

Tailoring Treatment Targets for Early Autism Intervention in Africa

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Purpose of the Study

Naturalistic Developmental Behavioral Interventions (NDBIs), an evidence-based early autism spectrum disorder (ASD) intervention approach, target key behaviors that help language development. While efforts to use NDBIs are increasing worldwide, important gaps in our knowledge remain on whether the behaviors targeted by NDBIs are cross-culturally valid. Our study in South Africa, a multi-cultural setting, will provide critical information on NDBI treatment targets and a novel digital outcome measure of treatment response.

Aim 1: Characterize NDBI child treatment targets in South African children with ASD using standardized assessments and digital technology, and determine whether these patterns differentiate children with ASD from their peers with developmental delay and typical development. An exploratory component of Aim 1 will assess whether 12 sessions of NDBI caregiver coaching result in changes in child treatment targets assessed using digital technology.

Aim 2: In the ASD group, determine the caregiver-child context for South African dyads, by identifying common family routines and characteristics of caregiver-child dyadic exchanges.

Aim 3: In the ASD group, describe strategies caregivers use during caregiver-child interactions and evaluate whether there are changes in caregiver-specific strategies following NDBI caregiver coaching.

Aim 4: Adapt the NDBI caregiver coaching intervention and assessment of caregiver NDBI strategies for telehealth delivery in order to maintain services for young children with ASD impacted by COVID-19. Explore the acceptability, feasibility, and appropriateness of the adapted intervention and assessment approach.

Background

Autism early detection and intervention is increasingly recognized as a critical public health focus globally. Early detection and intervention can result in positive gains in cognitive, social, language, and adaptive behaviors, and as well as decreases in the long-term costs of special education, sheltered living and supported employment. Naturalistic developmental behavioral interventions (NDBIs), a type of empirically-based early intervention methods, are derived from the principles of applied behavior analysis and developmental science.⁴ Caregiver use of NDBI strategies during caregiver-child interactions, promotes child joint attention and affective engagement, which promote language acquisition—a key predictor of long-term functional outcomes. Efforts to implement NDBIs in community settings are increasing worldwide.

Limited research examines the underlying assumptions of NDBIs outside of Western contexts. The majority of behavioral and developmental research is conducted in non-representative populations, as less than 3% of participants come from Africa, Central and South America, Asia, and the Middle East.

In addition, autism spectrum disorder (ASD) research has disproportionately low representation from minority groups, multilingual families, and participants with lower socioeconomic status. Anthropological theorists posit that many of the social constructs targeted in NDBIs have varied norms

and baseline frequencies across cultures. Cross-cultural variation in eye contact, facial expressions, play, and language use may result in biases in ASD symptom recognition in culturally-diverse groups when using instruments normed on Western samples. NDBIs are carried out in daily routines, using materials that families have in their homes. However, current NDBIs are based on Western cultural contexts, and cross-cultural variations in materials and adult participants in routines have been reported. In addition, cross-cultural variations have been reported in caregiver-child dyadic exchanges, including the degree to which mothers focus on face-to-face interaction and object-based play with their young children, as well as maternal reactions to child communicative cues.

The evidence base for determining whether NDBIs improve outcomes across cultures is lacking, and certainly not as strong as the evidence for their efficacy in monolingual, English-speaking, middle-socio-economic status participants from Western cultural contexts. As such, important research gaps exist and what remains unknown is whether NDBI treatment targets are valid in non-Western contexts, particularly when caregivers are the ones delivering NDBI strategies to their child.

Assessment of child response to NDBI-intervention is a significant challenge in low-resource settings. 'Gold standard' tools are costly, administered by professionals, and may not be culturally valid. mHealth tools that assess ASD behavioral risk markers can help address this challenges, by enabling point-of-care detection by non-specialists. Atypical eye gaze is one of the most promising behavioral risk marker of ASD. In addition, studies suggest that individuals with ASD show a reduction in certain facial expressions in response to stimuli. Portable, low-cost technologies that perform eye tracking and automatically analyze facial expressions are being developed and piloted. Some of this piloting has occurred in South Africa. Exploring whether digital health tools, can overcome barriers to assessing child treatment response is an exciting and necessary avenue of discovery in global health. The rapid developments in technologies around the globe, and increasing global access to the internet and mobile technologies, make this a particularly important avenue for exploration.

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 impact of an intervention on targeted health outcomes. Use of NDBI strategies by caregivers during joint activity routines with their child, at fidelity, is important to track because it can result in changes in child social-communication outcomes. However, measurement of acquisition of caregiver NDBI strategies presents a significant challenge in low-resource settings as fidelity measurement is time consuming and conducted by highly skilled clinicians, which are a limited resource in most parts of the world. If widespread community implementation of NDBI is to occur, tools need to be developed that enable point-of-care detection of growth in caregiver NDBI strategies in response to intervention.

Dr. Franz (PI) is currently leading a study on NDBI-informed caregiver coaching in South Africa. The study aims to adapt a caregiver coaching version of the Early Start Denver Model (ESDM), an NDBI, for implementation by non-specialist early childhood development workers, employed by the Department of Education. South Africa is a multi-cultural, multi-lingual nation, marked by stark health disparities, where policies have emerged on the importance of early detection and intervention for developmental disorders, including ASD. The South African adapted intervention utilizes Community ESDM materials, which are currently being piloted in rural, low resource parts of the U.S. The session skill is introduced by “Help is in your hands” Community ESDM videos, then early childhood development workers coach caregivers on the session skill and support caregiver reflection and skill generalization. A pre-pilot with 2 caregiver-child dyads has recently concluded. The pre-pilot yielded promising early indications that the intervention training and supervision are feasible, and that the measures used to assess child clinical outcomes are sensitive to change. Both child participants in the pre-pilot demonstrated significant growth in social and communication subscale scores on the Griffiths Scales of Child Development and the Vineland Adaptive Behavior Scales, following 12 sessions of NDBI-informed caregiver coaching, delivered by non-specialists.

Alongside efforts to implement NDBIs in multi-cultural settings, we need to ensure that our treatment targets are valid, and that NDBIs are relevant to family life of diverse cultural groups. The overall objective of the R21 is to assess the validity of NDBI treatment targets and determine whether scalable digital technology can assess treatment response in a multicultural, low resource South African setting. Addressing this main research question is critical to designing effective early interventions that may be adapted for pilot testing across sub-Saharan Africa.

Understanding the validity of NDBI targets across diverse populations will help match interventions to increasingly diverse populations in the U.S. In the U.S. African American and Hispanic/Latino children are diagnosed and access services at a later age as compared to Caucasian children. The majority of states have passed legislation that mandates insurance benefits for early intervention and there are increasing efforts to implement NDBIs in diverse communities. However, knowledge of how to tailor these interventions to diverse communities is incomplete. As such, the R21 aligns with NIMH Strategic Objective 4: To strengthen the public health impact of NIMH-supported research; and objectives of the Federal Interagency Autism Coordinating Committee Strategic Plan: To reduce disparities in early detection and outcomes for underserved populations.

Design & Procedures

The R21 will build on collaborations and infrastructure established in Dr. Franz's NIMH K01. The K01 aims to adapt a caregiver coaching version of the Early Start Denver Model (ESDM), an NDBI and the first empirically-validated comprehensive intervention for toddlers with ASD, for implementation by non-specialists in South Africa. Following a significant amount of formative work and capacity building, a pilot study will begin in January 2019, and enroll 20 ASD caregiver-child dyads from culturally diverse, low-resource backgrounds.

The R21 will evaluate NDBI child, caregiver-child, and caregiver treatment targets, and a digital outcome measure of treatment response. The study design will include both a baseline cross-sectional phase and a longitudinal pre-post phase, nested within the ongoing K01. The R21 will extend ASD group recruitment by 1 year, allowing for 30 ASD caregiver-child dyads to be recruited in total. In addition, the R21 will facilitate recruitment of 30 children with developmental delay and 30 with typical development

who, along with the ASD group, will participate in the baseline cross-sectional phase of the study. The ASD group will then participate in the longitudinal pre-post phase of the study, where they will receive 12 NDBI-informed caregiver coaching sessions delivered by non-specialists.

COVID-19 adaptations: Transition to telehealth will only occur for the ASD group who receive the caregiver coaching intervention. Baseline assessments of the TD and DD group will be on hold until COVID-19 in-person restrictions are lifted by the University of Cape Town IRB.

The intervention all children in the ASD group (only) will receive is ESDM-informed caregiver coaching, delivered to the caregiver-child dyad by a non-specialist early childhood development practitioner. All children who receive intervention have a diagnosis of ASD. Twelve, one-hour sessions of individual caregiver coaching occur. In the 12 sessions, the session skill is introduced by “Help is in your hands” Community ESDM videos. Session skills include specific strategies caregivers can use to increase their child’s attention to people and their child’s communication; strategies to identify, create and use joint activity routines to engage with and teach their child; in addition to ways to use the ABCs of learning to teach their child new behaviors. “Help is in your hands” Community ESDM materials also provide video examples of other caregivers using the session skill with their child. The early childhood development practitioner then coaches the caregiver in the session skill, in at least two activities. The goal of coaching was to provide enough support for the caregiver to experience success in implementing the new skill with their child. Coaching is followed by caregiver reflection and a discussion of generalization of the new skill across various daily activities, using a daily activities visual aid.

In the baseline cross-sectional phase 30 caregiver-child dyads with ASD, 30 with typical development, and 30 with developmental delay will be recruited. ASD caregiver-child dyads will continue to be recruited from Western Cape Department of Education Autism Schools (as per K01 recruitment approach). Children with developmental delay will be recruited from Neurodevelopmental Clinics at Red Cross Children's Hospital. Children with typical development will be recruited from Early Childhood Development Centers. Inclusion criteria are as follows: (1) the child is between 18 and 72 months of age; (2) the subject’s family speak isiXhosa, isiZulu, Afrikaans, or English (~ 97% of all household languages spoken in the Western Cape province); (3) the child’s ethnicity/race is African or Coloured (a South African term for mixed race); and (4) the child lives within an area served by the recruitment sites. Additional inclusion criteria are group specific. For the ASD group: (1) the child meets criteria for an ASD diagnosis based upon DSM-5 criteria and informed by the ADOS-257 administered by research reliable raters; and (2) the caregiver is \geq 18 years old. For the developmental delay group: (1) the child screens positive on the Ten Questions; (2) screens negative on the autism behavior checklist (ABC); and (3) has been diagnosed with developmental delay by a developmental pediatrician. For the typically developing group: The child (1) screens negative for a developmental delay on the Ten Questions; and (2) screens negative on the autism behavior checklist (ABC).

COVID-19 adaptations: Because we aim to assess the acceptability, feasibility, and appropriateness of the adapted telehealth coaching intervention - views of multiple stakeholders involved in the implementation of the intervention will be assessed. This includes the child's caregiver, Early Childhood Development Practitioners, Early Childhood Development Practitioner School Supervisors, and ESDM therapists who provide supervision and oversight of the caregiver coaching session. Inclusion criteria are as follows: For the Early Childhood Development Practitioners (n=2) and Early Childhood Development Practitioner School Supervisors (n=2) group: the ECD worker and/or school supervisor are 1) employed by our participating recruitment partners (Western Cape Education Department Schools) and 2) involved in delivery of the caregiver coaching sessions, either in person or

remotely. For the Early Start Denver Model supervisors (n=3): the local supervisors are 1) trained ESDM therapist, 2) supervise weekly coaching sessions in the schools, and/or 3) supervise remote intervention delivery sessions.

Exclusion criteria for the ASD group include: (1) the presence of a neurological disorder of known etiology (e.g., Fragile X); and (2) a caregiver-child dyad that is unable to attend assessments and 12 coaching sessions. Exclusionary criteria for all groups include: (1) significant sensory or motor impairment; (2) major physical abnormalities; and a (3) history of serious head injury and/or neurological disease.

The baseline cross-sectional phase will be used to investigate Specific Aim 1: Validity of child NDBI treatment targets, and Specific Aim 2: Characterization of caregiver-child NDBI treatment targets. Specific Aim 1 will utilize all the groups of participants (ASD, developmental delay, and typical development). Specific Aim 2 will only utilize the ASD group.

Baseline assessments in the ASD group include:

- Demographic questions (completed by caregiver)
- The Vineland Adaptive Behavior Scales, Third Edition (Vineland-3): (completed by clinician) The Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) is an individually-administered measure of adaptive behavior that is widely used to assess individuals with intellectual, developmental, and other disabilities. The Vineland-3 contains 5 domains each with 2-3 subdomains. The main domains are: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior. The Caregiver Interview Form uses the Vineland semistructured interview technique to elicit information about the examinee's adaptive functioning from a parent or caregiver. Sparrow, S.S., Cicchetti, D.V., & Saulnier, C.A. (2016). *Vineland Adaptive Behavior Scales, Third Edition*. San Antonio, TX: Pearson.
- Griffiths Scales of Child Development, Third Edition (Griffiths III): (completed by clinician) The Griffiths Scales of Child Development, Third Edition (Griffiths III) is a comprehensive, developmental measure for continuous use from birth to 6 years (72 months). Although not standardized in South Africa (standardization samples are from the United Kingdom and Ireland), this developmental assessment is widely used in South Africa. The Griffiths III provides an overall measure of a child's development, as well as an individual profile of strengths and needs across five areas: Foundations of Learning; Language and Communication; Eye and Hand Coordination; Personal-Social-Emotional; and Gross Motor. Green, E., Stroud, L., Bloomfield, S., Cronje, J., Foxcroft, C., Hurter, K., Lane, H., Marals, R., Marx, C., McAlinden, P., Paradice, R., Venter, D. (2015). *Griffiths Scales of Child Development, Third Edition*. 2015. WPS.
- Autism Diagnostic Observational Schedule – Second Edition (ADOS-2): (completed by clinician) Semi structured standardized observation that measures autism symptoms in social relatedness, communication, play and repetitive behaviors. A standardized severity score based on codes within these domains can be calculated to compare autism symptoms across modules. Lord, C., Rutter, M., DiLavore, P.C., Risi, S., Gotham, K., Bishop, S. *Autism diagnostic observation schedule, Second Edition*. Torrance, CA: Western Psychological Services; 2012.
- Child Mental Health: The Strengths and Difficulties Questionnaire: (completed by caregiver) 25-item emotional and behavioral screening measure for children. R. Goodman, The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness

and consequent burden. *Journal of child psychology and psychiatry, and allied disciplines* 40, 791-799 (1999); published online EpubJul

- The Patient Health Questionnaire: (completed by caregiver) 9-item depression scale K. Kroenke, R. L. Spitzer, J. B. Williams, *The PHQ-9: validity of a brief depression severity measure*. *Journal of general internal medicine* 16, 606-613 (2001); published online EpubSep
- The Generalized Anxiety Disorder 7-Item Scale: (completed by caregiver) 7-item screener for Generalized Anxiety Disorder. R. L. Spitzer, K. Kroenke, J. B. Williams, B. Lowe, *A brief measure for assessing generalized anxiety disorder: the GAD-7*. *Archives of internal medicine* 166, 1092-1097 (2006); published online EpubMay 22 10.1001/archinte.166.10.1092).
- The Alcohol Use Identification Test Scale: (completed by caregiver) 10-item screener designed to identify hazardous drinking T. F. Barbor, J. C. Higgens-Biddle, J. B. Saunders, M. G. Monterio, *The Alcohol Use Disorders identification Test. Guidelines for use in primary care*. (World Health Organization, Department of Mental Health and Substance Dependence, Geneva, 2001).
- The Life Stressor Checklist-Revised: (completed by caregiver) 30 item measure of traumatic life events. J. Wolfe, R. Kimberling, in *Assessing psychological trauma and PTSD*, J. Wilson, T. M. Keane, Eds. (Guilford, New York, 1997), pp. 192-238.
- Caregiver competence: The Parent Sense of Competence Scale - (completed by caregiver) 16-item caregivers confidence and quality of affect associated with parenting C. Johnston, E. J. Mash, *A measure of parenting satisfaction and efficacy*. *Journal of Clinical Child Psychology* 18, 167-175 (1989).
- The Parenting Stress Index – Short Form: (completed by caregiver) 36 items magnitude of stress in the caregiver-child system R. Abidin, *Parenting Stress Index Professional Manual*. Third Edition. (Psychological Assessment Resources Inc, 1995)
- SenseToKnow App (completed by child) Total time to complete: 10 minutes SenseToKnow is an app developed for mobile devices that is designed to elicit autism risk behaviors. In order to administer the app, children sit on the parent's/guardian's lap with the mobile device at eye level for the child. The frontal camera in the iPad records video throughout the stimuli presentations at 1280 x 720 resolution, 30 frames/sec. The app is comprised of a set of stimuli (videos and games) that are designed to elicit autism spectrum disorder (ASD) symptoms, such as facial expressions. 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 (for example, the 'Make Me Laugh' video). Stimuli in total take 6 min. 40 secs. to administer. At three pre-specified times, an examiner positioned behind the child calls the child's name. Movies can be stopped and re-started if the child is fussy. Actors are of diverse ethnic/racial backgrounds. Right versus Left placement of the stimuli (counter-balanced across movies) takes into account the sensors and computer vision analysis capabilities (e.g. ability to track gaze to R vs. L side of screen). Overall, the entire task takes approximately 10 minutes. Children are allowed to take breaks between videos and games as needed. A research assistant is present at all times to answer questions. Stimuli included in the app have been informed by previous studies overseen by investigators of this protocol [1-6]. Dependent variables include multiple behaviors, all of which have been found in previous studies to be present in children with ASD, including total duration attending to screen; duration of attention to social vs. nonsocial stimuli; frequency and latency to orient to name; frequency of social referencing; range, frequency, intensity, and duration of facial affect; and postural sway.

- In the study, we will evaluate the reliability and validity of SenseToKnow for eliciting autism symptoms by comparing the responses to the app in children with and without autism. In addition to evaluating group differences, the SenseToKnow app will be piloted to assess treatment response, following 12 sessions of caregiver coaching, delivered by non-specialists. The study will not make any determination of diagnosis using the SenseToKnow app. Diagnoses will only be made by using already established and validated methods and communicated by trained clinicians.
- While the study team does not anticipate any direct risk related to use of the SenseToKnow app, the following precautions will be taken to protect the privacy of participants and maintain confidentiality of research data. Data that is collected by the SenseToKnow app will be stored locally on the devices until data is securely moved by trained study staff. Project staff at the University of Cape Town will upload data to a secure shared Duke Box folder, from where Duke project staff will transfer the data to a secure folder on the file server at Duke University. Data stored on the device will be automatically erased immediately after data transfer to the secure database is completed by a trained staff member. The devices will be hardened according to guidelines from Duke Office of IT Security. For additional security we will add a user password to this application so that no one other than those that were given the password set on the device can have access to this data through the device itself. Study team members and collaborators will have access to data according to their roles and responsibilities as determined by the Principal Investigator, described in the research summary, and delegation of authority logs. This transfer of data would not occur prior to University of Cape Town and Duke University Institutional Review Board approval.
- Technology Questionnaire and Qualitative Interview of SenseToKnow App feasibility/appropriateness (completed by caregiver)
- Joint Engagement Rating Inventory (JERI): (Video recorded caregiver child interaction. Coded by trained coder) The Joint Engagement Rating Inventory (JERI) contains seventeen 7 point Likert scale items that characterize various aspects of joint engagement. The items span the range of possibilities observed during interactions with 18 to 30 month typically developing children and similarly aged and older children with developmental delay, including ASD. In order to assess joint engagement, a 10-minute video-recorded caregiver-child interaction will be scored in a Likert scale by a trained rater, blind to child diagnosis. Items focus on engagement states, child-specific codes, caregiver-specific codes, and shared topics. All individuals coding the JERI in this study will undergo reliability training involving dual coding of video-recorded caregiver-child interactions. Using Nvivo coding software, videos will be coded using the JERI coding manual. Nvivo coding software allows coder inconsistencies to be identified during reliability training so that each difference can be discussed until consensus is reached. This process will continue for each coder until 80% reliability is achieved. After training, 15% of JERI study data will be double coded to ensure maintenance of reliability. Adamson, L.B., et al., Rating parent-child interactions: joint engagement, communication dynamics, and shared topics in autism, Down syndrome, and typical development. *J Autism Dev Disord*, 2012. 42(12): p. 2622-35.
- Early Social Communication Scales (ESCS) (Completed by child, with support from clinician. Video recorded and coded by trained coder). Mundy, P., Delgado, C., Block, J., Venezia, A. and Siebert, J., 2003, Early Social Communication Scales (Coral Gables, FL: University of Miami). Joint

attention skills will be measured using the Early Social Communication Scales (ESCS). The ESCS assesses nonverbal communication skills, is normed for typically developing children 18 to 30 months of age in addition to children with developmental delay expressive language level is in approximately the same range. Scores are assigned from video recordings of child behavior during a series of tasks administered by a trained examiner. Administration takes between 15-25 minutes. All individuals coding the ESCS in this study will undergo reliability training involving dual coding of ten ESCS administrations. Using Nvivo coding software, child behaviors video recorded during the ESCS will be coded in each frame using the ESCS coding manual. This time stamped software will allow for coder inconsistencies to be identified during reliability training so that each difference can be discussed until consensus is achieved. This process will continue for each coder until 80% reliability is achieved on initial codes. After the training, 20% of ESCS study data will be double coded to ensure maintenance of reliability.

- Parent Survey of Home and Family Experiences (Completed by caregiver) Balton, S., 2009, Family-based activity settings of typically developing three to-five year old children in a low income African context, Electronic Thesis and Dissertations, University of Pretoria, UP Space. URN no: etd-10172009-122119. A structured interview schedule consisting of a written list of closed ended and open-ended questions to assess child home and family routines.

COVID-19 Adaptations: Remote baseline assessments in the ASD group who will include the following approved measures from above: a, b, j, m, n, p. Note that n. is coded by a trained coder from video-recorded caregiver child interaction. It would not be feasible to complete the full battery of measures remotely.

Baseline assessments in the Typically Developing and Developmental Delay groups include:

- Demographic Questions (Completed by caregiver)
- The Ten Questions Questionnaire (TQ) (Completed by caregiver) The Ten Questions Questionnaire (TQ) is a disability screening tool, extensively used in both epidemiological studies and clinically in low resource settings, including South Africa. The TQ consists of 10 questions; one each addressing the child's vision, hearing, movement and seizures, six on cognition competence, and one extra question regarding other serious health problems. Durkin, M.S., et al., Evaluating a ten questions screen for childhood disability: reliability and internal structure in different cultures. *J Clin Epidemiol*, 1995. 48(5): p. 657-66.
- Autism Behavior Checklist (ABC) (Completed by caregiver) The Autism Behavior Checklist (ABC) will be used to exclude autism spectrum disorder in the typically developing and developmental delay groups. The ABC is the most widely used screening tools for ASD in low and middle income countries; and the ABC age range aligns with our target recruitment age range. The ABC provides a checklist of 47 behaviors typical of autistic individuals for use during the initial screening process Krug, D., J. Arick, and P. Almond, *Autism Screening Instrument for Educational Planning* (3rd ed.). 2008, Austin, TX: Pro-Ed Copyrighted Instrument: <https://www.proedinc.com/Products/12742/asiep3-autism-behavior-checklist-record-forms-25.aspx>

- Griffiths Scales of Child Development, Third Edition (Griffiths III) – described in baseline assessments (ASD group)
- Joint Engagement Rating Inventory (JERI) – described in baseline assessments (ASD group)
- Early Social Communication Scales (ESCS) – described in baseline assessments (ASD group)
- SenseToKnow App – described in baseline assessments (ASD group)
- Technology Questionnaire and Qualitative Interview of SenseToKnow App feasibility/appropriateness
- In the longitudinal pre-post phase of the study all 30 ASD caregiver-child dyads will receive 12, 1-hour ESDM-informed caregiver coaching sessions delivered by non-specialist Early Childhood Development practitioners. The longitudinal phase has a single study arm, and all ASD caregiver-child dyads will receive the same assessments and the same intervention. The longitudinal pre-post phase of the study will be used to investigate the exploratory component of Aim 1: Changes in child treatment targets measured with SenseToKnow app; and Aim 3: Changes in caregiver strategies targeted by the intervention.

Longitudinal pre-post phase assessments in the ASD group include:

- Caregiver Early Start Denver Model Implementation Fidelity: (Completed by clinician) Likert-based five-point rating system used to assess caregiver mastery of ESDM techniques S. Rogers, G. Dawson, L. Vismara, ESDM Parent Fidelity Tool (unpublished work). (2012).
- Non-Specialist Coaching Fidelity: (Completed by clinician) Likert-based four-point rating system used to assess therapist mastery of parent coaching techniques. S. Rogers, G. Dawson, L. Vismara, ESDM Parent Fidelity Tool (unpublished work). (2012).
- The Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) – described in baseline assessments
- Griffiths Scales of Child Development, Third Edition (Griffiths III) – described in baseline assessments
- Caregiver competence: The Parent Sense of Competence Scale – described in baseline assessments
- Caregiver stress: The Parenting Stress Index – Short Form – described in baseline assessments
- SenseToKnow App – described in baseline assessments
- Joint Engagement Rating Inventory (JERI) – described in baseline assessments
- Qualitative Interview of Caregiver Strategies used during Caregiver-child Interactions (post-intervention in ASD group)

COVID-19 Adaptations: Remote follow-up assessments in the ASD group who will include the following approved measures from above: a, b, c, e, h, i. Note that a,b,h are coded by a trained coder from video-recorded caregiver child interactions. It would not be feasible to complete the full battery of measures remotely. We aim to evaluate implementation outcomes (acceptability, appropriateness,

feasibility) of the telehealth-delivered caregiver coaching approach. Acceptability, appropriateness, and feasibility will be quantitatively assessed using 4-item, pragmatic scales: The Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). Readability is at the 5th grade level. Higher scores indicate greater acceptability, appropriateness, and feasibility. In addition, acceptability, appropriateness and feasibility will be assessed qualitatively with stakeholder individual interviews. Questions in the interview guide will be tailored to stakeholder group and will be informed by previous studies that have examined implementation barriers and facilitators during the implementation of new treatment approach.

Specific Aims and Research Methodology

The overall goal of the R21 is to determine the validity of NDBI treatment targets and whether scalable digital technology can be used to assess child treatment response in a multicultural, low resource South African environment.

COVID-19 adaptations: We aim to develop and implement telehealth NDBI coaching and utilize a mixed methods approach to gather implementation and preliminary effectiveness data on the telehealth intervention.

We plan to accomplish this overall objective by pursuing the following three specific aims:

Aim 1: Characterize NDBI child treatment targets in South African children with ASD using standardized assessments and digital technology, and determine whether these patterns differentiate children with ASD from their peers with developmental delay and typical development. An exploratory component of Aim 1 will assess whether 12 sessions of NDBI caregiver coaching result in changes in child treatment targets assessed using digital technology.

This aim will utilize two phases of the study: firstly, the baseline cross-sectional phase, and secondly, the longitudinal pre-post phase. In the baseline cross-sectional phase, we will evaluate and compare joint attention, engagement states, and explore biomarkers indexing children's facial affective expressions and attention/orienting in South African children with ASD (n=30), developmental delay (n=30) and typical development (n=30). We hypothesize that, similar to children in Western cultures, South African children with ASD will show decreased responsivity to social bids for attention, make fewer intentional social overtures (cumulatively known as joint attention, assessed with the Early Social Communication Scales, ESCS), and will show decreased periods of joint engagement (assessed using the Joint Engagement Rating Inventory, JERI)15 as compared to South African children with developmental delay and typical development. Through the use of an app, child social interest, orienting, attention, and affect will be measured in the three groups. We will explore whether children in the ASD group show lower attention to social stimuli, consistency in orienting to name calls, and positive affective response to stimuli in relation to the developmentally delayed and typically developing groups. We hypothesize that, these behaviors will differentiate children with ASD from their peers.

Frequency scores for initiation of and response to joint attention (IJA and RJA), will be derived from behavioral observations during a series of tasks presented by an examiner blind to child diagnosis. In order to assess joint engagement, child engagement states will be coded from video-recorded caregiver-child interactions and scored in a Likert scale by a trained rater, blind to child diagnosis. For joint attention and joint engagement, the primary statistical comparisons will be to evaluate whether

the ASD group score lower on three co-primary endpoints: IJA and RJA for joint attention, and joint engagement. Our power calculation was based on a two-sample t-test with unequal variances, using as a reference the observed IJA scores from a similar sample of ASD and typically developing children from a Western setting. With two groups of 30, assuming mean (SD) IJA score of 16 (8) among typically developing children, we will have 90% power to detect a difference in mean scores of at least 7 between ASD and typically developing children. A similar analytic approach will be used for RJA and joint engagement. If a difference is observed, between the ASD and typically developing groups, a secondary comparison will be conducted to compare the ASD group and the developmentally delayed group, using a multiple comparisons adjustment to control for Type I error. In collaboration with experts at Duke, using digital technology, we will explore biomarkers indexing children's facial affective expressions and attention/orienting. Using the same statistical analysis approach described above, we will explore whether children with ASD show lower attention to social stimuli, consistency in orienting to name calls and positive affective response to stimuli in relation to the developmentally delayed and typically developing groups.

In the second phase, we will conduct a longitudinal pre-post study with children in the ASD group who receive 12 sessions of intervention. In order to account for the estimated 15% attrition, and ensure a final total sample size of 30 caregiver-child dyads in the ASD group for the pre-post phase of the study, 35 caregiver-child dyads will initially be recruited. Using digital technology we will re-assess child social interest, orienting, attention, and affect post-intervention and explore patterns of change in individual trajectories of these behaviors. Paired t-tests (or Wilcoxon rank-sum tests if appropriate), in conjunction with exploratory graphical analyses of individual trajectories over time, will be conducted to assess the pre versus post change following 12 sessions of NDBI-informed caregiver coaching.

Aim 2: In the ASD group, determine the caregiver-child context for South African dyads, by identifying common family routines and characteristics of caregiver-child dyadic exchanges.

Because NDBIs are delivered in the context of common family routines, it is essential to understand how such routines present in South African families. This provides key information about how to embed NDBI strategies within family life. K01 pilot data includes descriptions of caregiver-child interactions, primarily during play, from 22 ethnically diverse caregivers of young children with ASD in South Africa. Data indicated that caregivers regularly interact with their young child with ASD during object-based play and sensory social routines. During object-based play, caregivers described dyadic interactions, where they joined with their child in child-preferred activities and tried to incorporate learning into those interactions. During sensory-social routines, caregivers reported awareness of child affect and social communication cues, and a variety of adult and child play participants. Additional data is needed to examine family routines; however, caregivers did spontaneously describe interactions with their child during family routines of mealtime and bath time.

During the baseline cross-sectional phase of the study, a mixed methods approach will assess caregiver-child context in the ASD group (30 caregiver-child dyads). Quantitative and qualitative data will be collected in a simultaneous, balanced arrangement, with equal importance being given to both. Quantitative data will describe characteristics of the caregiver-child context using standardized tools. Qualitative data will explore culturally-relevant categories not included in the standardized tools, developed for Western contexts. At the interpretation phase, results will be triangulated. The process of conceptual triangulation will be followed. This involves: (1) conducting qualitative and quantitative research, (2) distinguishing salient results, (3) examining confidence in the results, (4) developing criteria

for inclusion of results, and (5) constructing conceptual models describing the caregiver-child context in which NDBI strategies can be embedded.

Quantitative data will describe types of family routines (assessed via the Family Routines Inventory) and characteristics of caregiver-child dyadic exchanges (assessed via the JERI). Routine frequency scores will be derived from the Family Routines Inventory. Caregiver-child dyadic exchanges will be scored on a Likert scale by a trained rater, from video-recorded caregiver-child interactions, for (1) fluency and connectedness, and (2) shared routines and rituals.¹⁵ Exploratory graphical assessments will be used to understand and represent the distribution and patterns in family routines and dyadic interaction item scores.

Qualitative individual interviews, conducted with caregivers using a semi-structured interview guide, will facilitate a broader understanding of South African family routines. Questions will be derived from routine categories included in the Family Routines Inventory. Probes will elicit caregiver narratives on additional family routines, and routine participants. Individual interviews will be audio-recorded, transcribed verbatim and cross-checked for accuracy. Data will be inductively analyzed via content analysis using NVivo software.

Aim 3: In the ASD group, describe strategies caregivers use during caregiver-child interactions and evaluate whether there are changes in caregiver-specific strategies following NDBI caregiver coaching.

K01 pilot data suggests caregivers can implement Early Start Denver Model (ESDM) strategies as a result of 12 sessions of caregiver coaching by non-specialists. In the K01 pre-pilot, the first caregiver almost reached 80% fidelity, while the second caregiver surpassed 80% fidelity. This suggests potential for successful caregiver implementation of ESDM strategies as a result of the adapted intervention.

Using a mixed methods approach we will utilize both the baseline cross-sectional phase and the longitudinal pre-post phase of the study in the ASD group (30 caregiver-child dyads), to assess caregiver strategies. Our approach will be similar to that described in Aim 2. A conceptual model of South African caregiver strategies will be constructed. Since the caregiver plays a key role in delivering NDBIs, it is essential to understand strategies used by South African caregivers, how readily these strategies change when NDBI-informed interventions are delivered, and caregivers' perception of the NDBI strategies used.

Quantitative assessment of caregiver strategies at baseline and follow-up will be via the JERI, and include: (1) scaffolding, (2) following in on a child's focus, and (3) caregiver affect. These items will be scored on a Likert scale by a trained rater, from video-recorded caregiver-child interactions. We hypothesize that 12 sessions of NDBI-informed caregiver coaching will result in significant changes in the frequency and quality of caregiver strategies. Quantitative data will be analyzed with a paired t-test (or Wilcoxon rank-sum test if appropriate) to evaluate the change in caregivers strategies pre versus post intervention. In order to account for the estimated 15% attrition, and ensure a final total sample size of 30 caregiver-child dyads in the ASD group for the pre-post phase of the study, 35 caregiver-child dyads will initially be recruited. We will thus have 90% power to detect a standardized effect size (Cohen's d) of 0.60 using a paired t-test, assuming we standardize the difference between pre and post scores to have mean 0 and standard deviation 1.

Qualitative caregiver perceptions of strategies used during caregiver-child interactions will be collected at follow-up. Interview scripts will be developed to facilitate a broader understanding of strategies that are culturally-relevant to South African caregivers. Individual interviews will be audio-

recorded. Data will be transcribed verbatim and cross-checked for accuracy, and inductively analyzed via content analysis utilizing NVivo.

Aim 4: Adapt the NDBI caregiver coaching intervention and assessment of caregiver NDBI strategies for telehealth delivery in order to maintain services for young children with ASD impacted by COVID-19. Explore the acceptability, feasibility, and appropriateness of the adapted intervention and assessment approach.

The study team will adapt current session content for a telehealth platform. Each session skills will be adapted for delivery using simple pictures with few words via a WhatsApp message. The session structure will be maintained as best possible; as it supports adult learning. Sessions will include 12 telephone-based coaching sessions with: (1) Joint viewing and supported caregiver reflection of pre-recorded caregiver-child interaction; (2) Joint review of simple pictorial session skill sent to the caregiver via a WhatsApp message; and (3) Facilitated discussion of skill generalization across various caregiver-child daily routines.

We aim to evaluate implementation outcomes (acceptability, appropriateness, feasibility) of this adapted approach. Views of multiple stakeholders, including: (1) Caregivers; (2) Early Childhood Development Practitioners; (3) Early Childhood Development Practitioner School Supervisors; and (4) Early Start Denver Model supervisors will be assessed. Mixed methods will be used to understand the implementation processes, and the barriers and facilitators associated with the approach. Acceptability, appropriateness, and feasibility will be quantitatively assessed using 4-item, pragmatic scales: The Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). In addition, acceptability, appropriateness and feasibility will be assessed qualitatively with stakeholder individual interviews. Questions in the interview guide will be tailored to stakeholder group and be informed by previous studies that have examined implementation barriers and facilitators during the implementation of a new treatment approach.

Remote baseline assessments will include questions about demographics; questions about technology use; a caregiver-child interaction that will be recorded on the caregivers' smart phone and uploaded to a HIPPA compliant Duke Box folder; and the VABS-3. Audio-recorded individual interviews will be conducted with caregivers in the ASD group at baseline to assess family routines and strategies they use to interact with their child. In addition, these caregivers will complete the Family Routines Inventory. Remote post-intervention assessment in the ASD group will include a caregiver-child interaction will be recorded on the caregivers' smart phone and uploaded to a HIPPA compliant Duke Box folder; and the VABS-3. Following each telephone-based coaching session a caregiver-child interaction will be recorded on the caregivers' smart phone and uploaded to a HIPPA compliant Duke Box folder. The recorded caregiver-child interactions will occur in authentic environments of the child, with every day materials that the child are caregiver are familiar with.

Once Covid-19 restrictions are lifted and the risk of seeing participants are judged as acceptable by our partner sights and University of Cape Town IRB we will offer participants a choice of in-person

caregiver-coaching delivery. Should restrictions be reinstated the above procedures and methods will be implemented as necessary.

Selection of Subjects

The proposed research will be conducted within the Cape Town metropolitan region, South Africa, in autism schools, neurodevelopmental clinics, and early childhood development centers. The (1) baseline case-control study (autism spectrum disorder: ASD; developmental delay: DD; and typical development: TD) and the (2) longitudinal pre-post design intervention study (ASD group only and their caregivers) will evaluate naturalistic developmental behavioral intervention (NDBI) treatment targets and involve 120 human subjects (30 ASD caregiver-child dyads=60, 30 DD, 30 TD). In order to account for the estimated 15% attrition, and ensure a final total sample size of 30 caregiver-child dyads in the ASD group for the pre-post phase of the study, 35 caregiver-child dyads will initially be recruited. Therefore, 130 participants total will be enrolled in the study.

Inclusion criteria are as follows: (1) the child is between 18 and 72 months of age; (2) the subject's family speak isiXhosa, isiZulu, Afrikaans, or English (~ 97% of all household languages spoken in the Western Cape province); (3) the child's ethnicity/race is African or Coloured; and (4) the child lives within an area served by the recruitment sites. Additional inclusion criteria are group specific. For the ASD group: (1) the child meets criteria for an ASD diagnosis based upon DSM-5 criteria and informed by the ADOS-257 administered by research reliable raters; and (2) the caregiver is \geq 18 years old. For the developmental delay group: (1) the child screens positive on the Ten Questions and negative on the Autism Behavior Checklist (ABC); and (2) has been diagnosed with developmental delay by a developmental pediatrician. For the typically developing group: The child screens negative for a developmental delay on the Ten Questions and negative for ASD on the ABC.

COVID-19 adaptations: Because we aim to assess the acceptability, feasibility, and appropriateness of the adapted telehealth coaching intervention - views of multiple stakeholders involved in the implementation of the intervention will be assessed. This includes the child's caregiver, Early Childhood Development Practitioners, Early Childhood Development Practitioner School Supervisors, and ESDM therapists who provide supervision and oversight of the caregiver coaching session. Inclusion criteria are as follows: For the Early Childhood Development Practitioners (n=2) and Early Childhood Development Practitioner School Supervisors (n=2) group: the ECD worker and/or school supervisor are 1) employed by our participating recruitment partners (Western Cape Education Department Schools) and 2) involved in delivery of the caregiver coaching sessions, either in person or remotely. For the Early Start Denver Model supervisors (n=3): the local supervisors are 1) trained ESDM therapist, 2) supervise weekly coaching sessions in the schools, and/or 3) supervise remote intervention delivery sessions.

Exclusion criteria for the ASD group include: (1) the presence of a neurological disorder of known etiology (e.g., Fragile X); and (2) a caregiver-child dyad that is unable to attend assessments and 12 coaching sessions. Exclusionary criteria for all groups include: (1) significant sensory or motor impairment; (2) major physical abnormalities; and a (3) history of serious head injury and/or neurological disease. Exclusionary criteria for the DD and TD groups: (1) an autism diagnosis based on DSM 5 criteria.

Subject Recruitment and Compensation

Recruitment procedures utilized in Dr Franz's K01 will continue in the R21 and potential subjects in the ASD group will be identified by participating recruitment sites, Western Cape Autism, and if participants are interested in screening, they will be referred to the Project Coordinator who will meet with them in a private location to conduct the screening. Participants will be asked to provide oral consent to be screened. The Project Coordinator will then screen participants for most inclusion (ADOS-2 will be performed at baseline assessment for the ASD group) and exclusion criteria. Potential subjects who meet eligibility criteria will be informed of the study, and invited to participate.

Similar recruitment procedures will be followed for the DD and TD groups, with potential subjects being identified by participating recruitment sites (Neurodevelopmental clinics at Red Cross hospital for DD group, and early childhood development centers in the Cape Town metropolitan region for TD group). If participants are interested in screening, they will be referred to the Project Coordinator who will meet with them in a private location to conduct the screening. Participants will be asked to provide oral consent to be screened. The Project Coordinator will screen participants in the DD and TD groups using the Ten Questions questionnaire and the Autism Behavior Checklist. For the DD group, the child will need to screen positive on one or more questions on the Ten Questions in order to be eligible to participate in the study, and screen negative on the Autism Behavior Checklist. For the TD group, the child will need to screen negative on all questions on the Ten Questions questionnaire, in addition to screening negative on the Autism Behavior Checklist. If a child in the TD group screens positive on the Ten Questions, the Project Coordinator (who is an occupational therapist by training) will provide the caregiver with appropriate referral information for the Neurodevelopmental clinic at Red Cross hospital. If children in the DD or TD group screen positive on the Autism Behavior Checklist, an ADOS-2 will be administered by a research reliable South African clinician to help inform decisions on whether the child has ASD. If concerns remained for ASD following ADOS-2 administration, the Project Coordinator will provide the caregiver with appropriate referral information for the Neurodevelopmental clinic at Red Cross hospital. The Project Coordinator will then screen potential subjects in the DD and TD group for additional exclusion criteria. Potential subjects who meet eligibility criteria will be informed of the study, and invited to participate.

Participants will be informed throughout the recruitment process and study sessions that participation is voluntary and that they may refuse to answer any question for any reason. In addition, the caregivers of their child may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which they are otherwise entitled.

We are aware of the ethical considerations in providing participant compensation to people who may be living in poverty because providing cash payments can unintentionally coerce participation in research. Thus, we will restrict compensation to cover the basic costs of participation by providing a travel reimbursement at each study visit (ZAR 300, for baseline assessment and ZAR 100, for each intervention session).

Covid-19 adaptions: where Covid-19 regulations and restrictions does not allow for in-person recruitment and enrollment procedures a system that enables remote enrollment and consent of ASD caregiver-child dyads will be developed and implemented. Eligible families, with a child with ASD within the age range of 18-72 months will be identified by our participating recruitment partners (Western Cape Education Department Schools). Our partner sites have records of children with ASD (who have received an ASD diagnostic assessment) who are waiting for public sector special education services. Families will be invited to participate in the study by School Staff. Those who are interested will be

contacted by the Project Coordinator who will explain the study and gather the screener questionnaire data. If the child meets checklist criteria and caregiver provides informed consent (through a telephone-consent process), the child and family will be enrolled.

Study Interventions

The study aims to adapt a caregiver coaching version of the Early Start Denver Model (ESDM), an evidence-based early intervention for autism spectrum disorder, for implementation by non-specialist early childhood development workers, employed by the Department of Education. The South African adapted intervention utilizes Community ESDM materials, which are currently being piloted in rural, low resource parts of the U.S. Participants receive 12, 1 hour, weekly sessions of caregiver coaching. The session skill is introduced by "Help is in your hands" Community ESDM44 videos, then early childhood development workers coach caregivers on the session skill and support caregiver reflection and skill generalization.

COVID-19 adaptations: The study team will adapt current session content for a telehealth platform. Each session skills will be adapted for delivery using simple pictures with few words via a WhatsApp message. The session structure will be maintained as best possible; as it supports adult learning. Sessions will include 12 telephone-based coaching sessions with: (1) Joint viewing and supported caregiver reflection of pre-recorded caregiver-child interaction; (2) Joint review of simple pictorial session skill sent to the caregiver via a WhatsApp message; and (3) Facilitated discussion of skill generalization across various caregiver-child daily routines.

Data Analysis & Statistical Considerations

Aim 1: Characterize NDBI child treatment targets in South African children with ASD using standardized assessments and digital technology, and determine whether these patterns differentiate children with ASD from their peers with developmental delay and typical development. An exploratory component of Aim 1 will assess whether 12 sessions of NDBI caregiver coaching result in changes in child treatment targets assessed using digital technology.

This aim will utilize two phases of the study: firstly, the baseline cross-sectional phase, and secondly, the longitudinal pre-post phase. In the baseline cross-sectional phase, we will evaluate and compare joint attention, engagement states, and explore ASD behavioral risk markers indexing children's facial affective expressions, attention/orienting, and postural sway in South African children with ASD (n=30), developmental delay (n=30) and typical development (n=30). We hypothesize that, similar to children in Western cultures, South African children with ASD will show decreased responsivity to social bids for attention, make fewer intentional social overtures (cumulatively known as joint attention, assessed with the Early Social Communication Scales, ESCS), and will show decreased periods of joint engagement (assessed using the Joint Engagement Rating Inventory, JERI) as compared to South African children with developmental delay and typical development. Through the use of an app, child social interest, orienting, attention, affect, and postural sway will be measured in the three groups. We will explore whether children in the ASD group show lower attention to social stimuli, consistency in orienting to name calls, positive affective response to stimuli, and greater postural sway in relation to the developmentally delayed and typically developing groups. We hypothesize that, these behaviors will differentiate children with ASD from their peers.

Frequency scores for initiation of and response to joint attention (IJA and RJA), will be derived from behavioral observations during a series of tasks presented by an examiner blind to child diagnosis. In order to assess joint engagement, child engagement states will be coded from video-recorded caregiver-child interactions and scored in a Likert scale by a trained rater, blind to child diagnosis. For joint attention and joint engagement, the primary statistical comparisons will be to evaluate whether the ASD group score lower on three co-primary endpoints: IJA and RJA for joint attention, and joint engagement. Our power calculation was based on a two-sample t-test with unequal variances, using as a reference the observed IJA scores from a similar sample of ASD and typically developing children from a Western setting. With two groups of 30, assuming mean (SD) IJA score of 16 (8) among typically developing children, we will have 90% power to detect a difference in mean scores of at least 7 between ASD and typically developing children. A similar analytic approach will be used for RJA and joint engagement. If a difference is observed, between the ASD and typically developing groups, a secondary comparison will be conducted to compare the ASD group and the developmentally delayed group, using a multiple comparisons adjustment to control for Type I error. In collaboration with experts at Duke, using digital technology, we will explore ASD behavioral risk makers indexing children's facial affective expressions, attention/orienting, and postural sway. Using the same statistical analysis approach described above, we will explore whether children with ASD show lower attention to social stimuli, consistency in orienting to name calls and positive affective response, and greater postural sway to stimuli in relation to the developmentally delayed and typically developing groups.

Because the main predictors of response are age, sex and group (ASD, DD, TD), by balancing the age and sex distribution across the three groups we will be able to better isolate differences in child joint attention, joint engagement, and ASD behavioral symptoms, between the groups that are attributable to whether the child is ASD, DD, or TD. This will answer a fundamental question of whether our NDBI treatment targets are valid. Addressing this main research question is critical to designing effective early interventions that may be adapted for pilot testing across sub-Saharan Africa.

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 joint attention, joint engagement, and ASD behavioral symptoms in histograms to better understand the shape and spread of the distribution of each. We will overlay the shape of the distributions (e.g. as kernel density plots) in each of the three groups, using the data from the 30 children in each group, with each curve plotted in a different color. We will then move from these individual data distributions to the pairwise relationships between joint attention, joint engagement, and ASD behavioral symptoms, by plotting the values in scatterplots and color-coding the three groups. For example, with initiation of joint attention on the horizontal axis and response to joint attention on the vertical we can clearly show the distribution of joint attention and how that distribution differs by the three groups. Similarly, we will summarize joint attention, joint engagement, and ASD behavioral symptoms and covariates by the three groups (ASD, DD, TD) using means and standard deviations, median and interquartile ranges or counts and percentages, as appropriate. In terms of inference, we can compare joint attention, joint engagement, and ASD behavioral symptoms between the three groups by performing a one-way ANOVA on each, or by using the alternative non-parametric Kruskal-Wallis test, if needed. Whilst statistical inference is valuable, we anticipate that we will elicit most information through careful data visualization. If, in fact, other covariates, such as maternal education or socioeconomic status, are identified as being important we will be able to extend to a regression modeling framework in which we would separately analyze joint attention, joint engagement, and ASD behavioral symptoms, by

regressing each on group and adjusting for the additional covariates. We will be cautious about adjusting for multiple covariates given the relatively small sample size (30 per group). Nevertheless, as noted above, since age and sex are expected to be the strongest predictors, over and above group (ASD vs. DD vs. TD), we do not anticipate the need for extensive regression modeling, if any.

In the second phase, we will conduct a longitudinal pre-post study with children in the ASD group who receive 12 sessions of intervention. In order to account for the estimated 15% attrition, and ensure a final total sample size of 30 caregiver-child dyads in the ASD group for the pre-post phase of the study, caregiver-child dyads will initially be recruited. Using digital technology, we will re-assess child social interest, orienting, attention, affect, and postural sway post-intervention and explore patterns of change in individual trajectories of these behaviors. Paired t-tests (or Wilcoxon rank-sum tests if appropriate), in conjunction with exploratory graphical analyses of individual trajectories over time, will be conducted to assess the pre versus post change following 12 sessions of NDBI-informed caregiver coaching.

When focusing on changes in ASD behavioral symptoms and caregiver strategies in the ASD group following 12 intervention sessions (exploratory component of Aim 1 and Aim 3) we will again use comprehensive data visualization with scatter plots of the pre and post-intervention measures of each outcome for the 30 ASD children. For inference, paired t-tests will be used, or if assumptions of the t-test are not met, the Wilcoxon signed rank test will be used. Additionally, given that severity (measured by ADOS-2 comparison score) may predict changes over time, we will perform stratified analyses separately for high severity from low severity children. Specifically, we will examine all data visualizations by severity category. Likewise, we will perform inference separately for the high and low severity children. We may explore regression modeling strategies where we regress change in each outcome measure on severity category (or severity score, if appropriate), a strategy that would allow us to additionally adjust for age and/or sex. Nevertheless, we recognize that with a total sample size of 30, we will be cautious when performing and interpreting our inferential statistics and, if modeling assumptions are not satisfied, we will not proceed with the analysis. As noted above, data visualization and summary statistics will provide us with a wealth of information.

Aim 2: In the ASD group, determine the caregiver-child context for South African dyads, by identifying common family routines and characteristics of caregiver-child dyadic exchanges.

Because NDBIs are delivered in the context of common family routines, it is essential to understand how such routines present in South African families. This provides key information about how to embed NDBI strategies within family life. K01 pilot data includes descriptions of caregiver-child interactions, primarily during play, from 22 ethnically diverse caregivers of young children with ASD in South Africa. Data indicated that caregivers regularly interact with their young child with ASD during object-based play and sensory social routines. During object-based play, caregivers described dyadic interactions, where they joined with their child in child-preferred activities and tried to incorporate learning into those interactions. During sensory-social routines, caregivers reported awareness of child affect and social communication cues, and a variety of adult and child play participants. Additional data is needed to examine family routines; however, caregivers did spontaneously describe interactions with their child during family routines of mealtime and bath time.

During the baseline cross-sectional phase of the study, a mixed methods approach will assess caregiver-child context in the ASD group (30 caregiver-child dyads). Quantitative and qualitative data will be collected in a simultaneous, balanced arrangement, with equal importance being given to both.

Quantitative data will describe characteristics of the caregiver-child context using standardized tools. Qualitative data will explore culturally-relevant categories not included in the standardized tools, developed for Western contexts. At the interpretation phase, results will be triangulated. The process of conceptual triangulation will be followed. This involves: (1) conducting qualitative and quantitative research, (2) distinguishing salient results, (3) examining confidence in the results, (4) developing criteria for inclusion of results, and (5) constructing conceptual models describing the caregiver-child context in which NDBI strategies can be embedded.

Quantitative data will describe types of family routines (assessed via the Parent Survey of Home and Family Experiences) and characteristics of caregiver-child dyadic exchanges (assessed via the JERI15). Routine frequency scores will be derived from the Parent Survey of Home and Family Experiences. Caregiver-child dyadic exchanges will be scored on a Likert scale by a trained rater, from video-recorded caregiver-child interactions, for (1) fluency and connectedness, and (2) shared routines and rituals. Exploratory graphical assessments will be used to understand and represent the distribution and patterns in family routines and dyadic interaction item scores.

Qualitative data from open ended questions in the Parent Survey of Home and Family Experiences, will facilitate a broader understanding of South African family routines. Probes will elicit caregiver narratives on additional family routines, and routine participants. Data will be inductively analyzed via content analysis using NVivo software.

Aim 3: In the ASD group, describe strategies caregivers use during caregiver-child interactions and evaluate whether there are changes in caregiver-specific strategies following NDBI caregiver coaching.

K01 pilot data suggests caregivers can implement Early Start Denver Model (ESDM) strategies as a result of 12 sessions of caregiver coaching by non-specialists. In the K01 pre-pilot, the first caregiver almost reached 80% fidelity, while the second caregiver surpassed 80% fidelity. This suggests potential for successful caregiver implementation of ESDM strategies as a result of the adapted intervention.

Using a mixed methods approach we will utilize both the baseline cross-sectional phase and the longitudinal pre-post phase of the study in the ASD group (30 caregiver-child dyads), to assess caregiver strategies. Our approach will be similar to that described in Aim 2. A conceptual model of South African caregiver strategies will be constructed. Since the caregiver plays a key role in delivering NDBIs, it is essential to understand strategies used by South African caregivers, how readily these strategies change when NDBI-informed interventions are delivered, and caregivers' perception of the NDBI strategies used.

Quantitative assessment of caregiver strategies at baseline and follow-up will be via the JERI, and include: (1) scaffolding, (2) following in on a child's focus, and (3) caregiver affect. These items will be scored on a Likert scale by a trained rater, from video-recorded caregiver-child interactions. We hypothesize that 12 sessions of NDBI-informed caregiver coaching will result in significant changes in the frequency and quality of caregiver strategies. Quantitative data will be analyzed with a paired t-test (or Wilcoxon rank-sum test if appropriate) to evaluate the change in caregiver strategies pre versus post intervention. In order to account for the estimated 15% attrition, and ensure a final total sample size of 30 caregiver-child dyads in the ASD group for the pre-post phase of the study, 35 caregiver-child dyads will initially be recruited. We will thus have 90% power to detect a standardized effect size (Cohen's d) of 0.60 using a paired t-test, assuming we standardize the difference between pre and post scores to have mean 0 and standard deviation 1.

Qualitative caregiver perceptions of strategies used during caregiver-child interactions will be collected at follow-up. Interview scripts will be developed to facilitate a broader understanding of strategies that are culturally-relevant to South African caregivers. Individual interviews will be audio-recorded. Data will be transcribed verbatim and cross-checked for accuracy, and inductively analyzed via content analysis utilizing NVivo.

Aim 4: Adapt the NDBI caregiver coaching intervention and assessment of caregiver NDBI strategies for telehealth delivery in order to maintain services for young children with ASD impacted by COVID-19. Explore the acceptability, feasibility, and appropriateness of the adapted intervention and assessment approach.

Acceptability, feasibility and appropriateness of the telehealth approach will be evaluated. Views of multiple stakeholders: (1) Caregivers; (2) Early Childhood Development Practitioners; (3) Early Childhood Development Practitioner School Supervisors; and (4) NDBI supervisors will be assessed. Mixed methods will be used to understand the implementation process, and barriers and facilitators. Acceptability, feasibility, and appropriateness will be quantitatively assessed using the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). In addition, acceptability, feasibility and appropriateness will be assessed qualitatively. The interview guide will be tailored to the stakeholder group and be informed by previous studies that have examined implementation barriers and facilitators during the implementation of a new treatment approach; including some of our previous work. At the interpretation phase, results will be triangulated. The process of conceptual triangulation will be followed.

Child social communication will be assessed with the Socialization and Communication standard scores from the Vineland Adaptive Behavioral Scale Third Edition (VABS-3). The VABS-3 will be administered telephonically at the baseline and follow up. We will evaluate pre-post change on the VABS-3 among dyads receiving the telehealth intervention using a paired t-test, under the null hypothesis of no change over time (in the case that the outcome data is heavily skewed, a Wilcoxon signed rank test will be used instead). Assuming the same standard deviations as the R21 pilot data (7.5 for Socialization and 8.3 for Communication), we will have 90% power to detect mean pre-post changes of at least 5.7 for Socialization and 6.3 for Communication.

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 impact of an intervention on targeted health outcomes. Pilot R21 data (n=10) suggests that South African caregivers can learn to implement core NDBI intervention principles. After 12 sessions: mean fidelity scores increased from 2.93 to 3.73. However, when interventions are adapted to fit a new target population, delivery setting, location or organization, maintaining intervention fidelity is of particular importance. As the intervention is adapted for delivery on a telehealth platform, fidelity is critical to monitor. Fidelity ratings can be completed from video-recordings of caregiver-child interactions. Caregiver child interactions will be recorded on the caregivers' Smartphone and uploaded to a HIPPA compliant Duke Box folder. Caregiver-child interactions will occur in the child's home, an authentic environment of the child, with every day materials that the child and caregiver are familiar with.

The Caregiver ESDM Fidelity Rating System provides a method for assessing fidelity; namely the degree to which a caregiver is using intervention principles in a joint activity routine with their young child. The 13 item rating scale includes ratings of performance on core intervention strategies from 1 to

5; where 1 represents a lack of an effective display of the practices specified, and 5 represents the best possible example of this teaching behavior. Fidelity of implementation of NDBI strategies will be manually coded by certified ESDM therapists at baseline, for each of the 12 intervention sessions, and at follow up. Mean fidelity scores (with SD) will be calculated across study participants in order to assess change in NDBI strategies. As with in-person intervention, we expect that caregivers will learn to implement core NDBI intervention principles after 12 intervention sessions. Pre-post change in the telehealth delivery group will be assessed using a paired t-test (or Wilcoxon signed rank test, as appropriate). Assuming the same standard deviation (0.6) as the R21 pilot data, we will have 90% power to detect a mean pre-post change of at least 0.5.