

NCS Formative Research Template for OIRA Clearance

TO BE COMPLETED BY STUDY CENTER:

LOI #: LOI-2-QUEX-8
Title of Formative Research: Development and Validation of an Autism Case Confirmation Approach for Use in the National Children's Study
Participating Institutions: Johns Hopkins University, Kennedy Krieger Institute, Drexel University, Battelle, Mt. Sinai School of Medicine, UC Irvine, UCLA, University of Miami, University of Washington, University of Wisconsin
Recruitment Study Arms:
SME: Jack Moye
COTR: John Lumpkin, Gitanjali Taneja, Carl Hill, Kate Winseck, Maria Lopez, Eric Lorenzo

Purpose of the Study: The project will develop and test case-confirmation approaches for autism spectrum disorders (ASDs) suitable for inclusion in the NCS. The NCS is considering using short parent self-report screeners as a first stage in ASDs case-finding. The latest data on recommended parent-report ASD screeners (e.g., the M-CHAT) suggest sensitivity and specificity as high as 95% and 99%, respectively. However, with population ASD prevalence estimated to be 1.1%, a first stage screener with these performance characteristics applied in a community sample of 100,000 children would still be expected to yield nearly the same number of false positives (~989) as true positives (~1079). Therefore, some second-stage case-confirmation of screen positives in the NCS will be necessary. In recent NIH RFAs, the Autism Diagnosis Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) have been required as case-confirmation tools. Administration time for these instruments can exceed three hours, however, as the setting is ideally a specialized research clinic. Furthermore, assessors not only typically have existing clinical experience but also undergo extensive instrument-specific training and reliability establishment. Therefore, our goal is to develop a second-stage case-confirmation approach with good performance characteristics that is not overly burdensome in terms of participant time or study resources, can be reliably administered by NCS field staff with no previous ASD expertise and will also generate dimensional measures of ASD severity.

Benefit to NCS Vanguard or Main Study: The development and validation of a more streamlined ASD case-confirmation approach that can be implemented by NCS study staff without special expertise in ASD will facilitate accurate active identification of ASD cases at three years of age, allowing the study to rapidly address etiologic questions relevant to this outcome in a timely and affordable manner.

Study Design: This is a cross-sectional criterion validity study contrasting ASD case classification as determined by a battery of three brief novel assessments (a video-guided parent self-report; a parent interview, and a direct observation) that can be implemented by NCS field staff and compared to gold standard ASD case confirmation (an Autism Diagnostic Observation Schedule by a research-reliable assessor and a DSM-based diagnostic assessment by a qualified clinician). The video-guided self report (VGPR) includes paired video clips showing children with typical development and ASD engaging in selected activities with voiceovers describing and contrasting the behaviors of the two children. Parents will answer questions that rate the relevant behaviors as absent, possibly present, or definitely present. The parent interview will be the recently developed Autism Diagnostic Interview-Screener (ADI-S), which includes 30-40 questions (depending on the language level of the child) about social communication and restricted and repetitive behaviors and interests. The direct observation will be an adaptation of the Screening Tool for Autism in Toddlers (STAT-NCS), which includes 12 items in the areas of play, imitation and communications each presented by field staff in a prescribed manner with the subject scored for each item on response to press, social engagement, and atypical behavior. Web-based training modules have been developed for the NCS staff that will conduct the study visit. Staff will complete these trainings at the start of the project.

Target Respondents: We will invite two convenience samples comprised of 33- to 39-month old children (and one of their parents) scheduled for neurodevelopmental evaluation at specialty clinics affiliated with autism research groups at NCS Study Center sites. However, these samples will be non-NCS participants. The principal convenience sample (the MAIN sample) will be comprised of children (and a parent) where ASD is suspected who are already scheduled, or are about to be scheduled, for an evaluation at the

NCS Formative Research Template for OIRA Clearance

collaborating specialty clinic. The children who are scheduled for evaluation will receive an Autism Diagnostic Observation Schedule (ADOS) from an assessor who has met standards for clinical or research reliability and a DSM-based diagnostic evaluation. The second convenience sample (the SUPPLEMENTAL sample) will be comprised of children (and a parent) where there is no suspicion of an ASD and who are scheduled for an evaluation of a suspected 'developmental delay' at these same clinics. The children in this SUPPLEMENTAL sample, because of the suspected developmental delay, may be more likely to test 'false positive' on a first-stage ASD screener (e.g., the M-CHAT). Data collection will involve one study visit at least one week prior to the scheduled non-study evaluation visit. At the study visit a parent will complete the informed consent process, complete the video-guided self report (VGSR, 20 minutes), answer questions during an interview (25 minutes), and remain with their child during the direct observation segment (20 minutes). The child will participate in the direct observation segment (20 minutes). The order of the assessments will be randomly determined prior to the subjects' arrival. Data from the scheduled clinical visit (which will occur subsequent to the study visit) will be provided by staff at partnering specialty clinics, which are funded through a contractual arrangement with the participating Study Centers. Parents will be asked to consent to this data transfer.

Sample Size Calculation: This study has planned for a 10-month enrollment and data-collection phase. As described below, Study Centers recruit through contacting families scheduled for research or clinical visits (that will include the required gold-standard evaluation described above) at the relevant specialty clinics affiliated with the autism research group collaborating with each participating Study Center. The table below lists the

seven participating Study Centers and anticipated numbers of subjects to be enrolled in each of the two samples. Based on the sites' experience, we anticipate approximately 85% of the MAIN and 10% of the SUPPLEMENTAL sample will be gold-standard confirmed ASD cases; consequently we expect to have approximately 275 true positive and 170 true negatives available for analysis that will focus on estimating criterion validity, sensitivity (Sn) and specificity (Sp), of the novel case-classification assessments. We used exact methods described by Chu and Cole (*J Clin Epidemiol* 60(11):1201; 2007) to estimate the minimum Sn and Sp that this study would be able to detect as being significantly greater than minimally acceptable Sn and Sp levels of 80%, respectively (one-sided p-value of 0.05) with 80% power. Based on this, the study will have adequate power to detect observed Sn of 86% and an observed Sp of 87% as being significantly above the minimum acceptable levels. (Note: the reason the minimum detectable Sp is close to the minimum detectable Sn at half the sample size stems from the "sawtooth" shape of the power function for this test - described in Chu and Cole, 2007).

NCS Center	Main	Supplemental
Johns Hopkins	40	20
Mt. Sinai	30	20
UC Irvine	60	20
UCLA	40	20
University of Miami	45	20
University of Washington	50	20
University of Wisconsin	40	20
Total	305	140

as being significantly greater than minimally acceptable Sn and Sp levels of 80%, respectively (one-sided p-value of 0.05) with 80% power. Based on this, the study will have adequate power to detect observed Sn of 86% and an observed Sp of 87% as being significantly above the minimum acceptable levels. (Note: the reason the minimum detectable Sp is close to the minimum detectable Sn at half the sample size stems from the "sawtooth" shape of the power function for this test - described in Chu and Cole, 2007).

Method of Recruiting: Investigators from the autism research groups collaborating with each participating Study Center will facilitate recruitment of age-eligible parent-child dyads from families who are scheduled or are being scheduled for research or clinical visits at specialty clinics (described above). Each site has different pools of subjects from which to recruit depending on the mix of ongoing studies and flow to affiliated specialty clinics. In instances where the collaborating autism research group has other ongoing studies enrolling children with either ASD or developmental delay suspicion in the age range of interest, the collaborating autism research group and the study staff will follow local IRB approved protocols for approaching these subjects. This can involve: 1) sharing of subject contact information with study staff, if the autism research group has received the participants' permission to share these data with other research efforts; or 2) staff from the autism research groups (contracted to the NCS) describing this project to their participating families and providing the family with information on how to contact study staff if they are interested (the attached flier is an example of information that can be given to families expressing interest). In instances where recruitment will occur from families scheduled or being scheduled for clinical visits, the process can involve: 1) study staff contacting families that meet age and diagnostic suspicion criteria directly by telephone when access to PHI is permitted through IRB-approved partial HIPAA waivers; or 2) specialty clinic staff informing families in the target age range and diagnostic suspicion groups about the study as upcoming clinic visits are being scheduled and then providing interested families with study staff contact information (the attached flier is an example of something that

NCS Formative Research Template for OIRA Clearance

can also be given to these families). Study staff will follow an IRB-approved telephone script (see attached example) during their initial interaction with families.

Confidentiality: Participating Study Centers will abide by the terms of their Data Use Agreements, which should reference all formative research efforts involving the collection or management of NCS restricted-use data. All participating Study Centers will have approved Data Use Agreements and Security Plans prior to launch.

At the time of consent, an anonymous study ID will be assigned. The link between the study ID and identifying information will be maintained locally.

IRB Approval: Local IRB clearance for this activity has been obtained by each of the participating Study Centers. Please see the attached IRB approval letters.

Incentives

An incentive of \$25 will be offered to participants for joining this project; the amount is consistent with the OMB approved incentive structure for the Phase 2 Vanguard Study. A non-monetary incentive in the amount of \$10 or less may be offered for those participants who have extended visit times.

Sensitive Questions: This data collection effort includes questions geared toward parents in identifying potential psychological problems and concerns about their child’s development. These questions are necessary for testing case-confirmation approaches for ASDs using parent screeners. The ASI-D also includes a question about household income.

Proposed Project Schedule: We will begin this project upon receipt of all regulatory approvals.

Data Collection Burden:

Estimates of Annual Hour Burden

Data Collection Activity	Type of Respondent	Estimated Number of Respondents	Estimated Number of Responses per Respondent	Average Burden Per Response (in hours)	Estimated Total Annual Burden Hours
Recruitment contact	Parents	535	1	10/60	89
Data collection	Parents	445	1	Direct data collection - 60/60 Other time (wait during child observation) - 20/60 Total: 80/60	593
Data collection	Children	445	1	Direct data collection - 20/60 Other time (wait during parent data collection) - 60/60 Total: 80/60	593
TOTAL		980			1,275

Annualized Cost to Respondents

NCS Formative Research Template for OIRA Clearance

Data Collection Activity	Type of Respondent	Estimated Total Annual Burden Hours	Hourly Wage Rate	Respondent Cost
Recruitment contact	Parents	89	\$10.00	\$890.00
Data collection	Parents	593	\$10.00	\$5,933.00
Data collection	Children	593	\$0.00	\$0.00
TOTAL		1,275		\$6,823.00

Please check here after ensuring that all calculations have been verified

Estimated Costs: Staff hours: 2,550
Supervisor hours: 638

Attachments: Exemplar Informed Consent for main sample, Exemplar Informed Consent for supplementary sample, IRB approval letter, exemplar telephone script for recruitment contacts, exemplar recruitment flyer; study data collection instruments (including the VGPR, ADI-S, and STAT-NCS) to be completed by participants, IRB Protocol and a scheduled assessment summary sheet to be completed by the autism research collaborators at each site).

Please check here after ensuring that the OMB #: 0925-0661 and Expiration Date: June 30, 2015 have been inserted as first-page headers on each proposed instrument.

Please check here after ensuring that the following OMB burden statement has been inserted as a first-page footer on each proposed instrument. *Note that the XX below is replaced with either 20 or 25 minutes depending on the particular tool (this project use three data collection tools that involve participant burden).

Public reporting burden for this collection of information is estimated to average **XX** minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0661). Do not return the completed form to this address.