A+ Treatment/Feasibility: ACE Project 3

Sub-study: Feasibility trial of adapted ESDM-informed caregiver coaching delivered remotely for children with ASD and ADHD

Duke IRB Protocol Number: Pro00085179

Principal Investigator: Dr. Lauren Franz

Funded by: National Institute of Child Health and Human Development

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Summary of Changes

Version / Date	*Description of changes*	*Rationale*	*Date of Approval (iRIS version)*
V1.4/17 MAR 2022	*1. The protocol analysis section was updated/clarified to reflect the addition of a statistical analysis plan for the project. Primary outcomes, secondary outcomes, and exploratory outcomes were updated to match the plan.*	*1. The statistical analysis plan, protocol and CT.gov should all be in agreement to prevent any confusion.*	
V1.3/12 AUG 2021	*2. Removed 16 week physician check in.* *3. Clarified that if there is limited internet access participants can receive coaching through telephone and record interactions for both the PCI and ESDM sessions and upload to Duke BOX.* 4. Removed language that is not applicable to the protocol (section 6.4.1) - this section previously stated that participants will be asked to refrain from changing the type or intensity of other behavioral interventions during the study. 5. Removed information for Scott Kollins as former Co-I for the	*2. It does not impact the primary or secondary outcomes for the study and data (missed week 16 physician visits) is suggesting that participants are finding this to be a burden.* *3. We would like to ensure that parent coaching and study procedures are accessible to study participants that are unable to obtain high-speed internet access.* *3.and 4. – No longer pertinent to protocol. 3. was legacy language and this is a feasibility study so medications and behavioral interventions will not be restricted; if there*	*20 SEP 2021*

	ACE.	*is something that seriously impedes participation, then the study PI will take appropriate action to discontinue, withdraw, or provide participant with feedback on options .*	
V1.2/16 APR 2021	*1.Primary PI changed from Dr. Geraldine Dawson to Dr. Lauren Franz* *2.Updated inclusion criterion # 4 to allow for tele-ASD-peds used in clinic and further clarification of diagnostic assessment.* *3.Removing measures from protocol: CGI-I&S, ADHD-RS (clinician administered), and Sluggish Cognitive Tempo (AOA) questionnaire. Reducing the number of times the ADHD-RS (parent) caregiver completed form is assessed.* *4.Clarified what measures may need to be repeated if too much time has progressed through the assessment core (see SOA).* *5. Clarified procedures for conducting Qualitative Interview and consent process with*	*1.Dr. Franz has valuable experience to take on the PI role and this change helps balance other PI transitions across the ACE.* *2.We are including a telehealth assessment that is standard practice being used in younger children during COVID for ASD diagnosis.* *3.These assessments add additional time burden to the families and we feel that given the remote nature of the study they are not required assessments for primary end goals.* *4.Clarifying in the table of assessments what may need to be repeated* *5. The qualitative interview with staff, clinicians, and coaches requires a consent process and outlining of ways we will minimize bias and ensure*	*24 APR 2021 (iRIS Version 1.5)*

	stakeholders who are study staff.	*voluntariness.*	
v1.1 / *28 DEC 2020*	*Removed exclusion criterion (#5) which was based on presence of known genetic or other neurological condition; modified exclusion #1 to specify CNS active medications (not just ADHD medications) must be stable 4 weeks prior to baseline.*	*The presence of genetic or neurological condition alone is not expected to affect the suitability or applicability and potential benefit or risk profile of the intervention to children with these characteristics; removal of exclusion makes the sample more representative. It is ideal for all psychotropic medications to not change prior to baseline to reduce possibility of changes in medications/symptoms confounding data.*	*19 JAN 2021 (iRIS Version 1.3)*
v1.0 / *07 DEC 2020*	*First version, feasibility sub-study*	*Initiating feasibility sub-study*	*16 DEC 2020 (iRIS version 1.1)*

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

A+ Treatment: Feasibility trial of adapted ESDM-informed caregiver coaching delivered remotely for children with Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD); Duke Autism Center of Excellence (Duke ACE), Project 3; Protocol Pro00085179, v1.0 23 October 2020)

Study Description: This study will evaluate the feasibility of adapted ESDM-informed caregiver coaching in children with comorbid ASD and ADHD, who are between 36 and <132 months of age. There will be no study provided medication treatment in this study. Children will either be on ADHD medication prescribed by their own personal provider or will not be taking any ADHD medication (this will be documented by the study). The provided behavioral treatment will be eight ~60-minute sessions in ESDM-informed caregiver coaching remotely delivered weekly, for 8 consecutive weeks. The behavioral treatment is provided to children through Early Start Denver Model (ESDM)-informed caregiver coaching strategies, implemented within the child's typical daily routine by the caregiver. Pre-baseline procedures included screening and eligibility procedures, cognitive & diagnostic assessments. This was followed by baseline visit (Week 0), 8 subsequent weekly coaching sessions (Weeks 1 - 8), an endpoint visit (Week 9), and a follow up visit (Week 16).

Objectives: The overarching goal of A+ Treatment is to evaluate feasibility and gather

	pilot data of remotely-delivered ESDM informed caregiver coaching for children with ASD and ADHD which may inform future combination clinical trials (pharmacotherapy and behavioral intervention).
Primary Endpoint:	Using an implementation science approach we will characterize the acceptability, appropriateness, feasibility and fidelity of remotely behavioral intervention in the following ways: 1. Using 3 pragmatic measures: Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). 2. Conducting qualitative interviews (caregiver, clinician and staff) of perceptions regarding the intervention. 3. Assessing fidelity of intervention delivery, using adapted ESDM Fidelity rating scales.
Key Secondary Endpoints	The proximal outcomes of child and caregiver behaviors and sense of competence after the intervention. Key proximal outcomes will be change from baseline (pre-intervention) to 9-weeks (post-intervention) in caregiver sense of competence measured by the Parent Sense of Competence Scale and child behaviors measured by the sum of 4 items from the JERI (Joint Engagement, Attention to Caregiver, Responsiveness to Partner's Communication Bids, Fluency and Connectedness) coded by a trained, reliable coder who is naïve with respect to whether the observation is from baseline our outcome using video-recorded caregiver-child interactions.
Other Exploratory Endpoints	Additional exploratory outcomes will be change in caregiver ratings from baseline to 9-week in the following measures: a) ADHD-RS ratings of the child's attention; b) Aberrant Behavior Checklist (ABC), including inattention/hyperactivity, social withdrawal, stereotypies, irritability, and inappropriate speech; c) Social Reciprocity Scale-2 (SRS-2) ratings of child's social communication behavior; d) Caregiver Strain Questionnaire (CSQ) ratings of the impact of the child's condition on the family and caregiver and quality-of-life; e) Behavior Rating Inventory of Executive Functions (BRIEF) ratings of child's executive function; and f) Child Behavior Checklist (CBCL) ratings of child behavioral and emotional problems. Change from baseline (pre-intervention) to 16-weeks (8-weeks post-intervention) will be assessed for the VABS-3 Socialization and Communication Subscale Standard Scores.
Study Population:	~ 30-35 participants who are between 36 months and <132 months of age with comorbid ASD and ADHD.
Inclusion criteria	• Provision of a parent/guardian signed and dated informed consent form. • Stated willingness of parent/guardian to comply with all study

procedures and availability for the duration of the study.
- Child is between 36 months and <132 months of age at baseline.
- Child has a confirmed DSM-5 diagnosis of both ASD and ADHD, informed by results of assessments including: an ASD diagnostic assessment (Brief Observation of Symptoms of Autism [BOSA], Autism Diagnostic Observation Schedule, 2nd Edition [ADOS-2], or TELE-ASD-PEDS, and if applicable the Autism Diagnostic Interview - Revised [ADI-R]) and an ADHD diagnostic (a standardized ADHD Diagnostic Interview and the MINI psychiatric diagnostic interview).

Exclusion Criteria

- If continuing psychotropic (CNS-active) medications, must not have been changed within 4 weeks prior to baseline
- Significant visual, auditory or motor impairments that would preclude participation in ESDM-informed caregiver coaching or completion of key assessments.
- Inability of the caregiver participating in ESDM-informed caregiver coaching and responding to questionnaires to fluently speak English.
- Study clinician judgment that it is not in the best interests of the participant and/or the study for the child to participate (including presence of psychiatric conditions or psychiatric symptoms in addition to ASD and ADHD that in the opinion of the PI or based on senior clinical review, would confound assessments and/or affect participation in the study).

Description of Sites Enrolling Participants: Single academic center site in US.

Description of Study Intervention: All participants will receive eight consecutive weekly ~60-minute ESDM-informed caregiver coaching sessions.

Participant Duration: Total participation is expected to require a maximum of 20 weeks, including optional remote follow-up at 16 weeks. The A+ Treatment diagnostic and screening visits will generally occur between 1 and 6 weeks prior to baseline. ESDM-informed parent coaching will be delivered per the Schedule of Activities (SOA) for 8 weeks. Endpoint assessments will be completed after the final coaching visit. No medication will be provided by the study team. The final assessment will be obtained at 16 weeks after baseline.

1.2 Schema

Figure 1: A+ Treatment Schema A+ Treatment staff will meet with parents/caregivers to explain the study and to review the informed consent document with them. Eligibility in the A+ Treatment study will include meeting diagnostic and age criteria. ESDM-informed caregiver coaching begins after baseline assessments and will continue for 8 weeks. The primary outcome assessments will evaluate feasibility of ESDM-informed caregiver coaching in children ages 3-10. This study will be conducted remotely.

Week -2 to -1	Week 0	Weeks 1-8	Week 9		Week 16
Screen & Confirm Diagnose	Baseline	ESDM Sessions	Endpoint		Remote Follow-up
Diagnostic assessments Cognitive testing Parent questionnaires Vineland-3 parent report	Joint engagement Social communication ADHD symptoms AIM Parent questionnaires	ESDM Caregiver Fidelity ESDM Caregiver Self-Monitoring ESDM Coaching Fidelity	Joint engagement Social communication ADHD symptoms AIM Qualitative interview Vineland-3 parent report Parent questionnaires		Social communication ADHD symptoms Parent Questionnaires Vineland-3 parent report

1.3 Schedule Of Activities (SoA)

ACTIVITIES	Consent & Diagnostic Confirmation[&] & Feedback	Baseline/and call with Coach	Coaching W1	Coaching W2	Coaching W3	Coaching W4	Coaching W5	Coaching W6	Coaching W7	Coaching W8	Endpoint Assessments	Remote Follow-up
Typical Week offset from baseline[A]	prior	0	1	2	3	4	5	6	7	8	9	16
Informed consent	X											
Demographics, ACE subject Med Hx, ACE Fam Hx, Intervention Hx, [t]Spence	X											
Diagnostic & Cognitive testing	X											
ESDM-informed caregiver coaching		Brief call	X	X	X	X	X	X	X	X		
P-ESDM Caregiver Self-Monitoring checklist**			X	X	X	X	X	X	X	X		
ESDM coach fidelity *			*	*	*	*	*	*	*	*		
ESDM caregiver fidelity		X	X	X	X	X	X	X	X	X	X	
Remote PCIT JERI coding of child/ caregiver items		X									X	
Qualitative Interview											X	
AIM, IAM, FIM											X	
Caregiver Sense of Competence Scale		X									X	X
App S2K		X									X	X
ABC		X					X				X	X
Vineland-3 parent questionnaire	X										X	X
CBCL	X										X	X
ADHD-RS-parent	X										X	X
SRS-2	X	(X)[+]									X	X
Caregiver Strain Questionnaire		X									X	X
Condensed (non-ASD) Med Hx[2], AE's, Con Meds,		X	X	X	X	X	X	X	X	X	X	
BRIEF	X	(X)[+]									X	

A: no strict window for visits, but ideally post-baseline visits should be done within ± 7 days (relative to visit each time point from baseline); *: done once randomly

during sessions 2-8; **: completed by caregiver and coach; Green text: measures acquired in ARC and in P3; (X)+: only needs to be done if baseline done more than 3 months prior; 2: non ASD med history only done at baseline visit & diagnostic confirmation is informed by ARC assessments. Participants typically begin study participation within 1-3 months of completing the ARC evaluation (if the participant is eligible). However, we also expect that in some situations, (e.g., due to the COVID-19 pandemic) there may be a delay between the ARC evaluation and participation in the A+ Treatment/Feasibility sub-study. If this happens, the following assessments and/or parent-report forms may be repeated:

- If > 2 years since ARC completion: ASD diagnostic assessment (e.g., BOSA, ADOS, TELE-ASD-PEDS) and cognitive assessment (e.g., WPPSI/WISC, DAYC-2, DAS-2, Mullen)
- If > 6 months since ARC completion: CBCL
- If > 3 months since ARC completion of: SRS-2, VABS, ADHD-RS parent form

2 INTRODUCTION: SCIENTIFIC RATIONALE AND BACKGROUND INFORMATION

2.1 Rationale

The Significance on the Comorbidity of ASD and ADHD

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are highly comorbid, with ~40-60% of children with ASD having co-occurring ADHD and ~18% of children with ADHD exhibiting social communication deficits similar to those observed in ASD(11, 12). Multiple studies have shown that youth with ASD+ADHD often receive a delayed diagnosis of ASD, have worse clinical outcomes, require more restrictive environments and have caregivers experiencing higher levels of stress than those without ADHD(13-16). Studies that have examined the shared and distinguishing features of ASD and ADHD in school-age children suggest that each disorder is associated with a unique profile of attentional, behavioral, affective and cognitive processing problems that impact social communication and long term outcomes(17, 18). Specifically, ASD has been associated with difficulties in disengaging attention, reduced attention to social stimuli, reduced expression of positive affect and deficient early stage neural processing of social information. In contrast, ADHD has been associated with difficulties in selective and sustained attention and inhibitory control, challenging behaviors such as hyperactivity, increased negative affect, and deficient neural processing of higher order social information. Older children with comorbid ASD and ADHD have greater impairments than those with either ASD or ADHD alone. Thus, the difficulties typically associated with ADHD are likely to exacerbate the attentional, social, affective and neural processing impairments generally associated with ASD, leading to significantly greater initial and long-term impairments in children with ASD+ADHD. We posit that co-occurring ADHD symptoms also significantly impair the ability of children with ASD to respond to and fully benefit from ASD behavioral interventions, further increasing the functional gap between them and their peers with ASD alone throughout development. This idea is supported by a recent study reporting decreased efficacy of a social skills intervention for children with ASD+ADHD vs. peers with ASD alone or with ASD and comorbid anxiety(16).

Treatment Gaps for Young Children with ASD + ADHD

The impact of co-occurring ADHD symptoms on response to ASD behavioral intervention has not been studied. However, clinical observations suggest that ADHD behaviors significantly slow the pace of progress during intervention. Successful treatment depends upon increasing children's attention to social and nonsocial (e.g., toys) stimuli and sustained social engagement, both of which can be disrupted by inattention, hyperactivity, and negative affect, all of which are associated with ADHD. In addition, there is little information about the efficacy and tolerability of various medications to treat ADHD in children with ASD + ADHD. Finally, there are few ADHD medications available for children who are not able to swallow pills or capsules.

2.2 Background

Prevalence

Approximately half of children with autism spectrum disorder (ASD) have co-occurring attention-deficit/hyperactivity disorder (ADHD)(11, 12). Unfortunately, the long-term outcomes of individuals with comorbid ASD and ADHD (ASD+ADHD) are significantly worse than individuals with ASD or ADHD. Those with ASD+ADHD are often diagnosed with ASD significantly later and exhibit more behavioral problems, poorer peer relationships and increased use of restricted educational settings(13-15). As described in

the Duke ACE Overall Research Plan, we hypothesize that these negative outcomes in individuals with ASD+ADHD are, in part, the consequence of ADHD symptoms compromising the individual's ability to fully benefit from behavioral interventions for ASD, which all require the interventionist to acquire and sustain the child's attention. Consequently, we hypothesize that effective treatment of co-occurring ADHD symptoms will improve developmental and functional outcomes for children with ASD+ADHD.

ADHD Comorbidity with ASD Related to Impaired Verbal Working Memory and Verbal Delayed Recall

The main manifestations of ASD include impaired social interaction, communication, and restricted and repetitive patterns of behaviors. Although ASD is typically an exclusion criterion for ADHD according the DSM-5, several studies have reported ADHD symptoms co-occurring in subjects with ASD. A study by Andersen et al (19) studied 38 children with high functioning autism (HFA) with (+) and without (-) "attention problems" according to the Child Behavior Checklist, 79 with ADHD alone and 50 typically developing children. The children were administered a Letter-Number Sequencing test (LNS) where children are required to listen to a presentation of alternating letters and digits and afterwards asked to recall the numbers in ascending order and the letter in alphabetical order (19). It was found that children with HFA+ displayed significant impairment compared to other typically developing children in all three neurocognitive measures while those with HFA- only had greater impairments with working memory and acquisition measures. In addition, the HFA+ group scored significantly lower than the HFA- group and the ADHD group on verbal working memory and delayed recall measures.

Background and Justification for the Interventions and Neural Correlates to be Examined

Early Start Denver Model (ESDM(20)). ESDM is an empirically-validated, naturalistic, developmental, behavioral intervention for children with ASD who have mental ages between 12 and 60 months. Intervention strategies are delivered in the context of affectively- and socially-engaged joint activities between the child and adult. A key goal is to promote social attention and social engagement as a platform for teaching joint attention, imitation, language, motor, cognitive and social skills, and for reducing maladaptive, disruptive behaviors. Thus, this intervention provides an ideal context in which to evaluate our overall conceptual framework, which posits that ADHD symptoms impede the ability of children with ASD to acquire and improve sustained social attention and social engagement. ESDM was co-developed by Sally Rogers and Duke ACE Center PI Geraldine Dawson. An RCT demonstrated that, when delivered intensively by trained therapists, ESDM results in significant improvements in IQ, language, social abilities, and adaptive behavior. It was also found that children who received ESDM showed normalized brain activity, reflected in measures of EEG activity during viewing of social stimuli(21). ESDM also has been associated with significant reductions in clinician-rated maladaptive behaviors, with 68% of children showing reductions by 12 weeks and 79% after ~ 1 year(22).

Parent-delivered ESDM (P-ESDM) A parent delivered version of ESDM, parts of which will be used in this project, also has been developed, manualized, and evaluated. After the coach has assessed parent goals for their child, the therapist coaches that child's parents on ESDM strategies to increase social attention and motivation, social routines, joint activity routines, nonverbal

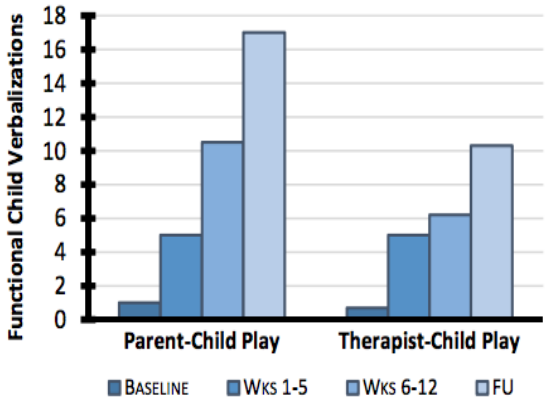

Figure 2: P-ESDM effect on communication[40]

communication, imitation, joint attention, speech development, functional and symbolic play skills, and management of challenging behavior in the context of parent identified social communication goals. The first study of P-ESDM evaluated the benefits of 1 hour/week of parent-coaching for 12 weeks in 8 children with ASD. Parents acquired the strategies and achieved fidelity by the 6th week(23). Children demonstrated sustained increases in joint attention, social engagement, social initiation, imitation and functional communicative behaviors (Figure 2).

Next, a larger (N = 98), NIH-funded RCT was conducted, evaluating the same brief 12-week, 1 hour/week of P-ESDM parent coaching vs. treatment-as-usual (TAU) in the community(21). The TAU group received significantly more hours of intervention, many of which were delivered by trained professionals. Both groups demonstrated similar statistically significant improvements in social symptoms and communication abilities, as measured by the ADOS social affect score and the Mullen Scales of Early Learning respectively. Parents in the P-ESDM group demonstrated significantly lower levels of parenting stress. A+ Treatment will utilize principles derived from P-ESDM for 8 caregiver coaching sessions.

Zhou et al. (24) evaluated the effects of a more intense version of P-ESDM that provided 1.5 hours/week of parent coaching for 6 months vs. treatment-as-usual in the community. The control group was comprised of children with ASD who did not live near the university where the study was being conducted, and, thus, could not feasibly attend weekly treatment. At baseline, there were no group differences in gender, birth history, parental education and income, parental age, or number of siblings. With appropriate controls for baseline scores and intervention hours received, the P-ESDM group showed significantly greater improvements on the Griffiths Mental Development Scales T-scores in the Social ($M = 5.4$ vs. -4.4; $p = 0.001$) and Receptive/Expressive Language ($M = 20.3$ vs. -6.6; $p < 0.001$) domains.

Research on the developmental impact of the intervention after parent coaching is relatively more limited, although the impact of therapist delivered ESDM is typically assessed after 1-2 years and benefits appear to increase over time.

Treatment of ADHD. Multiple treatment guidelines focused on ADHD in children recommend that initial treatment include behavioral management. In preschool children, behavioral treatment alone is recommended, while in school-aged children combined treatment with a stimulant medication and, if there is inadequate response, behavioral treatment is recommended (25). Although no specific form of behavioral treatment is recommended, general principles include: 1) modifying the environment to reduce distractions, facilitate organization (a specific logical place for each thing), and increase predictability; 2) setting small attainable goals, 3) providing visual tools for assessing progress and on task behaviors, 4) rewarding positive behaviors, 5) minimizing reinforcement of negative behaviors and 6) calm non-punitive discipline. Although behavioral interventions typically improve problem behaviors often associated with ADHD, there is no indication that they directly impact ADHD symptoms.

Multiple pharmacological treatments for ADHD have been demonstrated to have efficacy. These medications typically fall into the following categories: 1) stimulants within the methylphenidate class or the amphetamine class, 2) alpha adrenergic agents which seem especially helpful for hyperactivity, 3) norepinephrine reuptake inhibitors (atomoxetine, a selective norepinephrine reuptake inhibitor with a specific indication or venlaflaxine, which inhibits both norepinephrine and serotonin reuptake and does not have a specific ADHD indication), and other agents with theoretical actions that might increase dopaminergic tone. Stimulant medications are the mainstay of treatment because they act very quickly, have a well-established safety profile and their impact is readily apparent. Multiple different formulations of stimulants have been developed that vary primarily in terms of their formulations (liquid, tablet, capsule, transdermal) and their pharmacokinetic properties, generally with the goal of consistent benefit throughout the day with minimal on off periods. For any given stimulant medication,

approximately 70% of treated children with ADHD alone will respond. In the definitive clinical trial of methylphenidate and behavioral treatment of ADHD in school-age children the effect size of methylphenidate was 0.66 for parents and 1.33 for teachers (26, 27). Further, ~ 85% of school-aged children with ADHD alone will respond to some stimulant medication, suggesting the benefit of trying the other stimulant class or a different formulation if the initial stimulant medication is not beneficial. Methylphenidate preparations and amphetamine preparations have similar adverse effects, although one meta-analysis suggested that amphetamine preparations may be slightly better tolerated (28). However, more information is available about the use of methylphenidate preparations in very young children and in children with ADHD.

Impact of ADHD treatment of school-aged children with ASD+ADHD on Core ASD Symptoms. Jahromi et al. (44) evaluated a subset of 33 school-aged children with ASD+ADHD from the pivotal RUPP MPH study using an objective assessment of social communication functioning (the Joint Attention Measure from the Early Social Communication Scales, known as the JAMES). Optimal dose MPH, compared to placebo, resulted in significantly more joint attention initiations and responses during the assessment. In addition, the children demonstrated less negative affect during parent-child interactions while treated with MPH compared to treatment with placebo.

2.3 Specific Aims

Approximately half of children with autism spectrum disorder (ASD) have co-occurring attention deficit hyperactivity disorder (ADHD) (11, 12). Unfortunately, the long-term outcomes of individuals with comorbid ASD and ADHD (ASD+ADHD) are significantly worse than individuals with ASD or ADHD. Those with ASD+ADHD are often diagnosed with ASD significantly later and exhibit more behavioral problems, poorer peer relationships and increased use of restricted educational settings (13-15). We suspect these negative outcomes in individuals with ASD+ADHD are, in part, the consequence of ADHD symptoms compromising the individual's ability to fully benefit from behavioral interventions for ASD, which all require the interventionist to acquire and sustain the child's attention. Thus, we hypothesize that we can intervene to reduce negative outcomes in children with ASD+ADHD by concurrently providing ADHD treatment and ASD treatment.

The overall purpose of this project is inform the most feasible design of a future clinical trial combining ADHD treatment with ASD behavioral treatment in children with ASD+ADHD to test our hypotheses. To do this, we are evaluating the feasibility of various trial designs. This sub study will be delivered completely remotely and will allow participants and their families to choose whether to treat ADHD symptoms or not in consultation with community providers.

Aim 1. Assess implementation outcomes. Assess acceptability, appropriateness, feasibility, and fidelity of remotely delivered ESDM-informed caregiver coaching intervention which has been adapted for older children who have comorbid ADHD for delivery over a period of 8 weeks. Acceptability, appropriateness, and feasibility will be quantitatively and qualitatively assessed using 4-item, pragmatic scales and individual stakeholder interviews. Fidelity of intervention delivery, the degree to which programs are implemented as intended by program developers, is also an important implementation outcome. This will be monitored using an adapted version of the Parent Early Start Denver Model (P-ESDM) Caregiver Fidelity Rating System.

Hypothesis: we will be able to determine acceptability, appropriateness, feasibility, and fidelity by gathering this outcome data through selected endpoints.

Aim 2: Assess proximal and distal child and caregiver outcomes. Both proximal and distal outcomes will be measured. Key proximal outcome will be change from baseline (pre-intervention) to 9-weeks (immediately post-intervention) in caregiver sense of competence measured by the Parent Sense of Competence Scale and child behaviors measured by the sum of 4 items from the JERI (Joint Engagement, Attention to Caregiver, Responsiveness to Partner's Communication Bids, Fluency and Connectedness) coded by a trained, reliable coder who is naïve with respect to whether the observation is from baseline our outcome using video-recorded caregiver-child interactions.

Hypothesis: we will detect proximal changes in child and caregiver interactions and caregiver sense of competence.

Exploratory Outcome: In this exploratory outcome we will assess change in caregiver ratings from baseline to 9-week in the following measures: a) ADHD-RS ratings of the child's attention; b) Aberrant Behavior Checklist (ABC), including inattention/hyperactivity, social withdrawal, stereotypies, irritability, and inappropriate speech; c) Social Reciprocity Scale-2 (SRS-2) ratings of child's social communication behavior; d) Caregiver Strain Questionnaire (CSQ) ratings of the impact of the child's condition on the family and caregiver and quality-of-life; e) Behavior Rating Inventory of Executive Functions (BRIEF) ratings of child's executive function; and f) Child Behavior Checklist (CBCL) ratings of child behavioral and emotional problems. Change from baseline (pre-intervention) to 16-weeks (8-weeks post-intervention) will be assessed for the VABS-3 Socialization and Communication Subscale Standard Scores.

2.4 Risk/Benefit Assessment

2.4.1 Known potential risks

The caregiver coaching, questionnaires, and behavioral assessments to be used in this protocol present minimal physical or psychological risk; the probability and magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

There is a possibility that behavioral assessments and caregiver coaching and other tasks may at times cause some children or caregivers to experience fatigue or boredom or frustration. The clinicians and study staff are well-trained in working with families and children and have carefully designed activities that may be performed remotely through teleconference, telephone, and use of electronic surveys.

Clinicians and staff will explain activities or tasks to the caregiver by using educational materials, scripts, and speaking with them in advance as needed to explain what the remote assessments, interviews, and other study measures will entail. Study staff will use understandable language in verbal and written communication to help caregivers and the child prepare for visits, explain procedures to their child, and to help both the caregiver and child feel as comfortable as possible. Questionnaires and interviews may cause parents or children to feel uncomfortable. Breaks will be taken as needed. Participants will be

reminded that the assessments can be stopped at any time and their participation is completely voluntary.

Parents of children with ASD and/or ADHD symptoms may experience stress when results of diagnostic and cognitive testing are communicated to them. Before the child participates in the open-label study of A+ Treatment, they will have completed assessments with A+ Assessment. An experienced clinician will discuss the diagnostic results and any new findings (if applicable) with the family in a sensitive and competent manner and, whenever necessary, children will be referred for treatment or/and further evaluation at Duke University or in the community, as appropriate. Incidental findings could include receiving information about a child's cognitive functioning or diagnosis that was unexpected by the parent. This information would be explained to the parent by an experienced and licensed psychiatrist or psychologist, along with recommendations for services at Duke or in the community, if appropriate.

Children with ASD and ADHD may exhibit behaviors such as tantrums and other challenging behaviors, and can these worsen in severity without appropriate intervention. It is anticipated that these events could occur during the course of the study due to the nature of the child's conditions, and may occur during study activities. If they do happen, the study staff will reassure the parent they may take a break and coach them as needed to help address the behavior in the moment. Our staff and clinicians are well trained to address these difficulties with children with ASD, ADHD, and other developmental conditions.

There is a potential risk for a loss of confidentiality due to reasons beyond our control. Our study processes and data storage and security methods, overseen by the DMAC, are designed to minimize these risks. All information that is collected in connection with this study will remain confidential and will only be disclosed as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse and neglect of a child. Every foreseeable precaution to protect confidentiality will be taken. Nevertheless, despite such precautions, there are always risks to confidentiality with participation in any study of this kind as researchers will have access to subjects' medical records and protected health information.

2.4.2 Known potential benefits

All participants in this trial will receive 8 sessions of ESDM-informed caregiver coaching, a well-accepted parent coaching behavioral intervention from expert providers free of charge. The ESDM-informed caregiver coaching is expected to facilitate the caregiver's use of ESDM behavioral intervention strategies in multiple daily living contexts on a daily basis for an extended period. The caregiver implementation of these strategies and techniques is expected to promote the development of participants and to provide a sense of self efficacy for participating caregivers. Such therapy is currently often hard to access in the community so immediate access may be of benefit. Finally, the Vineland assessments may be useful in further treatment and/or educational planning. However, there is no guarantee that any one participant will benefit from participation.

2.4.3 Assessment of potential risks and benefits

The benefits outweigh the risks given that the caregiver can withdraw from the study at any time. They can decline to respond to any question or assessment at any time.

There is a scarcity of accessible and effective behavioral interventions for individuals with ASD and ADHD, and the current pandemic makes access to therapies and support even more challenging. Based on extant clinical evidence and empirical data on the positive impact that behavioral intervention and parent coaching (in the traditional format) has on child development, family wellbeing, improvement in ASD symptoms and daily functioning, it is our hope and belief that participation in the caregiver coaching component (remotely) may bring some benefit to the families in this study in both the short and long term. The study will also make this form of support and coaching more accessible to families that currently do not have such access. If the risks (such as psychological discomfort related to any of the assessments) outweigh this benefit for any one individual, they may withdraw at any time without any penalty or loss of services they would otherwise have access to. By maintaining contact with participants, and conducting assessments and questionnaires designed to measure participant wellbeing and symptoms during the course of their participation, study clinicians will be able to help detect and determine if it is no longer in the interest of the family to participate. This includes assessment of AEs which will allow us to track closely whether any symptoms are worsening or if new ones are to appear. Participants will be informed during the consent process and throughout their participation that their involvement is always completely voluntary and will always receive support in making decisions that beneficial to them and their child.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
PRIMARY	
Determine implementation outcomes including acceptability, appropriateness, feasibility, and fidelity.	Acceptability, appropriateness, and feasibility will be quantitatively and qualitatively assessed using 4-item, pragmatic scales and individual stakeholder interviews. Fidelity of intervention delivery, will be monitored using an adapted version of the Parent Early Start Denver Model (P-ESDM) Caregiver Fidelity Rating System.
SECONDARY	
Determine proximal changes in child and caregiver interactions and caregiver sense of competence	A key proximal outcome will be change from baseline (pre-intervention) to 9-weeks (immediately post-intervention) in caregiver sense of competence measured by the Parent Sense of Competence Scale and child behaviors measured by the sum of 4 items from the JERI (Joint Engagement, Attention to Caregiver, Responsiveness to Partner's Communication Bids, Fluency and Connectedness).
Other Exploratory behavioral outcomes at 9 weeks and 16 weeks	
Assess core ASD social	• Social Responsiveness Scale-2 (SRS-2)(66-68)

OBJECTIVES	ENDPOINTS
functions, ADHD symptoms, symptoms and adaptive functioning	• Aberrant Behavior Checklist-2 (ABC)(69, 70) • ADHD-RS • VABS-3
Assess other aspects of attention and executive function	• Behavioral Rating Inventory of Executive Function (BRIEF)(77, 78)
Other Relevant Behaviors	• Child Behavior Checklist (CBCL)(79)
Caregiver functioning & attitudes toward treatment	• Caregiver Strain Questionnaire (CSQ)(83, 84)
Safety assessments	• Treatment emergent adverse effects assessed based on spontaneous report from parent/caregiver

4 STUDY DESIGN

4.1 Overall Design

The overall study design and key outcomes and assessments are shown in the Schema in the synopsis.

The provided behavioral treatment will be eight consecutive weekly ~60-minute coaching sessions delivered remotely. The ESDM-informed caregiver coaching is a modification of the evidence-based behavioral treatment of ESDM, which is typically delivered as 20 hours/week of 1:1 interaction between the child and a trained therapist over a 2-year period. The ESDM-informed caregiver coaching modification reduces rigid time demands on families and is more likely to be sustainable and available in the current healthcare environment. Additionally, the remote implementation of the intervention allows this to be utilized in pandemic conditions and in rural communities where it may be difficult to travel to an academic center for sessions.

4.2 Scientific Rationale for Study Design

The intention of the study is *not* to evaluate the efficacy of the behavioral intervention, which is informed by a widely accepted, clinical intervention that has demonstrated efficacy compared to usual care treatment that did not include ESDM at the time. Instead, we are assessing the feasibility of an adapted caregiver delivered ESDM behavioral intervention given remotely in children with a dual diagnosis of ASD and ADHD.

Our hypothesis, shown below, is that children with ASD+ADHD have poorer outcomes than those with ASD alone because their ADHD symptoms interfere with their engagement in ASD behavioral interventions.

By understanding rates of enrollment, acceptability, appropriateness, and feasibility of a behavioral intervention delivered remotely to caregivers of children with both ASD and ADHD we can begin to develop a more informed **patient centered** phase 2 study which would address both a medication component and behavioral intervention for the treatment of ASD and ADHD.

4.3 Justification for Dose

No study-provided medication

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed the endpoint assessments of all phases of the study or has been withdrawn from both treatment and assessments in the study. If a participant chooses to stop behavioral treatment in the study before endpoint assessments, he or she will be requested to complete them on schedule if at all possible. The follow-up visit at 16 weeks following baseline is optional.

5 STUDY POPULATION

The planned sample size is 35 children. There are no limitations related to sex, race or ethnicity.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of a parent/guardian signed and dated informed consent form.
2. Stated willingness of parent/guardian to comply with all study procedures and availability for the duration of the study.
3. Child is between 36 months and <132 months of age at baseline.
4. Child has a confirmed DSM-5 diagnosis of both ASD and ADHD, informed by results of assessments including: an ASD diagnostic assessment (Brief Observation of Symptoms of Autism [BOSA], Autism Diagnostic Observation Schedule, 2nd Edition [ADOS-2], or TELE-ASD-PEDS, and if applicable the Autism Diagnostic Interview - Revised [ADI-R]) and an ADHD diagnostic (a standardized ADHD Diagnostic Interview and the MINI psychiatric diagnostic interview).

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. If continuing psychotropic (CNS-active) medications, must not have been changed within 4 weeks prior to baseline.
2. Significant visual, auditory or motor impairments that would preclude participation in ESDM-informed parent coaching or completion of key assessments.
3. Inability of the caregiver participating in ESDM-informed caregiver coaching and responding to questionnaires to fluently speak English.
4. Study clinician judgment that it is not in the best interests of the participant and/or the study for the child to participate (including presence of psychiatric conditions or psychiatric symptoms in addition to ASD and ADHD that in the opinion of the PI or based on senior clinical review, would confound assessments and/or affect participation in the study).

5.3 Lifestyle Considerations

None applicable.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the diagnostic portion and the study but are not subsequently enrolled. Individuals who initially express interest but do not consent to or attend ARC visits will also be considered as part of the number approached for determining rates of enrollment.

5.5 Strategies for Recruitment and Retention

The target sample size is 30-35. We anticipate that 20% or less of the sample will be female due to the lower prevalence of both ASD and ADHD among females. We expect that Caucasians will be modestly overrepresented in the sample due to increased historical comfort with clinical trials than minorities. Further, among minorities we anticipate that Hispanic individuals will be most underrepresented in the sample due to requirements that the parent participating in ESDM-informed caregiver coaching be fluent in English. We expect to enroll 1-3 participants per month.

Participants will be recruited from A+ Assessment, A+ Health, A+ Development, community advertisements, medical records, and physician contacts. Recruitment strategies include: developing radio and newspaper ads and brochures, using social media, attending community events, delivering community talks, meeting with various agencies who provide clinical and educational services for children, developing and maintaining active relationships with local autism and ADHD advocacy and support groups, and reaching out to community pediatricians, family practice doctors, child psychiatrists and psychologists, early intervention programs, and schools to make them aware of the treatment needs of children with ASD+ADHD and the availability of A+ Treatment. We will also approach churches and cultural institutions that serve primarily African American, Hispanic and/or Asian populations about giving informational talks and providing informational materials to increase minority recruitment.

Retention: A+ Treatment staff including behavioral therapists will maintain regular ongoing contact with all participants and their families to facilitate retention and discuss any concerns that may arise. We anticipate that any concerns will be adequately addressed during the weekly ESDM-informed caregiver coaching visits. If necessary, some parts of the diagnostic and major assessment visits can be split into 2 visits up to one week apart if the family prefers. In addition, the recruitment core may send birthday/holiday cards, distribute newsletters, and e-blasts; provide diagnostic reports that summarize testing results; provide clinical referrals; and give regular updates about Duke ACE Center and DCABD research and activities.

Incentives for Participation: We will provide participants with $50 for completing each visit and its associated assessments, for each coaching session, and for the remote follow-up assessment completion for a maximum of $550 to help compensate for participation in this protocol. We will also provide incentives for children during assessments and provide each child with a certificate when he/she completes the study. In addition, the opportunity to receive ESDM-informed caregiver coaching as part of the study without extensive waiting and at no cost is anticipated to be an incentive. We will also provide the participant with reports of Vineland and diagnostic assessments if requested.

Qualitative interviews and surveys with staff, coaches and clinicians: to prevent any undue influence, clinicians, coaches and staff will be asked by a non-supervisor team member whether they wish to do the qualitative interview/survey, and it will be stressed that they are free to say no, that their decision will have no impact on their employment, performance evaluations, or standing, and that they should only participate it if they are completely comfortable doing so. Those who *do* decide to participate in the interview and/or survey will not be provided with compensation beyond what they are paid for that time as part of their study role (this means the time taken to do the interview and/or survey will be done as part of, and will count towards, their regular working hours). To minimize bias when staff, clinicians, and coaches share about their experiences and opinions, and to ensure voluntariness in the consent process, we plan to have a study team member who is not the interviewee's supervisor or mentor conduct the interview and the consent processes.

Rationale for Selection Criteria: We have included children between 36 months and < 132 months of age in order to facilitate recruitment. We excluded children below 36 months' chronological age in order to ensure that ADHD can be reliably diagnosed. We are allowing additional comorbid diagnoses or symptoms because studies suggest that a substantial percentage of children with ASD+ADHD will have a third psychiatric diagnosis or other symptoms, and we would not be able to reach our recruitment goals if these children were excluded. Additionally, the study will not exclude participants solely on the basis of a known genetic or neurological condition, as this would unnecessarily prevent otherwise eligible children with ASD and ADHD from participating in and potentially benefiting from this intervention. Furthermore, behavioral intervention in not anticipated to pose an additional risk due to these characteristics; inclusion will also allow for a more representative sample. Participants may be found ineligible if, according to study clinician judgment, it is not in the best interests of the participant and/or the study for the child to participate (including presence of psychiatric conditions or psychiatric symptoms in addition to ASD and ADHD that in the opinion of the PI or based on senior clinical review, would confound assessments and/or affect participation in the study). All children will be administered the Child Behavior Checklist (CBCL), which is a widely-used, well-normed, and empirically validated tool to facilitate diagnosis of other psychiatric problems. If a child has clinically elevated scores, this will be followed up with a semi-structured diagnostic interview by an expert clinician.

Attrition: We conservatively estimate that ~15% will not be able to meet the time, technology demands of the study.

6 STUDY INTERVENTION

6.1 Study Interventions Administration

6.1.1 Study medication intervention description

No study medication provided. This study will enroll both participants who are on ADHD medication (prescribed by a personal provider) or those who chose to not take medication.

6.1.2 Medication dosing and administration

No study medication provided. This study will enroll both participants who are on ADHD medication (prescribed by personal provider) or those who chose to not take medication.

6.1.3 Study Behavioral Intervention Description

All participants and their caregivers will receive the same behavioral intervention. The therapist will discuss and identify appropriate goals for the participant in the first treatment session. Coaching sessions are a modification of the evidence-based behavioral treatment known as ESDM(20), which is typically delivered as 20 hours/week of 1:1 interaction between the child and a trained therapist for a 2 year period. ESDM-informed caregiver coaching modification reduces demands on families and is more likely to be available and sustainable in the current healthcare environment. Each participant and his/her caregiver(s) will meet with the behavioral therapist for eight ~60 minute consecutive weekly sessions. During these sessions, the therapist will coach the caregiver in developing specific skills and strategies to engage the child and promote the child's social, communicative and cognitive development. Sessions will begin with a free play session in which the therapist will assess parent fidelity to and comfort with previously taught strategies. Then the therapist will check-in with the caregiver regarding any issues or successes during the prior week and will review the new technique/strategy to be learned and practiced during the session. Subsequently, the caregiver will practice of the technique with his/her child with feedback and suggestions as needed from the therapist. At the end of the coaching session, the therapist and the caregiver will discuss potential opportunities for utilizing the strategy and other strategies presented in earlier sessions during the coming week (homework). The caregiver will also be provided with a book that describes some strategies used in ESDM-informed parent coaching. The caregiver is expected to utilize the strategies when interacting with his/her child in naturalistic situations on a daily basis. More than one caregiver may attend one or more coaching sessions, but the same caregiver is expected to commit to attending all coaching sessions. The therapists will have been trained in ESDM-informed caregiver coaching by a certified ESDM trainer.

If live Zoom recording of ESDM coaching sessions is not feasible (e.g., unstable or there is no high speed internet connection), participants will be allowed to record the ESDM sessions on their own device and upload the video to a unique Duke BOX link created by the study team for the participant. The ESDM sessions may also take place asynchronously (videos recorded before coaching feedback) and done over phone instead of Zoom. Participants will receive verbal and written instructions for how to self-record ESDM videos using their own device and upload into Duke BOX. Other strategies may also be used by

the team to facilitate access and engagement. For example, a hot spot may be provided to participants if they are in remote locations.

Participants will be asked at enrollment/screening/ ARC about access to internet and familiarity with technologies in order to help with planning of A+ Treatment sessions and internet/technology access needs.

The total number of caregiver coaching visits attended will be tracked, the parent's use of ESDM techniques will be assessed at coaching sessions 1-8 by the therapist (scale of 1-3), and the therapist's fidelity to the parent coaching model will be assessed from a video recording of one random sessions during the course of each participant's treatment by an independent rater.

6.2 Clinical Trial Supplies Preparation/Handling/Storage/Accountability

No study medication provided. This study will enroll both participants who are on ADHD medication (prescribed by personal provider) or those who chose to not take medication.

6.3 Measures to Minimize Bias: Randomization And Blinding

All participants will be treated openly with caregiver coaching with no randomization occurring and no blinding occurring. If participants choose to take ADHD medications that will be done separately from the study with no randomization or specific rules for treatment.

6.4 Study Intervention Compliance

No study medication provided. This study will enroll both participants who are on ADHD medication (prescribed by personal provider) or those who chose to not take medication.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

7.1 Study Halting Rules

The DSMB may choose to halt the study at any time they feel there is significant risk to participants as a result of study procedures or as a result of the study behavioral treatment (ESDM-informed caregiver coaching), or of specific study assessments. Since the behavioral treatment is well accepted in the community and does not appear to have specific safety concerns and the assessments are used in a wide variety of studies of young children with ASD and have never been shown previously to result in significant safety risks we expect there will be very low risk for study halting due to safety concerns.

7.2 Rules for Individual Participant Discontinuation in Study Interventions

Participants' caregivers may choose to discontinue the study behavioral caregiver coaching intervention at any time for any reason. Similarly, the study physician or therapist may choose to withdraw the participant at any time if the physician or therapist feels that it is not in the participant's best interest to continue.

7.3 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance,
- If any adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant,
- The entire study has been halted.

The reason for participant discontinuation or withdrawal from the study will be recorded on the End of Study CRF.

7.4 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to attend planned study visits over the time period described in the SOA and is unable to be contacted by the study site staff after 3 attempts by 2 methods including email and phone.

The following actions must be taken if a participant fails to attend required study visit:

- The site will attempt to contact the participant's caregiver by phone, email and/or regular return receipt mail at least 3 separate times over the period window (see SOA). These contacts will be recorded.
- If the study staff is able to reach the participant's caregiver, staff will counsel the participant's caregiver on the importance of maintaining the assigned visit schedule and ascertain if the participant's caregiver wishes to and is able to continue in the study. If the caregiver is willing to continue, study behavioral caregiver coaching visits will be resumed as soon as possible. Missed sessions will not be rescheduled outside the session window of +/- 3 days.
- If the study staff is able to reach the caregiver, every effort will be made to encourage the participant's caregiver to participate in the final outcome assessment.

8 STUDY ASSESSMENTS AND PROCEDURES

- **Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM).** (Weiner et al., 2017) These measures have been administered to a wide range of stakeholders to determine the extent to which they believe an intervention or implementation strategy is acceptable, appropriate, and feasible. Readability is at the 5th grade level. Higher scores indicate greater acceptability, appropriateness, and feasibility. The

AIM, IAM, and FIM have demonstrated content validity, discriminant content validity, reliability, structural validity, structural invariance, known-groups validity, and responsiveness to change. This measure will be completed with participants who enroll in the study, as well as coaches, clinicians, and support staff who consent to conduct the Qualitative Interview and AIM-IAM-FIM survey.

- **Two Early Start Denver Model (ESDM) fidelity scales will be utilized in this study:** (1) ESDM Coaching Fidelity Rating System; and the (2) Parent Early Start Denver Model (P-ESDM) Caregiver Fidelity Rating System. The ESDM Coaching Fidelity Rating System evaluates 14 coaching behaviors during the caregiver coaching sessions. Items are individually rated with a Likert-type rating scale with values that vary from 1 to 4, with higher scores reflecting a greater degree of fidelity. A portion of the items evaluate specific activities within the intervention session (e.g., warm-up activity, coaching on the topic) and the remaining items assess coaching characteristics which are evaluated across the entire session (e.g., reflective, nonjudgmental). The P-ESDM Caregiver Fidelity Scale provides a method for assessing the fidelity with which a caregiver is using ESDM principles in a joint activity routine with their young child. The 13 item rating scale includes ratings of performance from 1 to 3.

- **Caregiver Sense of Competence Scale** (also known as Parenting Sense of Competence) is a caregiver self-report measure that was initially developed by Gibaud-Wallston and Wandersman (1978) and was translated and revised by Johnston and Marsh (1989) to assess parenting sense of competence in 3-17-year-old children. It is a 16 item 6-point Likert scale questionnaire with ratings ranging from strongly agree (1) to strongly disagree. It includes 2 validated factors: satisfaction (9 items) and efficacy (7 items). Several of the items are reverse coded (highlighted in yellow on the form). There is an optional 17th question about the reward of being a good parent/caregiver.

- **Vineland Adaptive Behavior Scales—Third Edition (Vineland-3).** This assessment examines the child's adaptive functioning. These are day to day behaviors one uses to live and get along in the world. There are several domains including: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behaviors. The Parent/Caregiver Forms are administered through Q-global Remote On-Screen Administration (ROSA).

- **Parent-Child Interaction Task (PCIT)** is a remote six-minute free play task between a caregiver and child that serves as a naturalistic, observational measure of social engagement and dyadic interaction. Eight standardized toy categories are designated for this task, with toys being selected for each category from those available in the family's home. The PCIT is conducted remotely via a secure Zoom recording in the family's home. The PCIT consists of a pre-visit Zoom call with the caregiver, and then the separate PCIT session with the caregiver and child. During the pre-visit call, the examiner and caregiver work together to select toys for each category; to determine the best location in the home for the PCIT session; to determine the recording device and best camera angles for the recording; and to review the general plan for the PCIT session. The PCIT remote recording session involves a review of the room setup with the caregiver and instructions for just the caregiver, followed by the 6-minute play session with the caregiver and parent. After recording PCIT sessions, videos will be quality reviewed and trimmed. Behavioral coding of trimmed videos using selected items from the Joint Engagement Rating Inventory (JERI) will be conducted in Noldus Observer XT software. If live Zoom recording of PCI sessions is not feasible (e.g., unstable or there is no high speed internet connection), participants will be allowed to record the PCI videos sessions on their own device and upload the video to a unique Duke BOX link created by the study team for the

participant. The PCI sessions may also take place asynchronously (videos recorded before coaching feedback) and done over phone instead of Zoom. Participants will receive verbal and written instructions for how to self-record PCI videos using their own device and upload into Duke BOX. Other strategies may also be used by the team to facilitate access and engagement. For example, a hot spot may be provided to participants if they are in remote locations.

- **Qualitative interview** with stakeholders. Questions in the interview will be tailored to stakeholder group (Caregivers, Coaches, Clinicians, or Staff) and will be informed by previous studies that have examined barriers and facilitators during the implementation of a new treatment approach. Interviews will be conducted with caregivers after they have completed coaching sessions and with coaches and staff once they delivered the intervention and supported coaching activities. For study coaches, clinicians, and/or staff who are interviewed, they will be consented by the regulatory coordinator or other trained person who is not the PI and does not have a supervisory or mentoring relationship with the interviewee. Similarly, the interviewer will also be a trained individual who is not a supervisor or mentor of the interviewee. This will help ensure that the consent is voluntary and minimize bias in the answers and feedback given during the interview. A separate, IRB-approved consent form will be used for consenting staff, clinicians, and coaches who give their permission to complete the Qualitative Interview and AIM-IAM-FIM survey.

- **The Preschool or School age ADHD Rating Scale –** the parent rating version of the ADHD-RS will be used to assess ADHD symptoms.

- **SenseToKnow (S2K).** Children may complete this task remotely (app) . The app is delivered on a mobile device which uses computer vision analysis to code visual attention and affective expressions in response to brief videos presented on the device. Stimuli consist of a series of video clips including toys that make noise, a man blowing bubbles, bubbles cascading and popping, and a puppy video with unexpected events. Children will sit on the caregiver's lap or a chair with the mobile device at eye level for the child. Children will watch videos and play games that are presented on the mobile device. During the S2K administration, the app generates a video and audio recording of the child's responses to the stimuli in the movies. All sensor information gathered on the iPhone or iPad will be collected. At the completion of the S2K administration, either the study staff or the parent/caregiver will upload the saved recording of the enrolled participant to a secure study database for analysis. Overall, the entire task will take approximately 10-15 minutes. Children will be allowed to take breaks between videos and games as needed. A research assistant will be available to answer questions.

- **Aberrant Behavior Checklist – 2nd Edition Community Version (ABC)** is a parent report measure that was initially developed for use with intellectually disabled children and adults in residential settings but has been validated for use with individuals with ASD living in the community. Reference values are available from large samples of individuals with ASD. The ABC includes 5 subscales: irritability, attention, lethargy/social withdrawal, repetitive behaviors, and abnormal language. Each of the 40 items is rated from 0 – not at all a problem to 3 – very much a problem. Respondents are asked to rate behaviors in comparison to typically developing individuals. The ABC will be obtained at baseline and endpoint.
- **Behavior Rating Inventory of Executive Function (BRIEF)** The BRIEF is a caregiver report measure that assesses age appropriate executive function behaviors for children. The preschool BRIEF is for children between 3 years and 5 years 11 months and the BRIEF-2 is designed for children 6 and

older. The same version of the BRIEF will be used at baseline and endpoint to assess changes over time. The following domains will be examined: inhibition, shifting, emotional control, working memory and planning.

- **Caregiver Strain Questionnaire (CSQ)** The CSQ is a caregiver completed measure with 21 questions assessing the impact of a child with a developmental disorder or behavioral disorder on the caregiver and the rest of the family. Questions are rated on a 5 point scale from not at all a problem to very much a problem. In the original version one item is reverse scored. We will use a version in which the question is rephrased to avoid reverse scoring. The scale has 3 subscales: objective, internalizing and externalizing. It takes about 5 minutes to complete.
- **Child Behavior Checklist (CBCL)** The CBCL is a caregiver- completed scale that assesses problem behaviors using a 3 point scale (*not true*, *somewhat or sometimes true*, and *very true or often true*) over the prior two months. The preschool version is designed for children 1.5 to 5 years and contains 99 items. The school age version is designed for children 6-17 and contains 118 items. The behavioral domains that are assessed include Emotionally Reactive; Anxious/Depressed; Somatic Complaints; Withdrawn; Attention Problems; Aggressive Behavior and, in the older version, sleep problems. There are also DSM-oriented scales that are consistent with DSM-5 diagnostic categories. Depressive Problems; Anxiety Problems; Autism Spectrum Problems; Attention Deficit/Hyperactivity Problems; Oppositional Defiant Problems. The scale is standardized to provide a mean T score of 50 with a standard deviation of 10. Higher scores reflect more impairment. It has been studied in samples of both school-aged and preschool children with ASD, other psychiatric disorders and typical development(85, 86). It takes about 15 min to complete. http://www.aseba.org/preschool.html
- **Social Responsiveness Scale- Revised (SRS-2)** is a parent report version characterizing various social and repetitive behaviors associated with ASD. The scale's 65 items are rated between 1 and 4 and typically can be completed within 10 minutes. It is designed for use in children between the ages of 2 ½ – 18 years. It contains subscales assessing social awareness, social cognition, social communication, social motivation, and restricted and repetitive behaviors. The measure has been standardized on a large sample including individuals with typical development and demonstrated to be distributed along a continuum. Threshold scores suggestive of ASD have been determined separately for boys and girls. Caregivers of participants between ages 2.5 and <4 years will receive the Preschool SRS-2, and those ages 4 and above will be asked to complete SRS-2 School age version. The SRS will be obtained at baseline and endpoint.

8.1 Other Assessments

- **ACE Medical and Family History forms**: Caregivers will be administered the ACE Subject Medical History Form, and the ACE Family Medical History Form at the screening visit. The ACE Subject Medical History Form will provide a detailed developmental history and systematic review of problems in each body system using a standardized data dictionary shared across all ACE funded projects. The ACE Family Medical History Form elicits the developmental and neuropsychiatric history of parents, full- and half-siblings in a similar standardized and shared format. The study physician will review the ACE Subject Medical History and ACE Family Medical History forms completed by the A+ Assessment Core prior to interviewing and examining the participant and his/her parents.

- **The Condensed (non-ASD) Medical History Form** is completed at Baseline and Weeks 1-9. It is similar to that used by physicians during routine clinical visits and in clinical trials. It is focused on issues that aren't clearly related to the etiology of ASD and that may inform assessment of adverse events during the course of the trial.

- **Assessment of adverse events:** AEs are collected at Baseline and Weeks 1-9. At each of these time points, the participant's caregiver will be asked an open-ended question about new medical/behavioral problems or significant worsening of existing problems. Responses to these will be reviewed by study staff and the study physician to determine whether any further action is necessary to mitigate risks. Any treatment emergent adverse events (i.e. events not included in past medical history or present at baseline or events that significantly increase in intensity rating from the intensity at baseline or in the PMH) will be recorded. Upon resolution of the AE or at Week 9, each problem's relatedness to the study interventions will be assessed. The adverse event form will include information about intensity, start and stop dates, relatedness to study procedures and status of AE when it resolves or at Week 9.
- **Concomitant Medication Log**: At the first visit (Baseline), the physician will make a list of any medications the subject is currently taking. The concomitant medication log will also be completed at each of the Weeks 1-9 time points.

8.2 Adverse Events and Serious Adverse Events

8.2.1 Definition of adverse events (AE)

Adverse event means any untoward medical/legal occurrence that happens during the course of the study, whether or not the medical occurrence is considered intervention-related (21 CFR 312.32a). Adverse events will be specifically elicited using open ended queries. If an AE has a severe adverse event rating of "Severe" and is an Unexpected Problem (UP) (meaning a problem not previously seen or expected in children with ASD and ADHD), then the event must be documented and reported as a UP (see below, 8.3.2),. If a TEAE is a Serious Adverse Event (SAE), but not an UP, the SAE will be documented and reported accordingly (see below, 8.2.6).

8.2.2 Definition of serious adverse events (SAE)

An adverse event (AE) is considered "serious" if it results in any of the following outcomes: death, imminent threat of death, inpatient overnight hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or an offspring's congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.3 Classification of an adverse event

Intensity of Event:

- **Mild:** Mild events require minimal or no treatment and do not significantly interfere with the subject's daily activities for more than a day or two.

- **Moderate:** Moderate events lead to consideration of medical evaluation or treatment and typically cause some significant interference with functioning for multiple days.
- **Severe:** Severe events prevent a subject's usual daily activity for an extended period of time and are usually incapacitating during that period. Medical evaluation and treatment are generally required if such treatment exists.

Expectedness:

The study PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention or procedure or with typical experiences of children with ASD.

8.2.4 Time period and frequency for event assessment and follow-up

The occurrence of a treatment emergent adverse event (TEAE) or serious adverse event (SAE) may come to the attention of study personnel during study visits or other contacts with participants or communication from other medical providers caring for the study participant. All non-serious TEAEs will be followed up until satisfactory resolution or the child completes participation in week 9 of the study. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

8.2.5 Adverse event reporting

All AEs not meeting the criteria for SAEs will be captured in the through a general AE inquiry. Information to be collected initially includes event description, clinician's assessment of intensity, relationship to study procedures (note NO study medication provided). If the event has resolved that will also be collected. AEs will be followed to adequate resolution or the completion of the child's week 9 visit in the study. Any medical condition that is present at the time that the participant is screened or at the week 0 visit will be considered as past medical history and not reported as a treatment emergent AE unless there is a significant increase in the condition's intensity leading to a change in the intensity rating.

8.2.6 Serious ADVERSE EVENT REPORTING

An SAE is defined as an AE that meets certain conditions as defined in section 8.3.2. As soon as study staff become aware of a possible SAE, they will notify the study physician and study PI.

The study physician or PI will review and evaluate the potential SAE, obtaining external medical records if possible.

If the event is deemed to be an SAE:

- The ACE Center PIs will be notified within 24 hours.
- Record event in a NTF

- The study clinician (MD)will follow the trajectory of the SAE until it is resolved or deemed to be clinically stable or for 1 month following the week 16 visit.

Timeline for reporting of SAEs is:

- DSMB: The PI will report SAEs that are considered possibly related to study treatment to the DSMB within 14 days of being made aware of their occurrence.
- IRB: SAEs will be reported to the IRB in the context of the annual report or within 14 days of being made aware of the SAE's occurrence if it is considered related and unexpected or results in death.
- NICHD: The ACE center co-PIs and study PI will report SAEs that result in death to the NICHD program officer within 48 hours of becoming aware of the event, regardless of whether the SAE was related or expected. If SAE does not result in death or permanent disability, but is considered related and unexpected, we will report it to the NICHD program officer within 14 days of becoming aware of the SAE. SAEs that are not considered related or unexpected will be reported in annual progress reports.

8.2.7 Reporting events to participants

If any information emerges that the DSMB or IRB concludes significantly changes the risk: benefit profile of participation in the study, the information will be incorporated into a revised informed consent document for approval by the IRB and the caregivers of participants who are still active in the study will be reconsented with IRB approved revised consent at the earliest possible opportunity.

8.2.8 Reporting of pregnancy

Not-applicable due to age of participants.

8.2.9 Reporting of suspected child abuse or neglect

If any member of the study staff has significant concerns that a participant may be being abused or neglected, they will discuss it with the study PI. The study PI will attempt to obtain any additional information felt necessary to clarify the situation. If after this there is still concern about abuse or neglect, the PI will contact Child Protective Services and file a report.

8.3 Unanticipated Problems

8.3.1 Definition of unanticipated problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given both the research procedures that are described in the protocol-related documents, and the characteristics of the participant population being studied;
- Related or possibly related to participation in the research and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2 Unanticipated problem (UP) reporting

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

Timelines for reporting the UP are listed below. The FDA and IRB require different reporting based on the characteristics of the UP as noted below.

- Study PI within 24 hours of staff suspecting a UP
- ACE Center co-PIs within 7 days of the Study PI confirming a UP has occurred.
- DSMB: The ACE co-PIs and the study PI will report UPs that are considered possibly related to study treatment to the DSMB within 14 days of being made aware of their occurrence.
- IRB: The PI is responsible for reporting unanticipated problems according to the time frames below.
    - Unanticipated Problems that are also SAEs within 7 days of becoming aware of the event.
    - Any other Unanticipated Problem within 14 days of becoming aware of the problem.

8.3.3 Reporting unanticipated problems to participants

The informed consent document for the study will be revised to reflect the UP. After IRB approval of the revised informed consent document is received, all participants who are continuing to be treated within A+ Treatment will be reconsented. In addition, all participants who do not have a previously scheduled appointment within 2 weeks of the approval of the revised informed consent document will be notified by phone, email or mail that the UP has occurred and that a revised consent form now exists. They will be asked to contact study staff if they wish to discuss the event prior to the next scheduled study visit.

8.4 Overall Plan to Protect Patient Safety

Data Safety and Monitoring Board (DSMB) The study will have a three-person data and safety monitoring board that reviews the initial protocol prior to any participant being enrolled. After the first participant has enrolled and started the study, until the last participant has completed the week 16 visit, the DSMB will meet a minimum of two times a year to review the study's progress and the safety. Specifically, the following will be reviewed at each meeting:

1. enrollment as compared to proposed enrollment,
2. SAEs and UPs with any resulting changes in study procedures or consents,
3. participant discontinuation, study withdrawals, and study completions
4. adverse events separated by system organ class, severity and relatedness,
5. protocol deviations

The membership of the DSMB includes two child psychiatrists who are experts in psychopharmacological treatments for ASD and conducting clinical trials in ASD and a statistician. The DSMB will determine at each meeting whether there are any concerns, especially with regard to safety, that lead the board to conclude that the study should be suspended or that the protocol should be amended to provide greater protections for subjects. The DSMB may also raise concerns or provide suggestions to improve recruitment or procedures for the trial.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Since this is a feasibility study not an efficacy trial, the sample size was determined based on expected ability to recruit during the period of the study.

9.2 Population for Analysis

The primary analysis population will include all participants.

The safety population will include all participants

9.3 Statistical Analyses

9.3.1 General approach

We will conduct preliminary checks to identify potential outliers and missing data. We also will examine clinically meaningful subgroupings such as age, gender, and IQ. As part of the study design, efforts will be made to collect all outcomes on all participants, even when behavioral intervention is prematurely terminated.

A final statistical analysis plan will be developed and signed prior to final database lock.

9.3.2 Analysis of the primary efficacy endpoint

The primary feasibility analysis will focus on the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). These measures can be administered to a wide range of stakeholders to determine the extent to which they believe an intervention or implementation strategy is acceptable, appropriate, and feasible. Readability is at the 5th grade level. Higher scores indicate greater acceptability, appropriateness, and feasibility. The AIM, IAM, and FIM have demonstrated content validity, discriminant content validity, reliability, structural validity, structural invariance, known-groups validity, and responsiveness to change. Means and standard deviations will be reported for the AIM, IAM, and FIM. Descriptive statistics on caregiver completion rates for the 8-session treatment program will be reported.

Acceptability, appropriateness and feasibility will also be assessed **qualitatively** with stakeholder individual interviews. In the field of implementation science, qualitative methods are frequently used to shed light on key implementation challenges[8]. Questions in the interview guide will be tailored to stakeholder group (Caregivers, Coaches, Clinicians, or Staff) and will be informed by previous studies that have examined barriers and facilitators during the implementation of a new treatment approach[9-11]. Interviews will be conducted with caregivers after they have completed coaching sessions and with coaches, clinicians, and staff once they have delivered the intervention and supported coaching activities for a 6-month period. Qualitative analysis will use an iterative coding and review process informed by grounded theory[12]. To minimize bias and protect privacy, personal names and direct identifiers in transcripts of the interviews will be replaced with a code or descriptor. Qualitative data will initially be coded independently by two team members at a general level in order to condense data into analyzable units. Responses will be assigned codes based on a priori or emergent themes. Disagreements will be resolved by reviewing transcripts and additional discussion. A final list of codes will be developed through consensus. Axial coding will then be used to generate categories arranged in a treelike structure connecting segments into separate nodes, describing the relationship between codes and subcategories. Nodes and trees will be used to create a taxonomy of themes including a priori, emergent and new categories. Qualitative coding will then be quantified using frequency counts to identify primary themes. Participant quotes from individual interviews will inform assessments of acceptability, appropriateness, and feasibility of the adapted coaching approach.

Fidelity of intervention delivery, the degree to which programs are implemented as intended by program developers, is an important implementation outcome because it can moderate the effect of an intervention on targeted health outcomes2,4. When interventions are adapted to fit a new target population, delivery setting, location or organization, maintaining intervention fidelity is of particular importance. Fidelity of caregiver implementation of ESDM strategies will be assessed quantitatively, using an adapted version of the Parent Early Start Denver Model (P-ESDM) Caregiver Fidelity Rating System. The P-ESDM Caregiver Fidelity Scale provides a method for assessing the fidelity with which a caregiver is using ESDM principles in a joint activity routine with their young child. The 13 item rating scale includes ratings of performance from 1 to 5. Observations will be coded from video-recorded caregiver-child interactions completed at baseline (pre-intervention) and at 9-weeks (post-intervention), by certified ESDM therapists who are naïve with respect to whether they are coding the baseline or 9-week observation. Tabular and graphical summaries of pre and post caregiver implementation fidelity will be generated to assess the degree to which the average in the cohort changes over time. Inference on pre-post change will be based on paired t-tests or, if the assumptions are found to be untenable, the Wilcoxon signed rank test for paired samples.

9.3.3 Analysis of the secondary endpoints

Proximal child and caregiver outcomes. A key proximal outcome will be change from baseline (pre-intervention) to 9-weeks (immediately post-intervention) in caregiver) sense of competence measured by the Parent Sense of Competence Scale and child behaviors measured by the sum of 4 items from the JERI (Joint Engagement, Attention to Caregiver, Responsiveness to Partner's Communication Bids, Fluency and Connectedness) coded by a trained, reliable coder who is naïve with respect to whether the observation is from baseline our outcome using video-recorded caregiver-child interactions.

Aim 2 data analysis: Quantitative measures, including participant demographics, will be summarized using descriptive statistics. Means and standard deviations will be reported for continuous measures, and frequency and percentages are reported for categorical variables. Tabular and graphical summaries of each outcome measure at each assessment point will be generated to assess the degree to which the average in the cohort changes over time (e.g. boxplots of VABS-3 Communication at baseline and follow up). Inference on pre-post change will be based on paired t-tests or, if the assumptions are found to be untenable, the Wilcoxon signed rank test.

9.3.4 Safety analyses

There is no study provided medication in this sub-study. However, AEs will be collected. Each AE will be counted once only for a given participant. TEAEs will be presented by severity.

9.3.5 Baseline descriptive statistics

Baseline descriptive statistics will include demographics, ADOS/BOSA severity scores, cognitive function, adaptive behavior scores, ADHD-RS scores using descriptive statistics of mean value, standard deviation and range.

9.3.6 Planned interim analyses

No interim analyses are planned.

9.3.7 Sub-group analyses

If subgroup analyses are done, they will be purely non-inferential and hypotheses generating, given that this is a pilot study with a small sample size that is unlikely to have subgroups of sufficient size to draw meaningful conclusions.

9.3.8 Exploratory analyses

Additional Exploratory proximal and distal outcomes of interest include: a) caregiver ADHD-RS ratings of the child's attention. b) Aberrant Behavior Checklist (ABC), including inattention/hyperactivity, social withdrawal, stereotypies, irritability, and inappropriate speech; c) Social Reciprocity Scale-2 (SRS-2) ratings of child's social communication behavior; d) Caregiver Strain Questionnaire (CSQ) ratings of the impact of the child's condition on the family and caregiver and quality-of-life; e) Behavior Rating Inventory of Executive Functions (BRIEF) ratings of child's executive function; and f) Child Behavior

Checklist (CBCL) ratings of child behavioral and emotional problems. Our analysis will focus on graphical displays, which will be complemented by appropriate inferential statistical procedures. For the graphical displays, we will visualize the distribution of proximal and distal outcome measures in histograms to better understand the shape and spread of the distribution of each. In terms of inference, between group change at proximal and distal time points will be based on between group t-tests or, if the assumptions are found to be untenable, the Mann-Whitney U test. Whilst statistical inference is valuable, we anticipate that we will elicit most information through careful data visualization. Change from baseline (pre-intervention) to 16-weeks (8-weeks post-intervention) will be assessed for the VABS-3 Socialization and Communication Subscale Standard Scores.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical and Study Oversight Considerations

10.1.1 Informed consent process

Consent/Assent Provided to Participants. Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant's caregiver and documentation of informed consent is required prior to starting intervention/administering study intervention. Informed assent is not required of the participants due to their developmental status. DUHS IRB approved informed consent documents will be used for the preliminary screening study (A+ Assessment) and this study (A+ Treatment). These materials will be provided to the participants' caregivers when they express interest in the study and will be discussed with them as described below.

Consent Procedures and Documentation: Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms and consent procedures will be Institutional Review Board (IRB)-approved. The participant's caregiver(s) will be asked to read and review the document with sufficient time allowed prior to meeting with study staff. If the caregiver is still interested in participating or has questions that may influence his/her willingness to participate, the study coordinator and/or co-investigator or one of the study physicians will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the caregiver's comprehension of the purposes, procedures, and potential risks of the study and of their and their child's rights as research participants. A study physician will always be available to potential participants' caregivers to answer any questions. The caregiver will be encouraged to discuss the study with their family or their child's current providers prior to agreeing to participate.

If the potential participant's caregivers want the child to participate in the study, the caregiver(s) will sign the informed consent document prior to any procedures being done specifically for the study. Participants and their caregivers will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process, including the date the documents are signed, will be conducted as per existing Guidance Documents and study MOPs, and documented in the source documents, before the participant undergoes any study-specific procedures. REDCap will be utilized to conduct and document the consent process remotely. A teleconference meeting will be set up to review the consent form with the parent prior to signing the eConsent electronically. The consent process with staff, coaches and/or clinicians who elect to participate in the Qualitative Interview and AIMS-IAM-FIM survey, will be done by trained team

members who are not that person's supervisor or mentor, in order to minimize bias. Voluntariness will be stressed throughout the process.

10.1.2 Study discontinuation and closure

Individual Participant Discontinuation Please see section 7 for a full description of situations in which an individual might discontinue participation in the trial and for reasons why the entire study might be stopped. Briefly, individual participants may discontinue study treatment and/or participation in study assessments at any time without providing any reason for doing so. If participants/participant caregivers wish to discontinue participation in study interventions, they will be strongly encouraged to continue participation in other aspects of study interventions (e.g. discontinue study medication treatment but continue caregiver coaching) and/or study assessments. Similarly, if the study physicians feel it is in the best interests of the participant to discontinue some aspect of the study treatments or study assessments, they will be encouraged to have the participant continue other aspects of the study. If a participant is discontinued from the trial, the study team will provide and facilitate referrals to other appropriate clinicians for ongoing treatment.

Suspension of the entire study. This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. In addition, the study might be interrupted or prematurely terminated in the following situations or other as yet unanticipated situations.

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Withdrawal of financial support of the trial
- Determination that a sufficient sample can't be recruited.

If the concerns leading to study interruption can be satisfactorily addressed, the study may resume with the consent of the sponsor, IRB and/or Food and Drug Administration (FDA).

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator and, if applicable, funding agency or DSMB. Subsequently, the study PI will provide written notification documenting the reason for study suspension or termination to the study participants, funding agency or DSMB as applicable, FDA, drug manufacturer and IRB. If possible and if there are not safety concerns, the active participants in the study will complete their participation. Study participants will have the opportunity to contact the PI and other study staff to further discuss the decision to suspend the trial if they wish.

10.1.3 Confidentiality and privacy

Participant confidentiality and privacy is strictly held in trust by the study team, the funding agency, and regulatory authorities. All staff completing study activities remotely will utilize spaces that protect the privacy of participants and will use the security settings as dictated by the software and applicable OIT guidelines, including password protecting teleconference meetings. Participants will also be informed of these measures and encouraged to use spaces that protect their privacy while engaging in remote study activities, such as interviews or behavioral coaching.

Various documentation practices are maintained throughout each level of data collection and processing to maintain participant confidentiality. These practices are regularly checked though Quality Assurance practices. Documents containing personally identifiable information (such as the study consent forms and forms containing information used to generate a GUID) and documents containing study data will be stored in separate physical locations. Electronic files stored in the study server or on the study databases may directly or indirectly link personal information and identifiers with study data by being stored in the same electronic file or folder, or by being associated with the same record and ID. Any linkage and use of PHI will be based on the minimum necessary information to conduct the research activities and data collection and processing in an effective, secure, and valid manner. Participants will be identified by a unique subject ID (which will be used in place of names) in data collection forms. Some assessments and derived data in this study require information about the participant's age (birthdate) and gender but will not be linked to other identifying information such as full names or address. All data will be housed in secure locations.

The study monitor, other authorized representatives of Duke University and/or the National Institute of Child Health and Human Development (study sponsor), representatives of the Institutional Review Board (IRB), may inspect all documents and records required to be maintained by the investigator, including but not limited to, study source documents, medical records for the participants in this study.

The study participant's contact information will be securely stored at the site for internal use during the study and until the final results of the study have been shared with the participants and/or their caregivers. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

In this study, data identified only by the participant's globally unique identifier (GUID) will be uploaded into the National Database for Autism Research (NDAR) to facilitate additional analyses and discoveries to improve the understanding and care of individuals with ASD.

To complete the SenseToKnow app, participants will be asked to use their own or a borrowed iPhone/iPad. Alternatively, they may borrow a Duke-owned device. Participant data will be stored on the device(s) and securely uploaded to the study database. Participants who complete this measure will receive instructions on how to complete the measure, including any security settings in place (e.g., receiving a link and password). The study's physicians will be available to address any clinical concerns that arise during the course of the study and that may be related to the conduct of the study. If a concern is voiced by the participant or guardian, the physician will evaluate it and advise the caregiver as to whether or not it is likely to be related

To further protect the privacy of study participants, this study adheres to the Certificate of Confidentiality issued by the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 Future use of stored specimens and data

We do not plan to collect any specimens that will used in the future. The data collected in this study will be transferred to NDAR as described above, but will not be able to linked to a specific individual.

10.1.1 Safety oversight

There will be a DSMB to oversee the safety of participants in the study as described in section 8.4. All of these individuals are independent of Duke University and of the study. In addition, the study will be reviewed annually and more often if needed by the IRB.

10.1.2 Key roles and study governance

10.1.3 Clinical data monitoring

The Duke ACE Center Data Management and Analysis Core (DMAC) will undertake monitoring of this study using multiple procedures. First, data that is directly entered into the database will be checked for completeness by study staff during the in person visit related to the caregiver report. If items are left blank or are inconsistent the caregiver will be asked to clarify and complete the items in question. Caregivers will be urged not to leave any questions unanswered.

Data generated by study staff on paper forms will be double data entered. The DMAC will identify any inconsistencies in the doubly entered data points and a third person will resolve discrepancies and/or contact the appropriate study staff to clarify the data.

The Duke ACE Center DMAC will implement many data validation rules ((e.g., blank but required entries, out-of-range values, and skip patterns), that will be enforced by the EDC system during data entry. Other, more complex error conditions will be checked using custom error-check programs. Inconsistencies in data patterns across forms will be used to identify complex errors or confirm validity of data. The DMAC will continually monitor data quality as data are entered using a module named the Data Anomaly Detection and Resolution Module (DAD-RM), which we have successfully deployed in other studies. The DAD-RM system integrates built-in EDC data validity rules with external rules of arbitrary complexity to produce a database of potential data problems ("logical queries") that must be resolved by study staff and approved and documented by the DMAC. Using the DAD-RM system, project coordinators and the DMAC will be able to review all data query records via the Portal website. Each record must be annotated and marked as either resolved by data update, approved as an extreme value,

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or unrecoverable. The DAD-RM error checks and database update will be run daily, providing studies the

opportunity to address data issues early when the probability of resolution is highest. We will resolve individual and recurring problems with the data entry system during DMAC weekly staff meetings. These meetings will be used to discuss and resolve issues and answer operational concerns, such as data entry questions, use of technologies, and EDC. Dr. Compton will manage the data resolution process and host training sessions as needed. Procedures regarding QC will be performed to address inconsistencies that emerge following data validation processes and work with study staff to address data quality issues and to refine the data collection and reporting process.

In addition, the Duke ACE Center Regulatory Coordinator will conduct periodic monitoring during the course of the trial. During these times, she will monitor all regulatory documents, documentation of protocol deviations and violations, and correlations between randomly chosen source documents and the data base.

10.1.4 Quality assurance and quality control

All entered data will be subject to Quality Assurance (QA) Measures. QA processes will be overseen by the Administrative Core, in collaboration with Dr. Dawson. All study staff will be trained on center-wide Guidance Documents, tracking deviations, Good Clinical Practice (GCP) and human subjects research training. The Data Management and Analysis Core will provide the Administrative Core with information regarding timeliness of data submission from the study, protocol deviations and missing data, and NDAR submissions. This information will help identify areas of deficiency, aspects of GCP that need reinforcement, or additional training that may be required. If these steps do not correct deficits or GCP concerns, steps may be taken to discipline, relocate, or replace a staff member or modify study procedures. The Administrative Core staff will work closely with the DMAC, which will oversee consistent application of scientific standards and methodological rigor for data collection, processing, entry, cleaning, and analytics. The DMAC will be responsible for study specific QC for all behavioral, questionnaire data. This will be accomplished by the development of well-defined procedures, intensive training of staff, and Manual of Procedures (MOPs) with detailed instructions for procedures involved in data acquisition, processing, and upload to the Data Management and Analysis Core. Fidelity to research procedures will be accomplished by the development of well-defined protocols, intensive reliability training, regular in-person meetings to avoid drift, and internal monitoring and quality assurance. Protocol-specific training will be based on the delegated role of investigators and staff as defined in delegation of responsibility logs.

10.1.5 Data handling and record keeping

Data Collection and Management Responsibilities. Data collection is the responsibility of the staff at the site under the supervision of the project lead, Dr. Dawson. Dr. Dawson is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Hardcopies of the study visit worksheets or virtual electronic copies will be used as source document worksheets for recording data obtained by study staff for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data will be entered into the redcap database designed and provided by the Duke ACE Center DMAC, a 21 CFR Part 11-compliant data capture system. The data system includes password protection

and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

The participants' caregivers will receive emails from the study team/DMAC notifying them when they should complete rating scales online via REDCap or Q-global. If a caregiver does not wish to utilize the electronic rating scales, study staff will either complete the rating scale with them over the phone or provide them with a paper copy of the rating scale to complete.

At each assessment point, the study staff will document whether any assessments were not completed and the reason for noncompletion.

The Duke Autism Center DMAC will provide Dr. Dawson with a listing of expected but not entered data at least monthly.

Study Records Retention: All records will be retained for at least 2 years following publication of the final manuscript related to the study or for at least 3 years after submission of the study's Federal Financial Report submission.

10.1.6 Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The study staff will record any deviations as they happen and/or as they become aware of the deviation. Such deviations will include assessments occurring outside the allowed windows, failure to complete scheduled assessments, and issues with documenting consent. Study staff will also document the reason(s) for the deviation and the corrective actions that will be put into place to prevent future deviations. In addition, the study will keep a listing of all study visits that occur outside of specified study windows. All protocol deviations during the prior year will be reported to the IRB in the annual report.

Protocol violations will consist of inclusion of ineligible participants. Protocol violations will be reported to Dr. Dawson, the DMAC and the Duke Center for Autism Administrative Core within 14 days of becoming aware of the event. Subsequently, procedures must be put into place as soon as possible and within an additional 14 days to prevent similar events in the future. The IRB and DSMB will be notified of all protocol deviations at the time of the next scheduled report or sooner if there are safety concerns associated with the deviation.

10.1.7 Publication and data sharing policy

Every effort will be made to publish the results of this study in a peer reviewed journal as soon as possible after completion of the study. Authorship of resulting papers will be as inclusive as possible. If

there are conflicts about authorship, the Duke ACE Center Executive Committee will resolve the conflicts in accordance with the Center's publication policies.

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers 3 years after the completion of the primary endpoint by contacting Dr. Dawson or the Duke Center for Autism. Further, all data will be uploaded into the National Database for Autism Research (NDAR) for use by other investigators according to the specific agreement between NDAR and the Duke ACE Center. Data generated by Qualitative Interviews and surveys conducted with staff, clinicians and/or coaches will not be submitted to NDAR.

Genomic data will not be generated by this study.

10.1.8 Conflict of interest policy

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Duke ACE Center Administrative Core, in conjunction with the NICHD and Duke University School of Medicine, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Abbreviations

The list below includes abbreviations utilized in this protocol.

ABC	Aberrant Behavior Checklist
ACE	Autism Center of Excellence
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	Preschool Attention Deficit Hyperactivity Disorder Rating Scale
ADI-R	Autism Diagnostic Interview - Revised
AE	Adverse Event
AIM	Acceptability of Intervention Measure
ASD	Autism Spectrum Disorder
BRIEF	Behavior Rating Inventory of Executive Function
CBCL	Child Behavior Checklist
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CNS	Central Nervous System
COC	Certificate of Confidentiality

CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSHQ	Children's Sleep Habits Questionnaire
CSQ	Caregiver Strain Questionnaire
DMAC	Data Management and Analysis Core
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FIM	Feasibility of Intervention Measure
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
IAM	Intervention Appropriateness Measure
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRS	Impairment Rating Scale
JERI	Joint Engagement Rating Inventory
MOP	Manual of Procedures
NICHD	National Institutes of Child Health & Human Development
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SRS-2	Social Responsiveness Scale – 2nd edition
TEAE	Treatment Emergent Adverse Event
UP	Unanticipated Problem
US	United States
VABS	Vineland Adaptive Behavior Scales – 3rd edition

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A copy of Summary of Changes table for the current amendment follows the Protocol Title Page.

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