**PROTOCOL DEVELOPMENT**

**Protocol Development and Study Preparation**

1. Collaborate with Sponsor/Contributor to finalize a protocol and submit to NIH and the Sponsor/Contributor for review and approval in compliance with the timelines specified within the task order. When possible, input from patients and/or patient advocacy groups should be considered when developing the protocol. Provide all necessary documentation for the proposed clinical study to the Sponsor/Contributor required to secure the IDE approval and work with Sponsors/Contributors to submit documents for all requisite regulatory approvals (e.g., IRB and FDA submissions). Prepare the informed consent form (ICF) which contains appropriate reference to the NIH Privacy Act system germane to data collection for awarded task orders and all other protocol specific supporting documents (e.g., subject recruitment advertisements), and submit the final protocol, any protocol amendments, ICF and other documents to the institutional review board (IRB) for review and approval.
2. Throughout the process essential regulatory documents as specified in ICH guideline should be generated and stored in files/folders and be available for monitors and for use in the subsequent quantity option when executed. Essential regulatory documents may include but are not limited to: signed IRB approved protocol; informed consent form and advertisement for subject recruitment; IRB approval letter; IRB membership list; PI and sub-investigators curriculum vitae; licenses for PI and sub-investigators; investigator’s brochure; documentation outlining responsibilities for each key person listed in protocol; personnel training documentation (PHS/GCP); normal laboratory ranges; laboratory certification; financial disclosure documents; conflict of interest declaration; indemnification/insurance documents.
3. Prepare and deliver a Project Management Plan (PMP) within 60 calendar days after task order award and before consenting of the first subject. The PMP must be a single, well-organized document or folder that clearly connects document elements with the sections below. The PMP shall address and include, at a minimum, the following:
4. Project timelines including all contract deliverables;
5. Project-specific standard operating procedures (SOPs) for the conduct of clinical studies and for all other integrated and collaborating services;
6. Personnel listing including their roles and responsibilities to include an organizational chart;
7. Human subject considerations (e.g., federal wide assurance (FWA), initial and continuing human subject training/education for personnel, data and safety monitoring plan, consenting procedures, procedures for managing medical emergencies on-site, reporting of adverse events (AEs), serious adverse events (SAEs), unexpected adverse events, hospitalizations and procedures for prompt
8. reporting of SAEs in compliance with FDA regulations and NIH policies);
9. Develop Data Safety and Monitoring Plan (DSMP) in accordance with NIH guidelines and policies for DSM (https://grants.nih.gov/policy/humansubjects/policies-and-regulations/datasafety.
10. htm) for review and approval by the IRB;
11. Establish and coordinate an Independent Safety Monitor (ISM) or Data Safety Monitoring Board (DSMB) when applicable in accordance with NIH guidelines and policies for DSM for review and approval by the IRB;
12. Training program for clinicians, clinical site staff, data management staff and other support staff in the protocol procedures with every task order protocol in order to ensure reliability of evaluation, treatment and assessment procedures;
13. Recruitment and retention plan (e.g., enrollment of a diverse subject pool, including women and minorities, across the lifespan (if applicable), rate of subject accrual, subject retention, plans for deficient enrollment). Enrollment data shall be collected using categories required for the NIH Inclusion Enrollment Report Form (https://grants.nih.gov/grants/funding/phs398/enrollmentreport.pdf);
14. Data management procedures and systems planning that is in compliance as specified with the contract terms and conditions including but not limited to development of database and case report forms (CRFs), data collection, data monitoring, data safety review;
15. Plan and timeline for development of the statistical analysis plan (SAP);
16. Management procedures for receiving, storing, and implanting/applying investigational devices; also to be included a procedure for randomization and if appropriate stratification of eligible subjects;
17. Blinding plan, including during device use, clinical and data management activities, as appropriate;
18. Clinical and laboratory quality monitoring procedures;
19. Procedures for preventing, identifying, handling, reporting and resolving protocol deviations;
20. Quality control plans and procedures;
21. Establishment and demonstration for independence of oversight including quality assurance procedures;
22. Protection of Contributors’/Sponsors’ intellectual property and data procedures;
23. Archival plans for securing completed trial data according to regulatory requirements;
24. Contingency planning;
25. The plan for quality control and quality assurance, e.g., monitoring plans, data quality plans and audits; and
26. Close-out plan
27. Regulatory preparations and compliance:
28. If the study is either an NIH-defined or FDA-defined clinical trial, register the clinical trial in the National Library of Medicine’s Clinical Trials registry (http://www.clinicaltrials.gov);
29. Ensure all requisite regulatory approvals are in place (e.g., IRB and FDA submissions) including that the investigational device has appropriate FDA approval (e.g., IDE) confirming the device’s suitability for testing in humans prior to initiating recruitment;
30. Obtain any necessary Material Transfer Agreement (MTA) from Contributor/Sponsor;
31. Throughout the studies essential regulatory documents should be generated and stored in files/folders and be available for monitors and, at the end of the studies, all essential regulatory documents at the clinical research unit should be placed in the master regulatory file for archiving. Regulatory documents may include but are not limited to: IRB approved protocol, ICF and advertising; IRB approval letter; IRB membership list; PI and sub-investigators curriculum vitae; licenses for PI and sub-investigators; investigator’s brochure, normal laboratory ranges, laboratory certification, financial disclosure documents, indemnification/insurance documents, investigational device shipment receipts, etc. During the conduct of the clinical trial, all new relevant information/data must be appended to the
32. essential documents as it becomes available;
33. Ensure that the conduct of the clinical trials performed is in compliance with all FDA and ICH GCP regulations and guidelines;
34. Prepare a complete clinical study report in submission ready format for FDA unless otherwise specified. Additionally, the IDE report for annual filing requirements to the IDE application, as needed;
35. Ensure the confidentiality of all clinical records and information about subjects enrolled in the clinical trial conforms to all Privacy Act requirements (http://www.justice.gov/opcl/privacy-act 1974 and
36. http://www.hhs.gov/ocr/privacy).
37. Database Build
38. As required for the conduct of the study specified in the Task Order, the Contractor shall develop and validate a database for the clinical study for relevant data including Case Report Forms (CRF), adverse event (AE) and significant adverse event (SAE) logs, and other data as required for the clinical study.
39. The Contractor shall provide any required licenses, software, or dictionaries for the database.

**STUDY IMPLEMENTATION**

1. **Protocol Implementation: Compliance and Oversight**

**Clinical Study Initiation**

1. The Contractor’s clinical study team and support staff shall participate in a clinical study initiation meeting at the Contractor’s clinical research facility. The Contractor shall provide an invitation to NIH and the Contributor/Sponsor to participate in person or via video conferencing. Prepare and deliver a summary report of the initiation meeting to include but not be limited to the agenda and the list of participants.
2. Protocol Amendments:
	1. Prepare all protocol amendments and modifications;
	2. Upon COR approval, the Contractor shall submit the amended protocol and ICF to the lRB for review and approval;
	3. The Contractor shall provide the amended protocol to the COR and the Contributor/Sponsor;
	4. Upon IRB approval, the amended protocol and revised ICF shall be archived in the master regulatory file;
	5. The Project Management Plan (PMP), case reports forms and other supporting documents will be modified to reflect the protocol amendments; and
	6. If necessary, the PI or designee shall conduct a training session describing the protocol amendment and its impact on clinical study procedures and assessments.
3. Protocol Oversight:
	1. Oversee and ensure adherence to the protocol all clinical activities conducted at the clinical research facility and all collaborating sites including, clinical laboratory, data management center, imaging center and subcontracting sites; and
	2. Ensure that each participant: meets protocol entry criteria; has given informed consent and has undergone all the screening and baseline assessments as specified in the protocol
4. For each Task Order protocol:
5. Track subject enrollment and adherence to defined recruitment goals;
6. Review and assess participant data as specified within the data management plan, protocol requirements and/or quality assurance requirements. For example:
	1. Promptly provide all data reports for monitor review prior to the initiation of any device parameter changes;
	2. Monitor continuously for the validity and integrity of the accumulating data;
	3. Monitor continuously protocol adherence and compliance with current ICH GCP guidelines, DHHS Protection of Human Subjects regulations (45 CFR Part 46) and FDA regulations and report all protocol deviations;
	4. Report of any serious adverse events and/or unexpected adverse events to FDA, IRB and COR;
	5. Report all performance-related issues and proposed resolutions or corrective actions taken; and
	6. Database summary tables for monitoring and tracking purposes throughout the course of the clinical study including subject enrollment updates
	7. If the study is either an NIH-defined or FDA-defined clinical trial, update clinicaltrials.gov as required by NIH policy and Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (summarized here: https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf)
7. Data Management and Quality Control:
8. Maintain and update the clinical database throughout the study;
9. Modify the database to support any protocol amendments that are implemented during the conduct of the clinical study, as required; and
10. Provide quality control to ensure initial data entry within 24 hours and to correct or issue a data query within 48 hours and inform promptly the clinical research staff of any missing, incomplete and erroneous data
11. Audit Compliance

The NIH at their discretion may undertake an audit of the Contractor’s facility including all collaborating sites. The Contractor shall make available all facilities, records and files as related to any activity under Performance Area A or B. The Contractor shall submit a report describing the implementation of the corrective actions.

**B) Investigational Devices and Clinical Specimens**

1. Investigational Device:
	1. Maintain inventory records of investigational device in accordance to SOPs;
	2. Maintain documentation that the investigational device will be stored and quarantined under appropriate conditions according to the Sponsor/Contributor and regulatory requirements; and
	3. Mechanism for the return and/or destruction of unused investigational devices.
2. Clinical Specimens (if applicable)
	1. Ensure collection, processing, labeling, temporary storage under appropriate conditions and management of all collected biological specimens;
	2. Ensure shipping of biological specimens for testing and/or repository deposition, as specified in the protocol, in compliance with current Good Laboratory Practice (cGLP), cGCP and domestic laws and regulations; and
	3. Maintain current Clinical Laboratory Improvement Amendment certification (http://www.cms.gov/clia/ and The Joint Commission approval (http://www.jointcommission.org/)) or local equivalent, as appropriate.

**C) Clinical Study Analysis, Close-out and Final Clinical Study Reporting**

1. Close-out and Analysis

Following the last subject’s completion of clinical study procedures including any outpatient follow-up visits, the Contractor shall:

1. Continue to monitor any residual safety concerns (i.e., AEs & SAEs) until complete resolution;
2. Establish long-term follow-up plan for any patients retaining permanently implanted device;
3. Complete data editing/cleanup;
4. Finalize and lock the database;
5. Conduct the statistical analysis as described in the manual of operations;
6. Deliver the locked deidentified database in agreed upon format (e.g., R, SAS, SPSS, ASCII) and schedule as requested by the COR;
7. Provide to the COR with the final enrollment report using the NIH Inclusion Enrolment Report form: https://grants.nih.gov/grants/funding/phs398/enrollmentreport.pdf;
8. Provide support to Sponsor/Contributor during drafting/publishing of manuscript;
9. Provide annual IDE reports to the FDA and the COR within 60 days of the anniversary date the IDE went into effect for as long as the IDE remains open, or as recommended by current FDA guidance; and
10. If the study is either an NIH-defined or FDA-defined clinical trial, report trial results to clinicaltrials.gov prior in alignment with requirements.
11. Completion:
	1. Prepare for archiving the final dataset and all associated clinical study records. Clinical study records are considered case report forms and detailed documentation necessary to assess the final dataset with specific codes for all variables including all transformation that have been created (i.e., data dictionary);
	2. Prepare and deliver draft and final clinical study report; the study report must be in a format suitable for submission to the FDA; and
	3. Archive the final locked dataset with de-identified data for each clinical study conducted under each task order in Performance Area B in an agreed upon format (e.g., R, SAS, SPSS, ASCII) that is readily usable by NIH and Contributor/Sponsor.

**D) Facilities, Equipment and Other Resources**

The Contractor shall be responsible for the adequacy and availability of all facilities, equipment,

and other resources necessary for the conduct of a clinical study which may include but is not

limited to the following.

**Provide Clinical Research Facilities:**

1. Accreditation with a national or state accreditation board for the conduct of clinical studies;
2. Areas to allow for waiting, check-in and discharge;
3. Examination rooms to allow for protocol-related assessments;
4. Standard clinical support services for inpatient care, twenty-four hours/day, seven days/week;
5. Capability to recruit target populations;
6. Adequate and secure computing resources for communication and data management (e.g., entry editing, quality control);
7. Adequate and secure electronic access to the data management center;
8. Emergency care and a definitive plan for management of life-threatening adverse events including on-site resuscitation equipment and hospitalization procedures in the event a participant requires these services;
9. Adequate equipment, staff and services for performing routine safety evaluations (e.g., vital signs, ECG, neurologic exam), precisely timed phlebotomy, collection of cerebrospinal fluid (CSF), urine and other bodily fluids as necessary;
10. Capabilities for the collection of cerebrospinal fluid (CSF) via lumbar puncture or with a temporary in-dwelling catheter if required by the TOFRP;
11. Ability to provide experienced research staff to perform cognitive testing, using paper or computer based systems;
12. Ability to provide experienced staff to quantify activities of daily living;
13. Staff with expertise in the conduct of medical device clinical studies including but not limited to physicians, clinical specialists, registered research nurses, study coordinators, clinical research associates, research assistants, and Independent Safety Monitor(s) (ISM);
14. Documentation of staff qualifications for completion of specific outcome measures where such qualification is required or appropriate
15. Access to clinical specialists in the therapeutic and diagnostic areas covered by NIH and the NIH Blueprint MedTech program for additional safety and efficacy assessments that may be required in select clinical studies, such as ophthalmology exam or detailed neurologic examination; and
16. Capabilities for composition of serious adverse event reports and narratives

**Provide cGLP Clinical Laboratory Facility:**

1. Adequate space for the processing and temporary storage of biological specimens;
2. On-site sample storage facilities at room temperature, 4, -20 and -70 degrees Celsius;
3. Clinical laboratory support services with provisions of 24 hours/day testing if required by the protocol;
4. Histology/pathology capabilities, if required by the protocol;
5. Adequate and secure electronic access to the data management center; and
6. Have current certification and licensure for the performance of biological specimen assays and analyses

**Provide Clinical Imaging Facility:**

1. Adequate and secure electronic access to the data management center;
2. Adequate facilities and equipment for conducting protocol-required diagnostic and/or imaging procedures for diagnosis or special safety evaluations, including computerized tomography (CT), magnetic resonance imaging (MRI), proton emission tomography (PET), electromyography (EMG), and electroencephalography (EEG); Electroretinography (ERG);
3. Ability to compare investigational diagnostic devices against gold-standard imaging listed above, when applicable; and
4. Have current certifications and licensures for the performance of imaging procedures.

**Provide Data Management Center:**

1. Adequate computing resources to support data collection activities;
2. Personnel knowledgeable about data management activities and operations but not limited to data management planning and reporting, performance reporting, quality assurance and administrative support;
3. Clinical data warehousing capabilities/facilities in order to provide a centralized, integrated system for data storage, analysis, reporting and ad hoc query of clinical data;
4. Data management capabilities necessary to support the conduct of clinical research, such as case report form (CRF) design, data dictionary development, database programming, data base design and development in compliance with Good Clinical Practice (GCP) guidelines and Clinical Data Interchange Standards Consortium (CDISC); and
5. Provide other facilities and equipment, as may be specified by the task order protocols (e.g., biosafety laboratory facilities in compliance with Federal and state regulations)