SPECIMEN AND MATERIALS MANAGEMENT

## Specimen Handling and Tracking

Studies that include specimen collection should ensure that the process for collection, handling, storage, and tracking is clearly established and documented. Often this documentation will be included as a section in the MOP or as a stand-alone Standard Operating Procedure.

## Specimen and Other Materials

Materials necessary to conduct the protocol should be on-site prior to the initiation visit. CROMS and OCTOM will be responsible for verifying that all materials are available during the initiation visit. Materials could include specimen tubes and labels, packing and shipping materials, procedure equipment and supplies, paper CRFs (if applicable), and participant/subject informational or instructional material.

# CLINICAL SITE MONITORING

## Pre-Site Initiation Teleconference with OCTOM and CROMS

In order to help sites ensure that they are sufficiently prepared to begin participant enrollment, OCTOM, CROMS, and the Program Official may conduct a site initiation teleconference with the site PI and the study coordinator prior to the site initiation visit. Refer to the **Site Assessment Questionnaire** tool for samples of questions that may be asked of the study team during this teleconference(see the Clinical Monitoring folder of Clinical Tool Box and the NIDCR Toolkit). If this questionnaire is used, CROMS will pre-fill as much of it as possible to avoid unnecessary effort on the part of the clinical site. CROMS may request advance copies of key study documents for review (e.g., protocol, CD, MOP, CRF, study timeline) prior to the teleconference.

Teleconference discussions / questionnaire responses and review of the key study documents will guide the scheduling of the initiation visit.

CROMS has staff available to support sites with most aspects of the start-up and initiation process (e.g., familiarizing teams with available tools, supporting the establishment of timelines, preparing for the site initiation visit). Requests for CROMS support should be directed to the study’s Program Official, who will communicate with OCTOM.

## Clinical Site Monitoring Plan (CMP)

Clinical site monitoring is performed by a site monitor to provide information to NIDCR on study progress and conduct to ensure the study is conducted, recorded, and reported in accordance with the protocol, Good Clinical Practice standards, and any applicable regulatory requirements.

When assigned clinical monitoring responsibilities by OCTOM, CROMS will prepare a clinical monitoring plan (CMP) for the study. The clinical research associate (CRA) is the individual from CROMS (or elsewhere, if so designated) who will be responsible for preparing the CMP and for conducting site monitoring visits. The CRA will tailor the **Clinical Monitoring Plan Template** to meet the needs of the study (see the Clinical Monitoring folder of Clinical Tool Box and the NIDCR Toolkit). The document will be approved by OCTOM, but approval is not required prior to site activation. If monitoring is performed by a group other than CROMS, the monitoring plan and visit reports must be submitted to the Program Official and OCTOM.

## Site Initiation Visit (SIV)

The SIV is led by the site Principal Investigator and the site study team. Additional participants/attendees include the DCC team, the NIDCR Program Official, a representative of OCTOM, and the CROMS CRA. See Section 9.1 for additional details.

# SITE INITIATION, CTOA, AND ACTIVATION

This section details the process for site initiation, meeting the CToA, and site activation. See Appendix B for a summary of items that are recommended or required at each step.

## Site Initiation Visit (SIV)

When the Program Official and OCTOM determine that the site is sufficiently prepared to begin participant recruitment, CROMS will schedule an Initiation Visit to the site. The Site Initiation Visit (SIV) should be scheduled soon before the anticipated activation date so information discussed at the visit is retained by the site staff. If the study is not initiated at a site within 8 weeks of the Site Initiation Visit, appropriate material from the SIV will be reviewed again with the site staff. Participants will include the site PI, the CROMS study coordinator (if applicable) and/or the CROMS CRA, an OCTOM representative if needed, the Program Official, the site PI, all other relevant co-investigators, and site staff. Visits may be 1 or 2 days depending on the scope of the agenda. A **Site** **Initiation Visit Agenda Template** is available for study specific customization. Also available is an **annotated version of the SIV Agenda Template** which includes additional guidance about the meeting’s content and conduct (see the Clinical Monitoring section of Clinical Tool Box and the NIDCR Toolkit [non-annotated only]). Please refer to this agenda for activities that will occur during the visit. In general, the meeting will include protocol review and detailed discussion of study implementation; MOP/study procedures review; data handling and electronic systems training; investigational product distribution and handling (if applicable); specimen processing, storage, and shipping procedures; safety reporting; clinical monitoring; good clinical practice training: sponsor and investigator responsibilities; and record retention. If the Essential Document files have not already been reviewed and approved prior to the visit, CROMS and OCTOM will review during the visit.

A facilities tour is common and a review of other on-site study materials may be conducted.

CROMS will organize and guide the Site Initiation Visit when it holds responsibility for study management and other clinical services. If CROMS is not providing project management support for the study, the site PI will be responsible for the agenda and for guiding the visit.

CROMS will issue a visit report that details the findings from the visit. The report will include a list of action items and will clarify any items that remain outstanding and that must be completed prior to activation. The report will be reviewed by OCTOM, and the final version will be sent to the PI and site PI with a copy to the Program Official.

## Clinical Terms of Award

The NIH responsibilities associated with clinical terms of award (CToA) are well documented in [**NIDCR Clinical Terms of Award**](http://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/NIDCRClinicalTermsofAward.htm)**.** The Program Official tracks CToA in the electronic CToA system that is accessed via the CROMS website.

Awardees must comply with the Clinical Terms of Award which are incorporated into the Notice of Grant Award for grants and cooperative agreements that involve [human subjects](http://grants.nih.gov/grants/policy/hs/) and meet the NIH definition of “clinical research.”

Materials required to meet CToA include:

* IRB-approved clinical research protocol identified by protocol title, version number, and date, and including details of study design, proposed interventions, subject eligibility criteria, and plans for assessing, managing, and reporting adverse events and unanticipated problems.
* Documentation of IRB approval, citing the version number and date of the documents reviewed and approved.
* IRB approved consent document, identified by version number, date, or both.
* Plans for data and safety monitoring. This might be described in the protocol, be a separate procedural document, or be a charter of a safety oversight committee.

See the Clinical Terms of Award for detailed specifications of these requirements.

When CToA have been met, the Program Official will enter the information into the electronic CToA system. The system allows the Program Official to generate an email notification to the NIDCR Grants Management Branch that Clinical Terms of Award have been met. Grants Management will notify the institution’s business official and principal investigator that funds may be drawn down from the payment system to support subject enrollment. The Program Official will complete the Site Activation Checklist (See section 9.3 and Appendix A) when the CToA have been met.

## Site Activation

A site can be activated only after it has met CToA. See Appendix A for the Site Activation Checklist. This checklist will be prepared by CROMS with the Program Official, and used by the Program Official to determine when all additional requirements have been met for site activation. When all of these additional requirements have been met, CROMS will send the completed checklist to OCTOM for review. If all components of the Checklist are complete, OCTOM will sign the form and recommend to the Program Official that the site may be activated. The Program Official will verify that CToA have been met and will approve the site for activation by signing the Checklist. The Program Official will send a Site Activation Notification letter (see Appendix C) to the site PI and will provide a copy of the memo and Checklist to CROMS for the study file.

For studies that involve a study product, a process must be established to ensure that the product is not released for use in the study until the site has been approved for activation.

# APPENDICES

| APPENDIX A: Protocol <#> EXTRAMURAL SITE ACTIVATION CHECKLIST | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| <Protocol title> | | | | | | |
| Site Name: |  | | | | Site #: |  |
| Protocol Version and Date: | |  | | | | |
| Item | | | | | | Date |
| 1. IRB Approval Received for Protocol, Consent Form, and Other Applicable Documents | | | | | |  |
| 1. NIDCR Safety Committee (e.g., CSOC, DSMB, DSMC) review complete or confirmation that no Safety Committee will be required | | | | | |  |
| 1. Site Essential Document File Approved | | | | | |  |
| 1. Case Report Forms Final | | | | | |  |
| 1. Data Management System Ready for Data Entry and Clinical Data Management Plan Drafted | | | | | |  |
| 1. Study Materials on Site   {Instruction: List types of required materials separately (e.g., specimen labels and tubes, questionnaires, supplies for procedures).} | | | | | |  |
| 1. Site Initiation Visit Completed  * Trained on protocol, study procedures (MOP), electronic systems. (Note this requirement includes re-training, if site activation is more than 8 weeks after the site initiation visit.) * Facilities deemed acceptable | | | | | |  |
| 1. Action Items from Site Initiation Visit Required for Site Activation Completed | | | | | |  |
| 1. Study Specific Requirements Met   *{Instruction: Update with relevant list.}* | | | | | |  |
| 1. CToA Met and Notification of Award Sent | | | | | |  |
|  | | |  |  | |  |
|  | | |  |  | |  |
| CROMS/DCC Representative Completing the Checklist | | |  |  | | Date |
|  | | |  |  | |  |
| Activation Recommended by <OCTOM Representative>, OCTOM | | |  |  | | Date |
|  | | |  |  | |  |
| Activation Approved by <NIDCR Program Official>, NIDCR1 | | |  |  | | Date |

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

Forward an electronic version of this document that includes all signatures to the CROMS representative for storage in the study file.

**APPENDIX B: Requirements for CToA/Grant, Initiation, and Activation**

| **Item** | **CToA/Grant** | **Initiation** | **Activation** |
| --- | --- | --- | --- |
| IRB Approved Protocol | Required | Required | Required |
| IRB Approved Consent Document(s) | Required | Required | Required |
| IRB Approval of Study Materials | Not Required | Required | Required |
| Safety Oversight Committee Review of Protocol | Not Required | Recommended | Required |
| Manual of Procedures or Set of Study Specific Procedural Documents | Not Required | DRAFT Required | Required |
| Essential Document Packet Complete | Not Required | Required | Required |
| Essential Document Packet Approved by CROMS/OCTOM | Required | Not Required | Required |
| Safety Monitoring Plan | Required | DRAFT Required | Required |
| Case Report Forms | Not Required | Recommended | Required |
| Data Management System | Not Required | Recommended | Required |
| Clinical Data Management Plan | Not Required | Recommended | DRAFT Required |
| Quality Management Plan | Not Required | DRAFT Required | Required |
| Clinical Monitoring Plan | Not Required | Not Required | Recommended |
| Human Subjects Training | Required per Grant | Not Required | Required |
| IND or IDE1 | Required | Required | Required |
| Targeted/Planned Enrollment Table (PHS 398) | Required per Grant | Not Required | Required |
| Approval of Recombinant DNA Advisory Committee and Institutional Biosafety Committee1 | Required | Not Required | Required |
| Site Initiation Visit (SIV) Completed | Not Required | Not Required | Required |
| Completion of Action Items From SIV | Not Required | Not Applicable | Required |
| Study Drug Ready to be Dispensed1 | Not Required | Not Required | Required2 |

1Only when applicable.

2Study drug may not be dispensed until after activation.

**APPENDIX C: Site Activation Notification Template**

**TO:** <Site Principal Investigator>

**FROM:** <Program Official>

**SUBJECT:** Site Activation: <Site>

**PROTOCOL:** <Protocol Number: Title>

**DATE:** <Date>

**CC:** OCTOM

<Grant PI>

<Other involved parties as determined by Program Official>

I am pleased that you will be conducting the above referenced study. This Site Activation Notification confirms that your protocol, consent, and IRB approvals have been received and have met NIDCR Clinical Terms of Award, and clinical operational systems are in place. Your site is now activated and may begin subject enrollment.

In the future, to help ensure subject safety and data integrity, please provide me with copies of documents related to all major changes, including protocol amendments, changes to the consent, termination or suspension of subject accrual, changes in IRB approval, IRB continuing review, changes in key study personnel, and any problems or issues that could affect the safety of subjects or integrity of the study.

Please let us know if you have any questions or concerns regarding the initiation or conduct of this study.

**APPENDIX D: Clinical Trial Progression in Behavioral or Social Intervention Research**

A controlled study involving human subjects, designed to test a well-characterized behavioral intervention and to evaluate prospectively the effect of the behavioral or psychosocial intervention on one or more aspects of public health. “Behavioral intervention” is a broad term that describes an approach to preventing, maintaining or changing behavior through the use of non-medical or non-pharmaceutical techniques. Examples of behavioral interventions include, but are not limited to: health education, health promotion, teaching skills, providing social support, resolving family conflict, screening and brief intervention for health behaviors, establishing reward systems for healthy behavior, changing organizational structure, and more. Behavioral interventions range in intensity (very brief to intensive), duration (a single session to sessions over the course of years), mode of delivery (in person, computer, other technology), and complexity (simple messages to sophisticated strategies). Behavioral intervention research proceeds through different phases, which are similar to phases of drug or device development. The behavioral intervention research field tends to describe these phases as “stages”, to identify the research as behavioral.

**Stage 1a:** Behavioral intervention development work begins in Stage 1a. During this early stage, findings from basic or clinical science about behavior, and/or clinical observations about behavior, are translated into a draft behavioral intervention, and the target population and/or interventionists provide feedback to ensure the intervention is acceptable and feasible.

During this stage, investigators should: define the clinical problem of interest (i.e., the theory or logic model of the problem), and define the rationale for why the intervention is expected to address the problem (i.e., the theory or logic model of change). Essential to defining the rationale for the intervention is a clear identification of proposed mediators and moderators. Mediators are intermediate variables targeted by the intervention that are causally related to a desired outcome. For instance, an intervention to improve oral health may involve improving nutrition. Presumably, the nutrition intervention improves oral health indirectly, by improving a mediating variable, such as eating behavior. Moderators are variables for which the relationship between the intervention and the desired outcome varies. In the above example, if the nutrition intervention led to greater oral health improvements for women than for men, sex/gender would be a moderator of the intervention-outcome relationship.

Activities appropriate for Stage 1a behavioral intervention development may include collection of qualitative data from stakeholders as an early check on the relevance and acceptability of the intervention, and iterative feedback between this data collection and further adaptations of the draft intervention manual. One product of this stage of research should be a draft behavioral intervention that is described in sufficient detail--typically in an intervention manual--so that it can be delivered as intended.

Another activity appropriate for Stage 1a research—and each subsequent stage--is testing the proposed rationale or theory for the intervention. During Stage 1a, testing the intervention rationale may take the form of highly-controlled, small-scale, lab-based tests. For instance, let’s suppose that our nutrition intervention is expected to work by increasing the salience of healthy foods during meal times, which in turn increases choosing healthy foods. During Stage 1a, we could develop a psychometrically sound method for varying the salience of healthy foods, and then test our rationale by manipulating the salience of healthy foods, and measuring food choices. Testing the intervention rationale also may take other forms, such as in-depth case studies, within-subjects studies, time series studies, and more. Stage 1a activities may not involve analyses of statistical significance. However, if analyses involve tests of significance, adequate statistical power is expected.

Unlike other stages of behavioral intervention development that have analogous phases in drug or device development, Stage 1a is unique to behavioral intervention development research.

**Stage 1b:** Once a draft behavioral intervention manual is developed, the next stage involves testing the intervention for acceptability to the target population and to the intended interventionists, and testing the feasibility of conducting an efficacy trial in subsequent stages. Often, testing for acceptability and feasibility involves qualitative data collection rather than significance-testing using quantitative data. Some models of behavioral intervention development encourage investigators to conduct a small-scale, often under-powered, randomized clinical trial during this stage, in order to estimate the effect size of the draft intervention. The NIDCR model does not encourage under-powered randomized clinical trials. Instead, the NIDCR encourages investigators to ensure acceptability and feasibility in Stage 1b, typically using methods where statistical power and significance are not relevant. For instance, acceptability might be assessed by conducting focus groups with participants in the draft intervention. Feasibility of delivering the intervention might be assessed by tracking any problems that occur during initial delivery of the intervention to a small sample. Stage 1b activities may not involve analyses of statistical significance. However, if analyses involve tests of significance, adequate statistical power is expected.

The NIDCR views sufficiently-powered randomized clinical trials as appropriate for Stage 2 behavioral intervention research.

Stage 1b of behavioral intervention research is similar to Phase I in drug and device development.

**Stage II:** Once a behavioral intervention has been shown to be acceptable to the target population and interventionists, and has been shown to be feasible to deliver and test, Stage II research begins. The main goal of this stage is to identify causal relationships between the intervention and target outcomes. In other words, Stage II activities test the efficacy of an intervention, and further clarify variables that mediate and moderate the intervention’s effects. Typically—but not always--an efficacy test involves comparing the intervention to one or more control or comparison groups. If statistical analyses involve tests of significance, adequate statistical power is expected.

Clarifying mediators and moderators of a behavioral or social intervention may involve a variety of methods and study designs. Most experts in theory testing and in statistical mediation encourage certain considerations when studying mediation and moderation. Among these considerations are that hypothesized mediators and moderators: 1) are measured frequently enough to capture meaningful change; 2) are measured *before* target outcomes in order to establish temporal relationships; and 3) are measured in the experimental and comparison condition(s) to establish specificity of effects.

Strict controls are expected in Stage II behavioral intervention research. Whether conducted in a laboratory or community setting, or by researchers or community clinicians, Stage 2 research expects strict adherence to intervention fidelity, delivery by well-trained interventionists, a well-defined population, and sound measurement of outcomes and other variables.

Stage II behavioral intervention research is roughly analogous to Phases II and III in drug or device development.

**Stage III:** The purpose of Stage III research is to prepare and/or adapt an efficacious intervention to be delivered in community (non-research) settings by community interventionists in a sustainable way. Some models of behavioral intervention research call this stage “effectiveness research”, although the NIDCR draws an important distinction between typical effectiveness research and what we consider Stage III research. Specifically, we consider as vital to Stage III research rigorous measurement of deviations from fidelity, and of variables that might affect intervention delivery. Stage III is not meant to be a return to “black box” intervention research, but rather a systematic study of how an intervention can be delivered in a “real world setting”.

Examples of Stage III research activities include, but are not limited to: 1) comparing the adaptations community interventionists make to an efficacious intervention to accommodate different service delivery systems or specific populations; 2) adapting an efficacious intervention based on Stage II mediation and/or moderation analyses, and comparing the adapted version(s) to the standard intervention; 3) developing and testing methods of training and supervising community interventionists in an efficacious intervention; and 4) identifying organizational characteristics that facilitate delivery of an efficacious intervention.

Stage III behavioral intervention research is similar to Phase IV drug or device development in its attempt to meet the needs of the general population, and to continue to monitor limitations of an intervention’s effects.

1. In rare instances, the Medical Monitor may determine that an Independent Safety Monitor (ISM) will provide oversight in addition to or in lieu of a DSMB. NIDCR can provide further information. [↑](#footnote-ref-1)