NIDCD U01 Clinical Trials: Pre-Implementation Requirements and Targets Timeline

Protocol Development and Approval	Target Completion Deadline (After U01 Award)	Clinical Trial Operations
Contact CTP team to schedule **introductory meeting**.	Day of U01 award	
Submit Organization Table of Protocol Development Team. In addition to protocol chair(s), include staff responsible for document quality control (to ensure that all comments are discussed/incorporated), and team statistician.	**7 days post award** Send to CTP team and Program Officer (PO).	Submit **Operations Organization Overview.** An overview of the organizational structure, including an organizational chart and details of the operations of the study's PIs, Medical Monitor, Clinical Coordinating Center including Research Coordinator, Statistical and Data Coordinating Center including Statistician and Data Manager, and Performing Sites (site PIs/clinicians, site coordinator, intervention administration/surgeon, testing/evaluation staff, data entry, etc.).
Submit Official Intervention Detail and Instruction, for example: • Package Insert • Investigator's Brochure (IB) • Device Evaluation Strategy Table(s)/Device Specifications	**7 days post award** Send to CTP team and PO.	
Submit FIRST draft of protocol document to CTP team. Must include: • All sections of the NIH-FDA protocol template (Word version) completed, as per the Notice of Award (NoA). • Statistical sections written by the study team statistician.	**30 days post award** Send to CTP team.	Submit **Safety Monitoring Standard Operating Procedures (SOP).** Describes how adverse events (AEs) are submitted; how the team (including specification of team members responsible) will evaluate AEs, routinely monitor AEs, identify trends,

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• Below the Schedule of Activities table, include a section that describes the components of each type of visit as well as how they are conducted, e.g., face-to-face vs. phone call. • Efficacy Assessment section must include a description/components of each evaluation as well as interpretation of results, e.g., severity scale. • Adverse Event Reporting section must also include reporting timeline to NIDCD. • If applicable, address prior FDA comments. • For drug and biologic study interventions, a Clinical Management section must be included. This section provides guidance on how to handle adverse events (AEs) potentially induced by the drug/biologic based on the package insert/IB, to include but not limited to: Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Overdosage, and Patient Counseling Information, e.g., detailed clinical management instructions based on Severity/Grade of AE. This provides clinical management consistency across study clinicians. *[Can request an example template from the NIDCD Medical Officer.]*		and address findings; and how the team will ensure the timeliness of reporting to NIDCD, the U.S. Food and Drug Administration (FDA), and the Institutional Review Board (IRB).

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○ Include a statement that participant safety overrides protocol: It is understood that treating physicians will provide whatever available treatment is considered best to protect participant safety and well-being; compliance with study requirements must not compromise such treatment. • For Devices, include sections describing Post-Trial Transition Plan, Surgical Implantation, Device Components and Specifications (implanted components, software, hardware). • NIH Policy on Sex as a Biological Variable is addressed in the protocol. • Protocol version number and date. • Draft protocol reviewed and approved by members of the Protocol Development Team prior to submission to NIDCD CTP team. **Schedule meeting with NIDCD CTP team to discuss FIRST draft protocol comments.** You must build in 4 weeks turnaround for the CTP team to review the first draft protocol.		

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Meeting with NIDCD Medical Officer(s) and NIDCD Statistician to discuss NIDCD FIRST draft protocol comments (if necessary).	**60 days post award** Contact Medical Officer(s) and NIDCD Statistician to set up meeting.	Submit **Delegation Log** for Coordination Center and Performing Sites.
Submit SECOND draft of protocol document to NIDCD CTP team. Please note: • Protocol version control should be maintained, with a new protocol number and date for each draft version circulated. • Both the tracked changes and clean versions of the protocol document should be submitted. • All NIDCD comments should be addressed in this draft prior to submitting to NIDCD. • Draft protocol must be reviewed and signed off on by the Protocol Development Team prior to submission to NIDCD. • **Schedule meeting** with NIDCD CTP team to discuss second draft protocol comments.	**80 days post award** Send to CTP team.	Submit **Clinical Data Management Plan (CDMP).** • Identify the Data Coordinating Center (DCC) if one is used, and the lead investigator or person responsible for data management (provide name, degree, title, and institution). • Describe or reference the electronic data capture (EDC) or clinical data management system (CDMS), if used. • Describe or reference the clinical trial management system (CTMS), if used. • Provide verification of compliance with federal regulations. • Describe security and emergency backup. • Describe procedures to ensure quality assurance and quality control of data from clinical sites and laboratories, as appropriate.

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Establishment of Data and Safety Monitoring Board (DSMB) approved by NIDCD. No member of the DSMB should have any involvement in the conduct of the studies to be reviewed. The DSMB members are required to disclose information on potential financial, professional, and personal conflicts and should sign a Conflict of Interest (CoI) certification form. DSMB members are asked to: (a) Disclose any financial conflict with the institutions that are conducting clinical trials. (b) Disclose any financial conflict with pharmaceutical or device suppliers and sponsors. (c) Disclose any personal conflict with investigators: primary employment in the same department; research collaborations, mentor relationships, or research co-publications within the last three years; and public differences in opinion. (d) State if they can conduct unbiased assessment of the study or will recuse from reviewing the specific study. (e) Sign the CoI certification form.	**80 days post award** Send to CTP team. DSMB membership needs CTP team approval (note: Medical Officer will determine if NIDCD DSMB is appropriate). For NIDCD's review of DSMB membership, please provide each proposed member's name, degree, current position, employment/institution, and a brief rationale for selecting the member, e.g., expertise clinically as well as with clinical trials. Include all resumes and information to confirm there is no conflict of interest.	Submit **Quality Management Plan and Standard Operating Procedures (SOPs)** describing the tools, processes (including frequency), activities, reporting and corrective actions, and identification of specific staff for roles/responsibilities to ensure the quality of the work and oversight of this trial, as well as metrics to monitor quality improvement. Please include the following documents: • **Document Development, Review, and Version Control SOP.** All study related documents/official communications sent to NIDCD and other entities such as the FDA, IRB, DSMB, etc., and/or utilized by sites should follow this SOP to ensure that the documents are reviewed by specified study team members and clean/accurate prior to submitting. • **Study Conduct Quality Control and Quality Assurance SOP.** Describes how the study team will monitor the implementation and protocol/Manual of Procedures (MOP) compliance of the trial across sites. This should include continual processes/activities of the study

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		team (quality control) in addition to the separate auditing plan from the independent monitor contracted to conduct periodic visits (quality assurance). • **Data Management Quality Assurance and Quality Control SOP.** Describes measures taken to continually monitor and verify the quality and timeliness of data.
DSMB Charter prepared and approved by NIDCD.	**Day 1 of month 3 post award**	
Meeting with NIDCD Medical Officer(s) and NIDCD Statistician to discuss NIDCD SECOND draft protocol comments (if necessary).	**Day 14 of month 3 post award** Contact Medical Officer(s) and NIDCD Statistician to set up meeting.	
THIRD draft of protocol document submitted to NIDCD CTP team. Please note: • Protocol version control should be maintained, with a new protocol number and date for each draft version circulated. • Both the tracked changes and clean versions of the protocol document should be submitted. • All NIDCD comments should be addressed in this draft prior to submitting to NIDCD.	**Day 21 of month 3 post award** Send to CTP team.	

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• Draft protocol must be reviewed and signed off on by the Protocol Development Team prior to submission to NIDCD.		
NEAR-FINAL draft Informed Consent submitted to NIDCD. • Informed Consent should be reviewed and approved by Castilla McNamara, Ph.D., M.P.A., prior to finalization and submission to the IRB. • Informed Consent should correlate with the latest version of the protocol.	**Day 21 of month 3 post award** Send to CTP team (Attention: Castilla McNamara, Ph.D., M.P.A.).	
DSMB Safety and Progress Monitoring Open and Closed report template completed. Medical Officer will provide a sample template.	**Day 21 of month 3 post award** DSMB should approve template. Send to CTP team.	
DSMB review of NIDCD-approved final protocol draft, Informed Consent, Charter, and DSMB Open/Closed Monitoring report template.	**Day 21 of month 4 post award** Send to CTP team.	
Study team written response to DSMB Protocol and Charter Review recommendations (in one document).	**Day 1 of month 5 post award** Send to CTP team.	
NEAR-FINAL protocol prior to FDA submission. • Submit clean and tracked changes final draft versions to Medical Officer for approval prior to submitting to the FDA. • This near-final version should address study team, NIDCD, and DSMB comments.	**Day 1 of month 5 post award** Send to CTP team.	

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Submission to the FDA.	**Day 21 of month 5 post award** Anticipated FDA response: Day 21 of month 6.	
Forward the FDA's response to NIDCD CTP team (within 7 days of receipt).	**Day 1 of month 7 post award** Send to CTP team and PO. CTP staff will provide instructions for submitting documentation of FDA approval to NIDCD Grants Management.	**Manual of Procedures (MOP)** to include the following: Organizational table by study implementation responsibility (provide name, degree, title, and institution). For example, conduct screening (include screening log), informed consent, eligibility determination, randomization/enrollment, procedures to maintain blinding, evaluations/assessments/examination at visits, study coordination, intervention preparation/labeling and distribution, data entry, data manager, data QA/QC, administration or surgical placement of intervention (if applicable), collection and storage of biospecimens, safety monitoring.
IRB/ethics information for each site: Name, address, Federalwide Assurance (FWA) number.	**Day 1 of month 7 post award** Send to CTP team.	
FINAL protocol prior to IRB submission: • Submit clean and tracked changes final draft versions to Medical Officer for approval prior to submitting to the IRB. • This final version should address NIDCD, FDA, and DSMB comments.	**Day 14 of month 7 post award** Send to CTP team.	**Updated Independent Data Quality Auditing Plan (IDQAP)** [for studies requiring FDA oversight]. • Independent Data Quality Auditing is to verify that the clinical trial is being conducted and documented in accordance with the protocol,

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• **Release of Human Subjects Restrictions before recruitment may begin:** ○ This final version must be approved by NIDCD. ○ Notification of Release of Human Subjects Restriction from NIDCD Grants Management.		Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s). • Describe the person(s)/entity responsible for conducting the independent auditing, including qualifications and experience. • Describe the frequency of planned auditing activities, locations where the monitoring will occur (e.g., participating clinical sites, data center, clinical coordinating center) and what data will be reviewed. • Provide an overall description of the auditing plan to ensure adherence to the protocol, adequate documentation of the consenting process, and the quality and consistency of the study intervention(s), including fidelity monitoring for behavioral interventions. Include methods to monitor study intervention and the system to record and manage exceptions and deviations. If applicable, describe monitoring of participating facilities such as labs or pharmacies for adequate handling

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		and storage of investigational product(s) and study specimens. Include a description to ensure that the investigational product(s) accountability and reconciliation are performed adequately during and at the end of the trial per applicable regulatory requirements. • Describe plans for handling any deficiencies that are uncovered, and in cases of serious deficiencies, the appropriate reporting to relevant authorities, including but not limited to the IRB of record, DSMB if one is assigned, the FDA if applicable, institutional officials, and NIH.
Submit CRF (case report forms/data form templates). Include screening log documents used to capture screen failures and reasons for screen failures.	**Day 14 of month 7 post award** Send to CTP team.	
Submit Statistical Analysis Plan (SAP). Allow 3 weeks for the NIDCD Statistician, Chuan-Ming Li, M.D., Ph.D., to review.	**Day 14 of month 7 post award** Send to CTP team (Attention: Chuan-Ming Li, M.D., Ph.D.).	Submit **Recruitment and Retention Plan.** Any recruitment materials reviewed by the IRB. Link to website, if applicable. • Ensure recruitment materials align with protocol inclusion/exclusion criteria and case report form (CRF). State the demographic breakdown of the geographic area in which the science will be conducted to determine inclusion

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		enrollment by race and ethnicity; a recruitment plan focused specifically on engaging underrepresented minority populations should be included.
Submit IRB approval letter for final version of the protocol and Informed Consent. Letter should include final version, number, and date of the protocol approved by the NIDCD Medical Officer. • If participating sites have modified Informed Consents, these also need to be submitted, with the modifications highlighted/tracked. • Business office should submit to NIDCD Grants Management Specialist (GMS) AND copy the CTP team and PO. • Include the following language: This is the IRB approval for version [XX] dated [MMDDYYYY] (the final protocol version approved by the NIDCD Medical Officer).	**Day 14 of month 8 post award**	**Submit Protocol and study implementation training for staff/sites conducting study** (Medical Officer will attend if possible). • Send CTP team agenda and schedule. • After training, send CTP team training log, confirming study team staff trained. **For implanted device interventions, surgical staff training.** Send CTP team training log confirming completion of surgical staff training for clinical trial related procedures.
	Day 14 of month 8 post award Send summary to CTP team.	**Site initiation visits.** Conduct evaluations of site capabilities and readiness for the conduct of the clinical trial, verifying site readiness and providing recommendations for activation (allowing the initiation of enrollment) including review and evaluation of: • The availability and

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		delegation of appropriately trained clinical and technical personnel to conduct the clinical trial. • Completion of clinical trial required training. • Established essential document file and secure storage of study-related documents. • Clinical research infrastructure and resources for the screening, enrollment, intervention administration, primary and secondary endpoint evaluations, safety monitoring, and follow-up of study subjects. • Availability, appropriate storage, and accountability of the study intervention at site. • The recruitment and retention plan and feasibility for enrollment

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		target goals, including efforts to enroll underrepresented populations such as underrepresented minorities (if scientifically appropriate) when new sites are proposed by research teams. • When a major deficiency (such as a lack of qualified staff or equipment to conduct study evaluations, etc.) is observed, provide a verbal debriefing and resolution advice and a written report of the observation and recommendations.
	Day 14 of month 8 post award Send first report to CTP team. (CTP team may comment.) *Subsequent reports sent monthly to Medical Officer, PO, and Castilla McNamara only.	Submit **study team monthly Safety and Progress Monitoring Report.** Report utilized by the team and sent to the NIDCD Medical Officer and Castilla McNamara each month to monitor the safety and progress of the study. (NIDCD can provide a template, and the team can incorporate more detail.) Safety: as specified by the PI and Medical Officer.

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		Progress should include: • Enrollment status: including the number of subjects screened/enrolled/randomized. • Graph depicting anticipated vs. actual enrollment per month. • Participant status: the number of participants who completed major study milestones. • Participant dropouts: number and reason. • Participants off-treatment: number, time of discontinuation, and reason for premature discontinuation. • Protocol deviations. • Screen failure log to monitor issues that may be resolved with screening. • Corrective action plan for unmet enrollment targets.
Register the trial on ClinicalTrials.gov. Please ensure the full NIH project ID number is entered in the field "Other Study ID Number," e.g., 5U01DC012345 (U.S. NIH Grant/Contract). This will link your clinical trial to the NIH Research Portfolio Online Reporting Tools (RePORT).	**Day 14 of month 8 post award** Send to CTP team.	**Updated Milestone Table** (specify anticipated completion month/day/year). Include graphical depiction of anticipated enrollment by month (to be used on monthly reports to track anticipated vs. actual enrollment) as well as overall study timeline including: • Completion of regulatory approvals.

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		• Listing in ClinicalTrials.gov registry. • Enrollment of the first subject. • Enrollment of 25%, 50%, 75% and 100% of the projected recruitment time period for all study subjects, including women, minorities, and children (as appropriate) AND include enrollment target dates and percentages specified in the NOA. • Last participant enrolled. • Last participant complete last study visit. • Scheduled interim analyses. • Completion of data collection time-period. • Data closed and clean-up. • Completion of primary endpoint and secondary endpoint data analyses time period. • Posting of primary outcome results in ClinicalTrials.gov registry. • Completion of final study report.

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		• Detailed protocol-specific performance milestones and timeline; these milestones will be negotiated at the time of the award, if appropriate. Also include a contingency plan for not meeting enrollment targets, highlighting any differences from the Recruitment and Retention Plan.
	Day 14 of month 8 post award Send to CTP team.	**Confirm intervention availability and distribution to clinical trial performing site(s).**
Enrollment begins.	**Day 1 of month 9 post award**	**Enrollment begins.**