Can Novel Telemedicine Tools Reduce Disparities Related to Early Identification of Autism

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Background

With an estimated prevalence of 1 in 68, early accurate identification and treatment of young children with Autism Spectrum Disorder (ASD) represent a pressing public health and clinical care challenge. There is growing evidence that (1) accurate, stable diagnosis of ASD is possible during the second year of life and (2) very young children with ASD receiving early behavioral intervention services demonstrate substantial gains in functioning. American Academy of Pediatrics (AAP) guidelines endorse universal screening for ASD at 18 and 24 months of age, and at any point when caregivers express concerns. Currently when children screen positive on ASD risk instruments in pediatric settings, providers are most commonly making referrals to (a) tertiary diagnostic centers with tremendous waits for evaluation (months to over a year) and/or (b) early intervention systems that, in absence of a diagnosis, typically provide very low levels of non-specific developmental service. Despite large-scale initiatives to promote screening and early diagnosis the average age of diagnosis in the US is remains after four years of age for many children. Moreover, groups from traditionally underserved communities are much less likely to be diagnosed at young ages, including children from families of lower socioeconomic status, children whose parents report lower levels of educational attainment, children from racial and ethnic minority groups, and children in rural and geographically isolated communities. These diagnostic delays and health disparities contribute to substantial deleterious family stress and restrict access to meaningful evidence-based ASD intervention services.

Telemedicine offers tremendous potential for addressing these healthcare disparities related to early accurate identification of ASD in traditionally underserved communities. Telemedicine consultation potentially could alleviate time, travel, and geographic burdens for many families that often drastically limited access to services; speed entry into appropriate care; empower parents and medical providers to take a more active role in care; reduce wait times at specialty clinics; and help ensure that for those families for whom further assessment is recommended, the associated waits and expense are truly necessary. Our preliminary work suggests that telemedicine consultation in a rural pediatric clinic can potentially rapidly, accurately identify large percentages of young children with ASD with high levels of family and provider satisfaction, but this work to date has been powerfully constrained by the fact that no specific tools for telemedicine consultation of early ASD are available (i.e. preliminary work required both an expert clinician and a trained technician utilizing traditional assessment within community practice setting).

Study Purpose and Description

We propose an evaluation and comparison of two telemedicine assessment tools (TELE-STAT and TELE-ASD-PEDS) that could allow parents or naïve providers in remote locations to complete an Autism Spectrum Disorder (ASD) risk assessment via telemedicine consultation with an expert psychologist. These tools will be low cost, compliant with privacy rules, easily deployed in community practice settings, and explicitly designed to work within paradigms that may be pragmatically and financially viable for systems of care housing remote clinicians. Our telemedicine tools could provide methodologies wherein children could be rapidly linked to and appropriately assessed by ASD experts within practice locations where they are currently receiving care. In turn, these children, who without such assessment may wait months or over a year in many circumstances to access assessments and interventions, may be able to receive appropriate ASD assessments within days or weeks of screening/surveillance concerns within practice settings they are already accessing and familiar with (i.e. minimizing loss to referral and follow-up).

Study Aims

There will be two aims to the study. The first aim will include using the existing TELE-STAT and TELE-ASD-PEDS tools to assess and evaluate their acceptability/feasibility, clinical value for remote observation, and challenges that warrant revision. We will then use this data to modify the TELE-STAT and TELE-ASD-PEDS instruments to optimize fluid use. In the second aim, we will deploy the refined TELE-STAT (n=60) and TELE-ASD-PEDS (n=60) with new samples of clinically referred children (15-36 months of age) and rigorously evaluate their ability to facilitate accurate telemedicine supported diagnostic decision making. Remote clinicians will utilize telemedicine tools and generate ratings of diagnostic certainty, which will be compared to blinded comprehensive assessments using gold-standard tools. We will critically evaluate each tool independently and compare the characteristics of these tools to each other in additional to gathering feedback from participating families on acceptability and use.

Expected duration of the study

2 years

Accrual Goal: What is your total accrual goal at Vanderbilt?

60 parents and 60 children in Aim 1; 120 parents and 120 children in Aim 2

Total number of participants stated in the protocol to be studied at all sites (regardless of PI).

180

Aim 1:

Inclusion Criteria:

- Previously evaluated and diagnosed with autism or other developmental delay
- >/= 15 months of age and </= 36 months of age
- Parental (or other legal guardian) informed consent to participate
- English speaking

Exclusion criteria:

- significant sensory impairment (e.g., hearing or visual impairment, child not yet walking) or medical complexity that would make assessment instruments invalid.

Aim 2:

Inclusion Criteria:

- >/= 15 months of age and </= 36 months of age
- Concerns for autism or other developmental delay
- Parental (or other legal guardian) informed consent to participate
- English speaking

Exclusion criteria:

- Significant sensory impairment (e.g., hearing or visual impairment, child not yet walking) or medical complexity that would make diagnostic instruments invalid. These children will be referred to appropriate VUMC medical providers for diagnostic consultation and follow-up.

Behavioral Observations

Aim 1:

Each child and their caregiver(s) will participate in one appointment. After consent, they will be randomly assigned to one of two telemedicine procedures (TELE-STAT or TELE-ASD-PEDS). The child and parent will be led through the screening tool by a remote psychologists (approximately 30 to 45 minutes). The telemedicine procedure, regardless of which one the family is assigned to) involves behavioral interactions that are coded by the examiner on paper forms. Parents will be in the same room as their child at all times and will also be asked to interact with their child in specifid ways in order to elicit social, communication, and play skills in their child.

Aim 2:
Each child and their caregiver(s) will participate in one appointment. The appointment will include 2 parts: 1. telemedicine tool and 2. gold standard diagnostic evaluation. After consent and being randomly assigned to one of two telemedicine procedures, the child and parent will be led through the screening tool by a remote psychologist (approximately 45 minutes to 1 hour). Following the telemedicine procedure, the child will receive a gold standard diagnostic evaluation (2 to 3 hours) in person by a licensed clinician.

Behavioral Observation will be conducted in both the telemedicine and gold standard evaluations. This will be done as part of the TELE-STAT (telemedicine autism screener), TELE-ASD-PEDS (telemedicine autism screener), and ADOS-2 (gold standard autism test). Both the telemedicine screeners and the ADOS-2 procedures involve behavioral interactions that are coded by the examiner on paper forms. Parents will be in the same room as their children at all times and will also be asked to interact with their child in specific ways in order to elicit social, communication, and play skills in their child.
The TELE-STAT takes approximately 30 minutes. Parents will be walked through each task by a remote clinician. Children interact with their parent to complete 12 items (2 play tasks, 2 requesting tasks, 4 object spectacle/joint attention tasks, 4 imitation tasks). Behaviors are coded on a form based on the examiner's observations. The STAT yields a total score of 0-4 that indicates level of ASD risk. TELE-ASD-PEDS takes approximately 30 minutes. Parents will be walked through each task by a remote clinician. Children interact with their parent to complete 11 items (play tasks, directing attention tasks, requesting tasks). Behaviors are coded on a form based on the examiner's observations. The instrument is scored based on a 7-item rating scale. Mullen Scales of Early Learning (MSEL): The MSEL takes approximately 30 minutes to complete for children with suspected ASD who are within this age group.The MSEL is a standardized, well- validated measure of cognitive and developmental skills. Children are presented with standardized prompts within four domains: Visual Reception (nonverbal problem solving, e.g., putting pieces in a puzzle), Fine Motor (manipulating objects with hands; e.g., stacking blocks), Receptive Language (understanding words; e.g., following instructions), and Expressive Language (using words; e.g.,naming objects). Responses are coded as correct or incorrect based on the MSEL manual. Scores are standardized. ADOS-2: The ADOS-2 takes approximately 30-45 minutes to complete. There are 5 versions of the ADOS-2 dependent on a person's age and language level. All children who participate in this study will complete the Toddler Module, Module One, or Module 2. These modules, designed for very young children with limited verbal skills, involve activities such as blowing bubbles, requesting a snack, playing with developmentally appropriate toys (cars, blocks), and engaging in games. Behaviors are coded based on the trained examiner's observations and rated on a scale of 0-2 or 0-3, dependent on the item. The ADOS-2 yields a total score of 0-30 that indicates level of ASD risk. The ADOS-2 will be completed by a trained examiner. Parents can be asked to participate in a couple of the tasks.

Randomization
All participants will be randomized to TELE-STAT and TELE-ASD-PEDS using a random number generator program based upon enrollment order.

Blinding

Aim 1:

The clinician conducting the telemedicine procedure will be blind to the participant's existing diagnosis (autism or other developmental delay). Parents will be asked not to divulge this information in order to maintain research integrity.

Aim 2:

The clinician conducting the telemedicine procedure does not need to be blind because all participants will have necessarily not been evaluated before. The clinician who completes the gold standard diagnostic evaluation, however, will be blinded to the diagnostic impression and certainty of the clinician who conducted the telemedicine procedure. Parents will also be blinded to the results of the telemedicine procedure. They will not be blinded to any study procedures, the purpose of the study, or the results of the golf standard evaluation, which will include diagnostic feedback and recommendations.

This study
does not
involve
deception.

Procedures:

Please indicate all procedures and activities performed for research purposes only and the frequency at which they occur in the study (e.g., skin biopsy, 3 times).

Procedure/Activity	Frequency
TELE-STAT (occurs in Aim 1 and Aim 2)	1 time, approximately 30 minutes
TELE-ASD-PEDS (occurs in Aim 1 and Aim 2)	1 time, approximately 30 minutes
Diagnostic Certainty Form	Approximately 5 minutes
Comprehensive interview with parents (occurs only in Aim 1)	1 time, 30 to 45 minutes
VABS-3 (occurs only in Aim 1)	1 time, 30 minutes
MSEL (occurs only in Aim 1)	1 time, 30 minutes
ADOS-2 (occurs only in Aim 1)	1 time, 30 to 45 minutes
Medical History/Background Information (occurs only in Aim 1)	1 time, 15 minutes
Parent Feedback Form (occurs in Aim 1 and 2)	1 time, 10 minutes
ALFA-Q (completed by clinicians and parents, both in Aim 1 and Aim 2)	

Data and Safety

Aim 1:

Participants will be recruited from families who have come through our diagnostic clinics whose children have been diagnosed with autism or other developmental delays and who have previously signed consent to be contacted for research.

Aim 2:
Participants will be recruited from families already waiting for diagnostic evaluation services through VUMC. All families will be contacted and recruited by [redacted], who is the primary contact for all families seen through VUMC mechanisms. [redacted] has over a decade of experience working specifically with families of young children with ASD in both clinical and research settings. This includes explaining clinical versus research routes in ways such that families understand their options. Data will be de-identified and stored in RedCap. A list with the ID-to-name correspondence will be kept on a secure network server and will only be accessible to key study personnel as is necessary to conduct their responsibilities within this research study

Risks
There are minimal risks to this study.
Aim 1:
The telemedicine procedures are very brief and play-based. The parent and child will always be together and will be given a break if needed.

Aim 2:
The telemedicine procedures are very brief and play-based. The parent and child will always be together and will be given a break if needed.

Further, the gold standard assessment that every participant will receive will be the exact same evaluation that they would have received through the VUMC system, offered by the same licensed clinicians. The only difference is that they will have a shorter wait to receive this service and will also complete a very brief telemedicine screener. Children could become tired. However, we don't anticipate that participation in this study will be any more tiresome for children than participation in the evaluation for which they are already on a clinical waiting list at VUMC. We will structure sessions such that children can take breaks for snacks, diaper changes, or even short naps, if necessary. We will have parents present with children at all times to provide us with feedback about their children's well being so that we can pace sessions appropriately, as reflects the reality of working with toddlers and families. All KSP are very experienced working with this vulnerable population.

Data and safety monitoring plan
PI Warren will be responsible for the overall monitoring of participant safety as well as assessment and coding procedures. The PI will also be responsible for overall project and data integrity, including any adverse event reports to the IRB, if needed.

Monitoring the progress of trials and the safety of participants
All members of the research team are very familiar with working with young children with ASD and their families. They will be trained and instructed to immediately report any adverse events to the PI and the IRB. The research team already meets on a weekly basis to discuss ongoing clinical and research concerns. They will continue to meet regularly to review the status of data collection and analysis, and to discuss any concerns, or issues related to the safety of participants and collection of the data.

Adverse events (AEs)
All members of the research team will be trained to immediately report adverse events to the PI and the IRB. Evaluations will be conducted by licensed clinical psychologists and a licensed senior psychological examiner who are held to high ethical standards by their professional organizations and licensing board.

This includes regular training in ethics and safety as part of license renewal and VUMC compliance procedures. All AEs will be reported within 7 days to the IRB.

Statistical Design and Power

Specific Aim 1: We will deploy the *TELE-STAT* and *TELE-ASD-PEDS* to evaluate initial acceptability, feasibility, and potential clinical value for remote observation. Based on this feedback, we will modify instructions or procedures before the finalized tools are evaluated in the controlled trial of Aim 2. Given that this Aim relates to usability and entails an iterative design process, much of the data gathered will be compiled and analyzed descriptively. We therefore have carefully selected our sample size and embedded several explicit benchmarks of success to structure this critical design phase. To refine each instrument, we will recruit independent groups (n = 30 *TELE-STAT* and n = 30 *TELE-ASD-PEDS*) of children (18-36 months of age) and their caregivers, who have already been identified as having ASD (67%, n = 20) or non-ASD, but with other developmental concerns (e.g., language delay; 33%, n = 10). We will also recruit licensed psychologists from our clinical research center (n=10) that will coach parents through the procedures. All remote clinicians will have had previous training on the STAT and research reliability on the ADOS-2 as well as considerable expertise in routinely diagnosing ASD in children of this age range. This sample size ensures that the instruments will be utilized across a large number of clinicians and a large number of test cases representing both our primary population of interest (ASD) as well as our primary discriminator population (non-ASD developmental concerns).

We will collect user data (caregiver and telemedicine clinicians) on satisfaction, ease of implementation, and diagnostic certainty (clinicians only). Based on this feedback, we will modify any of the preliminary instructions and procedures that are part of the current versions of the tools. To systematically measure acceptability and feasibility of use we will utilize The Acceptability, Likely Effectiveness, Feasibility, and Appropriateness Questionnaire (ALFA-Q). The ALFA-Q measures different elements of users' perceptions of an innovation's compatibility with a particular context. Participating parents and remote clinicians will rate aspects of the tool on a 5-point Likert scale (from 1 "not at all" to 5 "extremely") to indicate whether it is acceptable, likely effective, feasible, and appropriate for ASD screening and decision making. An overall rating of 80% or higher (average ratings of >4 on Likert scale) will benchmark our success. We will also ask for free-form input, and team leads will briefly interview each clinician and parent about their experience.

After each telemedicine evaluation, participating clinicians will review results of the participant's previous comprehensive evaluation process. This will give clinicians the opportunity to provide concrete task evaluation data regarding whether the telemedicine tool effectively elicited crucial diagnostic behaviors or information. We will also examine overall patterns of classification agreement. Our ultimate marker and benchmark of clinical decision making utility will be based clinician ratings of certainty of diagnosis of ASD as well as non-ASD developmental conditions. Certainty is operationalized as the clinician forced choice and Likert rating of certainty in classification (i.e. clinician when given option of uncertainty/other chooses ASD with high certainty). To this end we our establishing the following a prior criteria for accuracy and success: a) $\geq$60% of children with ASD with certainty (b) $\geq$50% children without ASD with certainty, and (c) $\leq$10% of children will be misclassified with ASD with certainty.

Based on this data, our investigative team will collaborate with our clinical design team to suggest modifications to the procedures. This sample size of 30 for each instrument is deemed adequate for detection of user/functionality/acceptability issues and for gathering the feedback

necessary for honing the procedures utilized in our rigorous evaluation of measure use in Aim 2. Although we are examining diagnostic agreements in this study, the larger rigorous, blinded evaluation described in Aim 2 is ultimately necessary to adequately test and understand the potential added value of these tools.

Specific Aim 2: After optimizing use and administration characteristics, we will deploy the refined TELE- STAT (n=60) and TELE-ASD-PEDS (n=60) assessment tools with clinically referred, undiagnosed children and rigorously evaluate their ability to facilitate accurate telemedicine supported diagnostic decision making. Secondary analyses will also compare the characteristics of these tools across these independent samples as well as potential scoring thresholds for the instruments for subsequent evaluation. Our team of 10 clinical providers will be asked to complete 6 remote evaluations utilizing TELE-STAT and 6 remote evaluations with TELE-ASD-PEDS. At the end of the procedure, the psychologist will complete ratings of clinical best estimate (CBE) diagnosis and diagnostic certainty (Yes / No ASD; Yes / No / Uncertain classification, as well as Likert rating of certainty ranging from 1= 'uncertain' to 5 = 'very certain'). Families will then immediately participate in a blinded in-person comprehensive assessment conducted by a different licensed psychologist. This assessment will include administration of a measures of cognitive functioning (MSEL), adaptive behavior (VABS-3), autism symptoms (ADOS-2), as well as clinical interviewing surrounding medical, behavioral, and developmental history. The blinded provider will then independently assign diagnostic and certainty ratings, and provide clinical information to the family.

The sample size of 60 per instrument is deemed adequate for initial preliminary evaluation of performance characteristics. Given the diagnostic confirmation rates of the referral base for this study (roughly 2/3 ASD; 1/3 non-ASD), we will have data capable of describing the concurrent validity and agreement of remote diagnostic decision making and telemedicine tool use with clinical best estimate diagnosis using a traditional assessment battery. We will examine agreements (True/False Positives and Negatives) and corresponding sensitivity, specificity, as well as positive and negative predictive value related to both ASD and non-ASD classifications. Based on our preliminary data, we hypothesize that clinicians utilizing both of the telemedicine assessment procedures will be able to accurately identify: (a) $\geq$60% of children with ASD with certainty (b) $\geq$50% children without ASD with certainty, and (c) $\leq$10% of children will be misclassified with ASD with certainty. Certainty is operationalized as the clinician forced choice and Likert rating of certainty in classification (i.e. clinician when given option of uncertainty/other chooses ASD with high certainty). We will also utilize non-parametric comparisons (chi-square) to evaluate differential performance clinical diagnosis using these tools relative to one another and ADOS-2 classification scores. We will not be adequately powered to systematically examine variability related to certain child, family, and clinician related characteristics; however, we will have preliminary data that could be examined to foster future systematic exploration of these factors in a larger controlled study, if successful. In similar form, our sample size with each instrument will afford us the ability to preliminarily apply signal detection to potential cutoff scores from the adapted rating (*TELE-ASD-PEDS*) and scoring procedures (*TELE-STAT*) associated with these instruments.