CLINICAL STUDY PROTOCOL

Evaluation of a Novel Intervention for Infants at Risk for Neurodevelopmental Disorders

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Sponsor
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Synopsis

Study Purpose

This study entails a "proof of concept" evaluation of a novel intervention, Parents and Infants Engaged (PIE), for prodromal infants at-risk for neurodevelopmental disorders (NDs). The objectives of the current study are to examine whether the PIE intervention (a) transforms parent-infant transactions over time as intended, thereby facilitating increases in the time infants spend in joint engagement with their parents, and (b) is associated with improved social-communication functioning and positive changes in indices of autonomic self-regulation in infants at-risk for NDs.

Primary Objective

The positive association between parent responsiveness and better social-communication outcomes in children in general, and children with neurodevelopmental disorders (NDs) in particular, has driven the development of early interventions promoting parent responsiveness for these populations. Such intervention models assume that increases in parent responsiveness will improve child outcomes. However, for interventions targeting infants and toddlers at elevated likelihood of or diagnosed with NDs, such as autism spectrum disorder (ASD), the effects of parent responsiveness interventions have been modest in size and highly variable, rendering the evidence inconclusive for parent responsiveness as a mediator of infant/toddler outcomes.

We propose that ensuring a more effective parent-mediated intervention for this population depends on the guidance of a refined theory of change—one explicitly acknowledging that infant behaviors influence parent responsiveness. Developmental studies indicate that infants at elevated likelihood of NDs are likely to exhibit behaviors that either fail to elicit parent responses or elicit parent responses that do not effectively support the infant's engagement and learning. In addition, optimal features of parent responsiveness appear to vary as a function of children's developmental levels and other dynamic variables. To date, studies of parent-mediated interventions have not addressed these complexities. However, recent research points to key "child" variables likely to play transactional roles in communication development among infants and toddlers with or at-risk for NDs. These include aspects of children's prelinguistic communication characteristics (e.g., intentional communication, diversity of consonants) that are related to both parent responsiveness and children's later communication skills. Also, preliminary data from our team indicate infants' sensory reactivity (hypo- and hyper-reactivity) predicts not only parent responsiveness but also social-communication outcomes of infants at-risk for NDs. Arguably, increases in parent responsiveness lead to improved parent-infant dyadic engagement, which in turn mediates infants' communication outcomes. Finally, physiological self-regulation impacts social and communication outcomes in children, but may be disrupted in infants at-risk for NDs, associated with their difficulties modulating sensory reactivity.

In re-conceptualizing intervention for infants at-risk for NDs, we have integrated these variables into a new model, Parents and Infants Engaged (PIE), with two key content domains: Sensory Reactivity and Prelinguistic Communication.

Objective 1: The primary objective of this study is to examine whether the novel PIE intervention transforms parent-infant transactions over time as intended, thereby facilitating increases in the time infants spend in dyadic engagement with their parents. We will also evaluate whether dyadic engagement outcomes differ based on whether parents are coached first in the sensory reactivity domain followed by coaching in the prelinguistic communication domain, or are coached in the opposite order.

Secondary Objectives

Our secondary objectives will provide further insights into whether the PIE intervention is functioning as intended. Specifically, our secondary objectives are to:

- Objective 2: Estimate the separate and combined effects of the two PIE intervention domains on infant intention communication.
- Objective 3: Evaluate the differential changes in parent responsiveness following coaching on two individual Parents and Infants Engaged (PIE) intervention domains — responses to variable infant (a) sensory reactivity or (b) prelinguistic communication — as well as cumulative changes in parent responsiveness following coaching on both PIE domains.
- Objective 4: Determine the extent to which (a) autonomic indices of infant self-regulation, and (b) language, sensory reactivity patterns, response to joint attention, and social-communication skills change over the course of the PIE intervention.

General Design Description

The intervention phases of the study will use a randomized comparative trial design, with two phases. For Study Phase 1, dyads will participate in baseline assessments; then eligible parent-infant dyads will be randomized, stratifying by child age, to one of two treatment arms. Arm 1 families will participate in initial coaching on the PIE sensory reactivity (SR) domain, and Arm 2 families will participate in initial coaching on the PIE prelinguistic communication (PC) domain. Families will participate in 6 weekly coaching sessions in their respective treatment arms, and return for Posttest-1. For Study Phase 2, dyads in Arm 1 will receive 6 weekly coaching sessions on the PC domain, and dyads in Arm 2 will receive 6 weekly coaching sessions on the SR domain. Then families will return for Posttest-2.

Study Date Range and Duration

The study will start August 1, 2017, with data collection continuing for 22 months.

Number of Study Sites

There is one study site for data collection, at the University of North Carolina at Chapel Hill, Chapel Hill, NC.

Data processing, video coding, and statistical analyses will occur at two sites, the University of North Carolina at Chapel Hill and the University of Southern California, Los Angeles, CA.

Primary Outcome Variables

The primary outcome variable is parent-infant dyadic engagement. We define dyadic engagement as an observable pattern of mutual focus, active participation, and reciprocal exchanges within a parent and child interaction.

We will collect data on this outcome at baseline, posttest 1 (after families have been randomly assigned to an intervention arm and coached in one of the two PIE intervention domains), and posttest 2 (after families have been coached in both of the PIE intervention domains).

The rationale for choosing dyadic engagement as the primary outcome is that parent coaching in each domain is designed to assist parents in engaging their child in positive interactions with them and increasing the length of these periods of engagement through supporting the infants in regulating their responses to sensory stimuli and/or responding sensitively to infants' prelinguistic communication cues.

This outcome will be evaluated using an adapted version of a parent-child engagement state coding system originally developed by Adamson et al. (2009) and adapted by Bottema-Beutel et al., (2018).

Secondary and Exploratory Outcome Variables

Secondary outcome variables:

The first three secondary outcome measures will be assessed at three timepoints: Baseline, Posttest 1 (after families have been randomly assigned to an intervention arm and coached in one of the two PIE intervention domains), and Posttest 2 (after families have been coached in both of the PIE intervention domains). For these measures, we are particularly interested in whether there are effects specific to the initial PIE coaching domain (sensory reactivity or prelinguistic communication) at Posttest 1, and whether

there are order effects (differences between study arms) at Posttest 2.

1. Changes in parent responsiveness to infant sensory reactivity cues. [Measured via a project-developed rating tool.] This secondary measure is included to determine whether coaching in the sensory reactivity domain yields the expected specific effects on parents' responses to infant sensory reactivity cues.

2. Changes in parent responsiveness to infant prelinguistic communication cues. [Measured via a project-developed rating tool.] This secondary measure is included to determine whether coaching in the prelinguistic communication domain yields the expected specific effects on parents' responses to infant prelinguistic communication cues.

3. Changes in infant intentional communication. [Measured via a project-developed coding system.] The rationale for including this outcome measure is that parental responsive support of infant engagement will promote infants' increased use of intentional communication, previously found to predict later receptive and expressive language outcomes for preschoolers already diagnosed with autism (Yoder et al., 2015).

The following 8 secondary outcome variables will be measured at two timepoints: Baseline and Posttest 2. For these measures, we are particularly interested in examining the magnitude of change over the course of the full intervention, as well as whether there are order effects (differences between study arms) at Posttest 2.

4. Changes in infant respiratory sinus arrhythmia (RSA). This measure was chosen as an index of parasympathetic system functioning, and will be measured within a paradigm in which the infants are passively observing vignettes of infant-directed speech, as an intended experimental analog of the live parent-infant interactions we are videorecording to derive other outcome measures. We hypothesize we will see increased RSA levels during infant-directed speech, reflecting greater parasympathetic control, by Posttest 2.

5. Changes in infant skin conductance level (SCL). This measure was chosen as an index of sympathetic system functioning, and will be measured within the above described infant-directed speech paradigm. We hypothesize we will see decreased SCL levels during infant-directed speech, reflecting less elevation of sympathetic activity when observing infant-directed speech vignettes, by Posttest 2.

6 Changes in infants' receptive language. [Measured via the Mullen Scales of Early Learning (MSEL) Receptive Language scale, Mullen, 1995.] This measure is a more distal outcome measure that we hypothesize will improve in association with improvements in parent-infant dyadic engagement and infant intentional communication.

7. Changes in infants' expressive language. [Measured via the MSEL Receptive Language scale, Mullen, 1995.] This measure also is a more distal outcome measure that we hypothesize will improve in association with improvements in parent-infant dyadic engagement and infant intentional communication.

8. Changes in infants' responses to adults' bids to direct their attention to an new object (i.e., response to joint attention). [Measured via a subset of 6 Attention Following trials from the Joint Attention Protocol, Watson et al., 2003.] One frequent behavioral

characteristic of infants at elevated likelihood of later NDs is that they have difficulty in responding to joint attention bids that require them to redirect their attention away from their current focus to a new object. Potentially, improvements in parent-infant dyadic engagement will, over time, yield improvements in response to joint attention as parents learn to use new strategies to effectively engage their infant, and infants have more experiences in reciprocal interactions with their caregivers. Such changes could signal infants' decreased dependency on parents observing and responding to their immediate focus of attention, and provide a larger variety of learning opportunities.

9. Changes in infants' social-communication skills. [Measured via the Brief Observation of Social-Communication Change, BOSCC, Lord, Grzadzinski et al., 2017.] In analyses with other samples screened with the FYIv3.1, our team has documented that the positive predictive value of the tool specifically for autism is around 30-40%, varying with the age at screening (unpublished data). Due to the nature of the items on the FYIv3.1, infants meeting the threshold for being at elevated likelihood for NDs on the FYIv.3.1 will have parent-reported social-communication behaviors associated with autism. The BOSCC was designed to assess improvements in early social-communication skills that are usually impaired in young children with autism but also are known to change/improve over time. Thus, we are using the BOSCC to examine whether these skills change significantly over the course of the full PIE intervention.

10. Changes in observed infant sensory reactivity patterns. [Measured via the Sensory Processing Assessment for Young Children, SPA, Baranek, 1999a.] In coaching parents to be sensitive to their infants' cues related to sensory reactivity and to respond in ways that support their infants' regulation of these responses, another potential distal outcome of the PIE intervention would be improvements in extreme patterns of sensory reactivity (i.e., diminished hypo- and/or hyper-reactivity). Use of the SPA as an observational measure will provide us with the opportunity to assess whether any changes are observed by assessors who are blinded to the arm of the study to which families are assigned.

11. Changes in parent-reported infant sensory reactivity patterns. [Measured via the Sensory Experiences Questionnaire v. 2.1, SEQ, Baranek, 1999b.] As a complement to the SPA, we are using the SEQ to determine whether parents perceive improvements in their children's sensory reactivity patterns over the course of the full PIE intervention.

Study Population

The study population is infants between the ages of 11-16 months who are identified as being at elevated likelihood of a later neurodevelopmental disability diagnosis (e.g., autism spectrum, attention-deficit hyperactivity disorder, language delay/disorder, sensory processing disorder), along with a parent (or other primary family caregiver e.g., grandparent) for each child. Infants will be recruited from 6 central North Carolina counties that include rural and urban areas representing wide demographics. Parents initially will be asked to complete a screening questionnaire, The First Years Inventory, v.3.1b (FYIv3.1b; Baranek et al., 2014).. Study eligibility will be further evaluated for infants whose screening scores on the FYIv3.1b meet empirically determined thresholds for being at elevated likelihood for a later diagnosed neurodevelopmental disorder (ND),

as well as parent eligibility. At baseline assessments, infants must have a score of at least 1 standard deviation below the mean on the Receptive or Expressive Language scale (or both) of the Mullen Scales of Early Learning, as well as meeting clinical-determined criteria for elevated patterns of hypo-reactivity or hyper-reactivity (or both) on the Sensory Processing Assessment to be eligible for enrollment in the intervention trial. Infants will include both sexes, although given previous studies we expect a 2:1 (male:female) ratio, given that boys are more likely to score at elevated likelihood for neurodevelopmental disorders (e.g., ASD) targeted by the FYI.

Exclusion criteria: Infants with known genetic conditions (e.g., Down syndrome), and those with significant uncorrected vision/hearing/physical impairments will be excluded. We exclude infants with known genetic disorders due to our focus on testing PIE with infants at elevated likelihood of neurodevelopmental disorders based on behavioral markers, but whose eventual diagnosis remains unclear. We will exclude infants with significant uncorrected vision/hearing/physical impairments because they likely would not be able to fully participate in the assessment procedures, and the assessment results would be of questionable validity. Families who do not speak English as their primary language in the home (>50% of the time) will be excluded, because screening tools, assessments, and interventions are not available uniformly in other languages.

Number of Participants

We plan to enroll 44 infants at elevated likelihood of a later ND and a primary caregiver of each infant. Based on prior studies with similar populations, we anticipate approximately 1% of completed FYIs will yield a parent-infant dyad that meets all eligibility criteria and consents to enroll in the intervention trial. Thus, screening of ~4400 infants on the FYIv3.1 likely will be required to recruit this sample. All recruitment will take place at the University of North Carolina at Chapel Hill study site.

Visit Schedule Table (0ptional)

See attached table.

Study Flow Chart (optional)

See attached chart.

Abbreviations

Abbreviation	Explanation

Glossary of Terms

Glossary	Explanation

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1.1 Statement of Compliance

- The trial will be carried out in accordance with International Council on 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 IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) 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

2.1 Background

The positive association between parent responsiveness and better social-communication outcomes in children in general (Bornstein, 1995, Hudson et al., 2015; Tamis-LeMonda et al., 2014), and children with neurodevelopmental disorders (NDs) in particular (Brady et al., 2014; Dimitrova et al., 2016; Yoder et al., 2015), has driven the development of early interventions promoting parent responsiveness for these populations (Aldred et al., 2004; Kong & Carta, 2011; Siller et al., 2014). Such intervention models assume that increases in parent responsiveness will improve child outcomes. However, for interventions targeting *infants and toddlers at risk for or diagnosed with NDs*, such as autism spectrum disorder (ASD), the effects of parent responsiveness interventions have been modest in size and highly variable (Baranek et al., 2015; Carter et al., 2011; Green et al., 2015; Kasari et al., 2014), rendering the evidence inconclusive for parent responsiveness as a mediator of infant/toddler outcomes (Kong & Carta, 2011).

We propose that ensuring a more effective parent-mediated intervention for this population depends on the guidance of a refined theory of change—one explicitly acknowledging that infant behaviors influence parent responsiveness. Developmental studies indicate that infants at-risk for NDs are likely to exhibit behaviors that either fail to elicit parent responses or elicit parent responses that do not effectively support the infant's engagement and learning (Hudry et al., 2015; Northrup & Iverson, 2015; Leezenbaum et al., 2014; Warlaumont et al., 2014). In addition, optimal features of parent responsiveness appear to vary as a function of children's developmental levels and other dynamic variables (Haebig et al., 2013). To date, studies of parent-mediated interventions have not addressed these complexities. However, recent research points to key "child" variables likely to play transactional roles in communication development among infants and toddlers with or at-

risk for NDs. These include aspects of children's prelinguistic communication characteristics (e.g., intentional communication, diversity of consonants) that are related to both parent responsiveness and children's later communication skills (Yoder et al., 2015). Also, preliminary data from our team indicate infants' sensory reactivity (hypo- and hyper-reactivity) predicts not only parent responsiveness but also social-communication outcomes of infants at-risk for NDs. Arguably, increases in parent responsiveness lead to improved parent-infant joint engagement, which in turn mediates infants' communication outcomes. Finally, physiological self-regulation impacts social and communication outcomes in children (Calkins & Keane, 2004; Doussard-Roosevelt et al., 2001; Watson et al., 2010), but may be disrupted in infants at-risk for NDs (Dale et al., 2011; Feldman, 2007), associated with their difficulties modulating sensory reactivity (Schaaf et al., 2010).

In re-conceptualizing intervention for infants at-risk for NDs, we have integrated these variables into a new model, Parents and Infants Engaged (PIE), with two key content domains: Sensory Reactivity and Prelinguistic Communication. In the PIE intervention, coaches will guide parents in observing and describing their children's sensory reactivity and prelinguistic communication cues, observing their own responses to different cues and whether these responses serve to promote dyadic engagement between the parent and infant, and intentionally continuing their use of responsive strategies that promote engagement while also identifying and using new strategies to promote engagement.

3.1 Problem Statement

The main effects of parent-mediated interventions on outcomes of infants at elevated likelihood of later diagnoses of autism and other neurodevelopmental disorders (NDs) have been modest in size at best, and null for most measured outcomes. However, a previous trial of a parent-mediated intervention by our team (Watson et al., 2017) found that the intervention (Adapted Responsive Teaching) had moderately large effects on parents' use of responsive interaction strategies targeted by the intervention, and that these increases mediated the relation between group assignment (intervention vs. control) and mutliple infant outcomes of interest (e.g., autism symptom severity, language, social and communication adaptive skills) in the absence of main effects on infant outcomes. We propose that we can achieve better outcomes from an intervention founded on a refined theory of change, i.e., explicitly acknowledging that infants' and parents' behaviors have transactional impacts on one another, and that these impacts may not always operate in ways that support optimal adaptive development of the infant. We developed Parents and Infants Engaged (PIE) as an intervention that explicitly addresses the dynamic, transactional nature of parent-infant interactions in dyads that include infants at elevated likelihood of NDs.

3.2 Purpose of Study/Potential Impact

This study entails a "proof of concept" evaluation of a novel intervention, Parents and Infants Engaged (PIE), for prodromal infants at-risk for neurodevelopmental disorders (NDs). The objectives of the current study are to examine whether the PIE intervention (a) transforms parent-infant transactions over time as intended, thereby facilitating increases

in the time infants spend in joint engagement with their parents, and (b) is associated with improved social-communication functioning, better regulation of sensory reactivity, and positive changes in indices of autonomic self-regulation in infants at-risk for NDs. Our study design also permits us to examine whether dyadic engagement (primary outcome) and our secondary outcomes are variable based on the order in which parents are coached on the two PIE domains; although we hypothesize that there will be order effects on outcomes after all families have been coached in both PIE domains, finding order effects would prompt us to refine our theory of change further, thereby informing redesign of the intervention.

Testing this novel intervention model, PIE, will promote a refined theory of change for building more effective parent-mediated interventions for infants at-risk for neurodevelopmental disorders, such as autism. Results from this study will provide specific evidence regarding whether coaching parents on responding to two domains of infant behavior, sensory reactivity and prelinguistic communication, can impact parent-infant dyadic engagement and infant social-communication and self-regulation. These three variables are linked conceptually and empirically to long-term outcomes in children with NDs. Descriptive characterizations of treatment effects and estimated effect sizes resulting from this study will guide future large-scaled efficacy trials.

3.3.1 Potential Risks

Anticipated risks to children or families are minimal. Although the likelihood of a confidentiality breach is very low, the data collected (via parent survey, behavioral assessment/video coding, and physiology) yield information about participants' behaviors and demographics that could cause emotional distress if confidentiality was breached. We will take precautions to assure confidentiality of data (e.g., substituting codes for identifiers, limiting access to identified data, impressing on the research staff the importance of confidentiality, and storing research records/videos in locked file cabinets and electronic files on secure servers). There are only minimal risks involved in the collection of observational data on the children. Infants occasionally may become tired, frustrated or stressed by completing a developmental assessment. However, all of our tasks are play-based in nature, and we break up tasks and provide rest/snacks as needed, and access to caregivers at all times. Few infants in our previous studies have had difficulty in completing similar assessment batteries. As an additional protection, parents are able to end the assessment procedures at any time, and staff also follow written guidelines on when to discontinue an assessment in the event of infant signals of distress.

The PIE coaching intervention is implemented in the homes of families who have agreed to participate. Minimal risks to the infants and parents may involve fatigue, frustration or stress. All interventionists will be well-trained in intervention strategies and general behavioral management techniques by the study Principal Investigators (Watson and Baranek), and will use family-friendly coaching approaches and materials. We will individualize strategies to fit the family culture and needs.

Although unlikely to occur, investigators/research staff are required ethically and legally to report instances of suspected child abuse or neglect or instances in which a research subject is in danger of harming himself/herself or others. These circumstances under which

confidentiality would be broken will be conveyed to all participants in the consent form(s).

3.3.2 Potential Benefits

Risks to participants in this study are minimal, as outlined above, while potential benefits both to the participants and others are substantial. The primary benefit of this study is the development of a new intervention to benefit families who have an infant at elevated likelihood for later neurodevelopmental disorders (NDs). The intervention uses a parent coaching model intended to lead to improvements in infant outcomes in engagement, intentional communication and biobehavioral regulation. Regardless of group assignment or the presence or absence of effects on measured outcomes in two previous studies we have conducted involving parent-mediated intervention for infants at elevated likelihood of NDs, many parent participants in those studies have expressed that they felt supported by the project in learning more about their child's development and in navigating early intervention services available in their communities. We anticipate that many participants in the current study will also experience those benefits. At the conclusion of this project, we will have preliminary evidence addressing whether a novel intervention model that takes into account infant sensory reactivity and prelinguistic communication can impact parent-infant transactions and improve dyadic engagement, social-communication functioning, and physiological indices of self-regulation for infants at elevated likelihood of NDs. In addition, this project will yield descriptive characterizations of treatment effects and estimated effect sizes, thereby providing a foundation for a larger scale efficacy trial of the PIE intervention.

4.1 Hypothesis

This study has four specific objectives, with hypotheses associated with each objective. Understanding the study design will provide context for interpreting the hypotheses. Parent-child dyads will be randomized to one of two study arms. All dyads will receive the full Parents and Infants Engaged (PIE) intervention, but they will be coached on the two PIE domains (prelinguistic communication and sensory reactivity) in different orders. In Arm1, parents will first be coached in responding to their infants' prelinguistic communication cues. In Arm2, parents will first be coached on responding to their infants' prelinguistic communication cues. Posttest-1 assessments will follow the first domain of coaching for all participants. Then parents will be coached in the second domain of PIE, after which dyads will participate in Posttest-2 assessments.

1. Estimate the separate and combined effects of the two PIE intervention domains on dyadic engagement (primary outcome).
    - *H1a*: At Posttest-1, dyads coached in either PIE domain will exhibit moderately more dyadic engagement compared to Baseline (Cohen's d ≥ .40).
    - *H1b*: At Posttest-2, dyads in both study arms will show additional small to moderate increases in dyadic engagement compared to Posttest-1 (Cohen's d ≥ .25).
2. Estimate the separate and combined effects of the two PIE intervention domains on infant intentional communication.
    - *H2a*: At Posttest-1, infants in both groups will show no more than modest gains in

intentional communication (Cohen's d < .25).
    - *H2b*: At Posttest-2, infants in both groups will show moderate increases in intentional communication compared to Baseline (Cohen's d ≥ .40).
3. Evaluate the *differential* changes in parent responsiveness following coaching on two individual Parents and Infants Engaged (PIE) intervention domains — responses to variable infant (a) sensory reactivity or (b) prelinguistic communication — as well as *cumulative* changes in parent responsiveness following coaching on both PIE domains.
    - *H3a*: At Posttest-1, parents in both intervention arm will show increases in responses attuned to their infants' behaviors compared to Baseline, with parents coached in the sensory reactivity domain showing more responses attuned to infants' sensory reactivity, and parents coached in the prelinguistic communication domain showing more responses attuned to infants' signals of attention focus and communicative intent.
    - *H3b:* At Posttest-2 (after coaching in both PIE domains), there will be no between-arm differences in parent responses attuned to infant sensory reactions or prelinguistic communication leads, due to increases in parent responsiveness to the newly coached domain of infant behaviors.
4. Determine the extent to which (a) autonomic indices of infant self-regulation and (b) language, sensory reactivity patterns, response to joint attention, and social-communication skills change over the course of the PIE intervention. .
    - *H3b:* From Pretest to Posttest-2, infants will show limited changes in autonomic indices during exposure to nonsocial stimuli (Cohen's *d* <.25), but will show moderate-sized increases in respiratory sinus arrhythmia (RSA) and decreases in skin conductance levels (SCL) during exposure to child-directed speech (Cohen's *d* ? .40).
    - *H4b:* Infants will demonstrate small improvements in language, sensory reactivity patterns, response to joint attention, and social-communication skills over the course of the PIE intervention.

4.2 Primary Objective

The positive association between parent responsiveness and better social-communication outcomes in children in general, and children with neurodevelopmental disorders (NDs) in particular, has driven the development of early interventions promoting parent responsiveness for these populations. Such intervention models assume that increases in parent responsiveness will improve child outcomes. However, for interventions targeting infants and toddlers at elevated likelihood of or diagnosed with NDs, such as autism spectrum disorder (ASD), the effects of parent responsiveness interventions have been modest in size and highly variable, rendering the evidence inconclusive for parent responsiveness as a mediator of infant/toddler outcomes.

We propose that ensuring a more effective parent-mediated intervention for this population depends on the guidance of a refined theory of change—one explicitly acknowledging that infant behaviors influence parent responsiveness. Developmental studies indicate that infants at elevated likelihood of NDs are likely to exhibit behaviors that either fail to elicit parent responses or elicit parent responses that do not effectively support the infant's engagement and learning. In addition, optimal features of parent responsiveness appear to

vary as a function of children's developmental levels and other dynamic variables. To date, studies of parent-mediated interventions have not addressed these complexities. However, recent research points to key "child" variables likely to play transactional roles in communication development among infants and toddlers with or at-risk for NDs. These include aspects of children's prelinguistic communication characteristics (e.g., intentional communication, diversity of consonants) that are related to both parent responsiveness and children's later communication skills. Also, preliminary data from our team indicate infants' sensory reactivity (hypo- and hyper-reactivity) predicts not only parent responsiveness but also social-communication outcomes of infants at-risk for NDs. Arguably, increases in parent responsiveness lead to improved parent-infant dyadic engagement, which in turn mediates infants' communication outcomes. Finally, physiological self-regulation impacts social and communication outcomes in children, but may be disrupted in infants at-risk for NDs, associated with their difficulties modulating sensory reactivity.

In re-conceptualizing intervention for infants at-risk for NDs, we have integrated these variables into a new model, Parents and Infants Engaged (PIE), with two key content domains: Sensory Reactivity and Prelinguistic Communication.

Objective 1: The primary objective of this study is to examine whether the novel PIE intervention transforms parent-infant transactions over time as intended, thereby facilitating increases in the time infants spend in dyadic engagement with their parents. We will also evaluate whether dyadic engagement outcomes differ based on whether parents are coached first in the sensory reactivity domain followed by coaching in the prelinguistic communication domain, or are coached in the opposite order.

4.3 Secondary Objectives

Our secondary objectives will provide further insights into whether the PIE intervention is functioning as intended. Specifically, our secondary objectives are to:

- Objective 2: Estimate the separate and combined effects of the two PIE intervention domains on infant intention communication.
- Objective 3: Evaluate the differential changes in parent responsiveness following coaching on two individual Parents and Infants Engaged (PIE) intervention domains — responses to variable infant (a) sensory reactivity or (b) prelinguistic communication — as well as cumulative changes in parent responsiveness following coaching on both PIE domains.
- Objective 4: Determine the extent to which (a) autonomic indices of infant self-regulation, and (b) language, sensory reactivity patterns, response to joint attention, and social-communication skills change over the course of the PIE intervention.

5.1 General Design Description

This intervention trial will use a randomized comparative trial design. We will recruit participants by mailing the First Years Inventory v3.1 (FYIv3.1) to families of 11- 16-month-old infants based on public birth records for our catchment area (as in our prior studies), as well as distributing hard copies and links to an online version of the FYIv3.1 through area pediatric practices and public health clinics. Project staff will contact parents of infants who score at or above the threshold indicating an elevated likelihood of a future neurodevelopmental disorder (ND) diagnosis by phone to share the screening results and further screen for study exclusion criteria. If no exclusionary factors are identified, families will be informed about the overall study and specifically the baseline assessment. Families who provide consent for the baseline assessment will be assessed at our research offices, which include a child-friendly assessment suite. Final study eligibility will be determined by the baseline assessments (i.e., the infant must demonstrate receptive and/or expressive language scores one SD below the mean and meet clinically determined criteria suggesting extreme hypo- and/or hyper-reactivity). Parents of eligible infants will then be asked to consent to enrollment in the intervention trial. The project methodologist will randomize families of eligible infants (stratified for age < 14 months and ≥ 14 months) to be initially coached on either the prelinguistic communication domain (Arm1) or the sensory reactivity domain (Arm2) of PIE. Families will participate in 6 weekly in-home coaching sessions in their respective treatment arms before returning to our research offices for Posttest-1 assessments. After Posttest-1, Arm1 dyads will receive 6 weeks of coaching on the sensory reactivity domain, and Arm2 dyads will receive 6 weeks of coaching on the prelinguistic communication domain; coaching for each group will also include review of the respective content domain coached in Study Phase 1. Then families will return for Posttest-2.

5.1.1 Study Date Range and Duration

The study will start August 1, 2017, with data collection continuing for 22 months.

5.1.2 Number of Study Sites

There is one study site for data collection, at the University of North Carolina at Chapel Hill, Chapel Hill, NC.

Data processing, video coding, and statistical analyses will occur at two sites, the University of North Carolina at Chapel Hill and the University of Southern California, Los Angeles, CA.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary outcome variable is parent-infant dyadic engagement. We define dyadic engagement as an observable pattern of mutual focus, active participation, and reciprocal exchanges within a parent and child interaction.

We will collect data on this outcome at baseline, posttest 1 (after families have been randomly assigned to an intervention arm and coached in one of the two PIE intervention domains), and posttest 2 (after families have been coached in both of the PIE intervention domains).

The rationale for choosing dyadic engagement as the primary outcome is that parent coaching in each domain is designed to assist parents in engaging their child in positive interactions with them and increasing the length of these periods of engagement through supporting the infants in regulating their responses to sensory stimuli and/or responding sensitively to infants' prelinguistic communication cues. Dyadic engagement is a conceptually important outcome variable, as suggested by prior evidence that responsive parent language (i.e., language that follows-in to the child's focus of attention) is associated with future language and social-communication development in young children with autism, IF this language occurs during an engagement state in which the child and parent are responding reciprocally to one another, but not when parental follow-in language responses are given in the engagement states where the child does not provide any reciprocal responses to the parent (Bottema-Beutel et al., 2014). Reciprocity between the infant and parent is a key component of our definition of dyadic engagement. Thus, establishing and maintaining dyadic engagement states may be crucial to infants at elevated likelihood of NDs in providing them with optimal contexts for learning social-communication and language skills.

This outcome will be evaluated using an adapted version of a parent-child engagement state coding system originally developed by Adamson et al. (2009) and adapted by Bottema-Beutel et al., (2018). Variations of the Adamson et al. engagement state coding have been Research assistants will be trained to reliability on coding dyadic engagement on videos that have been consensus coded by project staff overseeing coding of this variable. Videos for the study will comprise a ~20-minute video of parent-infant interactions that includes free-play, a semit-structured "What's in the box?" activity, snack time, and cleaning up after the snack. Following coding training, one out of every five coded videos will be randomly selected for independent coding, in order to assess the reliability of our measure of dyadic engagement data for the trial. Coders will not be aware of which videos are being coded for reliability purposes. Periodic booster training for research assistants coding dyadic engagement will occur to limit the risk of observer drift.

5.2.2 Secondary and Exploratory Outcome Variables

Secondary outcome variables:

The first three secondary outcome measures will be assessed at three timepoints: Baseline, Posttest 1 (after families have been randomly assigned to an intervention arm and coached in one of the two PIE intervention domains), and Posttest 2 (after families have been coached in both of the PIE intervention domains). For these measures, we are particularly interested in whether there are effects specific to the initial PIE coaching domain (sensory

reactivity or prelinguistic communication) at Posttest 1, and whether there are order effects (differences between study arms) at Posttest 2.

1. Changes in parent responsiveness to infant sensory reactivity cues. [Measured via a project-developed rating tool.] This secondary measure is included to determine whether coaching in the sensory reactivity domain yields the expected specific effects on parents' responses to infant sensory reactivity cues. Parents will be rated on a 1-7 scale for their responsiveness to sensory reactivity for each of the 4 activities included in the parent-infant interaction session, using videorecordings of these sessions. A manual will be developed to describe the rating system and the level of responsivity associated with each of the 7 points on the scale. Research assistants will be trained to reliability by supervising staff. During rating of the project videos, one of 5 rated videos will be independently rated for reliability. Raters will be blind to study arm and timepoint of participants.

2. Changes in parent responsiveness to infant prelinguistic communication cues. [Measured via a project-developed rating tool.] This secondary measure is included to determine whether coaching in the prelinguistic communication domain yields the expected specific effects on parents' responses to infant prelinguistic communication cues. Manualization, training and reliability procedures are identical to those described for the parent responsiveness to sensory reactivity measure.

3. Changes in infant intentional communication. [Measured via a project-developed coding system.] The rationale for including this outcome measure is that parental responsive support of infant engagement will promote infants' increased use of intentional communication, previously found to predict later receptive and expressive language outcomes for preschoolers already diagnosed with autism (Yoder et al., 2015). Intentional communication acts are defined as acts that are directed toward a communication partner (in this case, the parent or other primary family caregiver present during the parent-infant interaction session) to convey a message, and include (a) vocalizations, (b) gestures, or (c) combinations of both vocalizations and gestures. A coding manual will be developed to describe the coding system and provide examples and nonexamples of Infant intentional communication acts. This measure will be coded from videos of the parent-infant interaction sessions. Research assistants will be trained to reliability by supervising project staff. One of every five coded videos will be randomly selected for independent coding by another research assistant. Coders will be blind to assigned arm of the intervention and to timepoint of the assessment.

The following 8 secondary outcome variables will be measures at two timepoints: Baseline and Posttest 2. For these measures, we are particularly interested in examining the magnitude of change over the course of the full intervention, as well as whether there are order effects (differences between study arms) at Posttest 2.

4. Changes in infant respiratory sinus arrhythmia (RSA). This measure was chosen as an index of parasympathetic system functioning, and will be measured within a paradigm in which the infants are passively observing (a) an instrumental music video without social images, and (b) three on-minute vignettes of infant-directed speech, as an experimental analog of parent-infant interactions. We hypothesize we will see increased RSA levels during infant-directed speech, reflecting greater parasympathetic control and improved

sensory response regulation, by Posttest 2. Data will be collected with the Firstbeat device, with 2 electrodes placed on the infant's chest, and covered with the infant's clothing. Records of interbeat intervals will be aligned with the video segments the infants viewed, edited using CardioEdit (Brain-Body Center, 2007) by a research assistant trained to reliability, and processed using CardioBatch (Brain-Body Center, 2007) to derive RSA.

5. Changes in infant skin conductance level (SCL). This measure was chosen as an index of sympathetic system functioning, and will be measured within the above described infant-directed speech paradigm. We hypothesize we will see decreased SCL levels during infant-directed speech, reflecting less elevation of sympathetic activity and improved sensory regulation when observing infant-directed speech vignettes, by Posttest 2. Data will be collected using the Shimmer device; records of SCL will aligned with the video segments the infants viewed, and processed using Kubios.

6 Changes in infants' receptive language. [Measured via the Mullen Scales of Early Learning (MSEL) Receptive Language scale, Mullen, 1995.] Prior research indicates that receptive language may be improved distal to with improvements in parent-infant dyadic engagement and infant intentional communication. The Receptive Language Scale is one of 5 MSEL scales assessing development for children birth-68 months. Each scale (Gross Motor, Fine Motor, Visual Reception, Receptive Language, Expressive Language) yields a T-score, percentile and age equivalent. The MSEL has been used as a standardized measure of development across domains in many treatment studies of young children with NDs.

7. Changes in infants' expressive language. [Measured via the MSEL Receptive Language scale, Mullen, 1995.] Based on prior research, we may also see improvements in expressive language distal to improvements in parent-infant dyadic engagement and infant intentional communication. See further details on the MSEL in item #6 above.

8. Changes in infants' responses to adults' bids to direct their attention to an new object (i.e., response to joint attention). [Measured via a subset of 6 Attention Following trials from the Joint Attention Protocol, Watson et al., 2003.] One frequent behavioral characteristic of infants at elevated likelihood of later ND is that they have difficulty in responding to joint attention bids that require them to redirect their attention away from their current focus to a new object. Potentially, improvements in parent-infant dyadic engagement will, over time, yield improvements in response to joint attention as parents learn to use new strategies to effectively engage their infant, and infants have more experiences in reciprocal interactions with their caregivers. Such changes could signal infants' decreased dependency on parents observing and responding to their immediate focus of attention, and provide a larger variety of learning opportunities. The Joint Attention Protocol was developed in conjunction with an earlier study by our team as a measure that could be scored reliably during administration, and has demonstrated sound reliability and validity for use with young children with autism (Nowell et al., 2018).

9. Changes in infants' social-communication skills. [Measured via the Brief Observation of Social-Communication Change, BOSCC, Lord, Grzadzinski et al., 2017.] In analyses with other samples screened with the FYIv3.1, our team has documented that the positive predictive value of the tool specifically for autism is around 30-40%, varying with the age at screening (unpublished data). Due to the nature of the items on the FYIv3.1, infants meeting the threshold for being at elevated likelihood for ND on the FYIv.3.1 will have parent-reported social-communication behaviors associated with autism. The BOSCC was

designed to assess improvements in early social-communication skills that are usually impaired in young children with autism but also are known to change/improve over time. Thus, we are using the BOSCC to examine whether these skills change significantly over the course of the full PIE intervention. For this study, we will use the 12-minute BOSCC interaction protocol during which an examiner interacts with the child, which will be videorecorded and scored later by trained research assistants blind to assignment arm and timepoint. As with other measures from videos, one of 5 scored videos will be randomly selected for independent scoring for reliability purposes. The research assistants working on this measure will meet regularly with the supervising staff to review scoring decisions to attentuate the risk of observer drift.

10. Changes in observed infant sensory reactivity patterns. [Measured via the Sensory Processing Assessment for Young Children, SPA, Baranek, 1999a.] In coaching parents to be sensitive to their infants' cues related to sensory reactivity and to respond in ways that support their infants' regulation of these responses, another potential distal outcome of the PIE intervention would be improvements in extreme patterns of sensory reactivity (i.e., diminished hypo- and/or hyper-reactivity). Use of the SPA as an observational measure will provide us with the opportunity to assess whether any changes are observed by assessors who are blinded to the arm of the study to which families are assigned. The SPA is a play-based assessment that measures approach-avoidance to novel sensory toys, sensory seeking behaviors, and orienting responses across three sensory modalities, and is sensitive to maturational changes. It has good inter-rater reliability (ICC = .91 to .99 for different scales), and discriminates different patterns of sensory response between children with autism and children with other developmental disabilities (Baranek et al., 2007).

11. Changes in parent-reported infant sensory reactivity patterns. [Measured via the Sensory Experiences Questionnaire v. 2.1, SEQ, Baranek, 1999b.] As a complement to the SPA, we are using the SEQ to determine whether parents perceive improvements in their children's sensory reactivity patterns over the course of the full PIE intervention. The SEQ is a 43-item questionnaire for children 6 months to 6 years that measures responses to various sensory stimuli in the context of daily activities. Factor scores for hypo- & hyper-responsiveness and sensory seeking are compatible with the conceptual model of the SPA. The internal consistency is acceptable (Cronbach's α =,80). It discriminates patterns unique to ASD and is sensitive to maturational changes (Baranek et al., 2006).

5.3 Study Population

The study population is infants between the ages of 11-16 months who are identified as being at elevated likelihood of a later neurodevelopmental disability diagnosis (e.g., autism spectrum, attention-deficit hyperactivity disorder, language delay/disorder, sensory processing disorder), along with a parent (or other primary family caregiver e.g., grandparent) for each child. Infants will be recruited from 6 central North Carolina counties whose far boundaries are within 90 miles of Chapel Hill, the location of the research offices for this study. The two primary sources of recruitment will be: (a) state birth registries (NC Vital records; 6 counties within 90 miles of Chapel Hill including Orange, Durham, Chatham, Alamance, Guilford, and Wake), and (b) primary care well-baby clinics — either through local pediatric practices or county health clinics, in rural and urban areas that represent wide demographics. Further, we will have booths at familiy-oriented fairs/events in our

catchment area offering child-friendly activities (e.g., bubble machines) and study information for parents, and disseminate information about the study including a link to an online version of our parent report screener through social media, cards distributed through child care centers, etc.

Parents initially will be asked to complete a screening questionnaire, The First Years Inventory, v.3.1b (FYIv3.1b; Baranek et al., 2014), developed to identify infants to elevated likelihood for later diagnosis of autism and other developmental conditions (e.g., attention deficit hyperactivity disorder; language delays/disorders; sensory processing disorders; global developmental delays). The screening cut-points on the FYIv3.1b were set in conjunction with a previous study for which we had access to diagnostic outcome information such that we capture about 1/3 of the infants who would go on to be confirmed as having a autism spectrum diagnosis while misclassifying less than 5% of the typically developing (TD) sample as at-risk. We know from previous studies using an earlier version of the FYI that many infants later diagnosed with other NDs also will have scores exceeding the threshold on the FYI (Turner-Brown et al., 2013).

For infants whose screening scores on the FYIv3.1b meet the threshold for being at elevated likelihood for a later diagnosis of an ND, the research coordinator will call the parents to further screen for infant and parent eligibility, offer information about the study, and invite families with no exclusionary factors to participate in a baseline assessment (with informed consent).

At baseline assessments, eligible infants will have a score of at least 1 standard deviation below the mean on the Receptive or Expressive Language scale (or both) of the Mullen Scales of Early Learning, as well as meeting clinically-determined criteria for elevated patterns of hypo-reactivity or hyper-reactivity (or both) on the Sensory Processing Assessment: "HYPO": Cut-point (equal or greater than) of 1.69 for Mean of the raw orienting score across 7 items, each with the range of 1 to 4 possible points). "HYPER": Cut-point (equal or greater than) of .333 for Mean of the raw approach/avoid novel toys score across 9 items, each with the range of 0 to 2 possible points) OR Any clear "defensive" response on orienting items or "Yes" to covering ears to sound (in stereotypies checklist). These inclusion criteria will ensure that infants are demonstrating delays or differences in areas of development that are targeted by the PIE intervention (sensory reactivity and communication).

Infants will include both sexes, although based on previous studies, we expect a 2:1 (male:female) ratio, given that boys are more likely to score at elevated likelihood for NDs (e.g., autism) targeted by the FYI.

Exclusion criteria: Infants with known genetic conditions (e.g., Down syndrome), and those with significant uncorrected vision/hearing/physical impairments will be excluded. We exclude infants with known genetic disorders due to our focus on testing PIE with infants at elevated likelihood of neurodevelopmental disorders based on behavioral markers, but whose eventual diagnosis remains unclear. We will exclude infants with significant uncorrected vision/hearing/physical impairments because they likely would not be able to fully participate in the assessment procedures, and the assessment results would be of questionable validity. Families who do not speak English as their primary language in the home (>50% of the time) will be excluded, because screening tools, assessments, and interventions are not available uniformly in other languages.

5.3.1 Number of Participants

We plan to enroll 44 infants at elevated likelihood of a later ND and a primary caregiver of each infant. Based on prior studies with similar populations, we anticipate approximately 1% of completed FYIs will yield a parent-infant dyad that meets all eligibility criteria and consents to enroll in the intervention trial. Thus, screening of ~4400 infants on the FYIv3.1 likely will be required to recruit this sample. All recruitment will take place at the University of North Carolina at Chapel Hill study site.

5.3.2 Eligibility Criteria/Vulnerable Populations

Eligibility

1. Infant is between 11 and 16 months (inclusive) at the time that the parent completes the FYIv3.1b.

2. Infant scores at or above threshold on the FYIv3.1b for being at elevated likelihood for a later ND diagnosis.

3. Infant scores 1 SD below the mean on the Receptive Language and/or the Expressive Language Scale of the Mullen Scales of Early Learning.

4. Infant meets clinical criteria for elevated hypo- or hyper-reactivity on the Sensory Processing Assessment at the in-person baseline assessments.

5. A parent or other primary caregiver of the infant is available for study participation.

6. Family lives within the catchment area for the study.

Exclusion criteria

1. Infant has a known genetic conditions (e.g., Down syndrome).

2. Infant has a known significant uncorrected vision/hearing/physical impairments.

3. Famiy who do not speak English as their primary language in the home (>50% of the time).

Vulnerable populations:

This study will enroll participants from the vulnerable population of children. This study aims to provide intervention during infancy, before the full emergence of behavioral symptoms that would lead to a neurodevelopmental disorder diagnosis (e.g., ASD, language disorder, or attention deficit hyperactivity disorder). The underlying premises for the study require the participation of children: 1) The first 2 years of life are an especially active period of neural development. Due to rapid synaptic proliferation and experientially-

influenced shaping of functional connectivity, interventions initiated in infancy may be powerful in promoting more typical neural connectivity. (2) Biologically-based differences in infants at-risk for NDs lead to observable differences in sensory reactivity and communication behaviors in most infants by 11-16 months, prior to the full emergence of diagnostic symptoms. (3) Differences in infant behaviors influence the quantity and quality of parent responses. (4) Parent-child transactional processes begin early in infancy and impact long-term child outcomes.

Protections:

All participants will be assigned a unique identification number and all materials related to a participant will use this number and not a child's or parent's name. Names associated with ID numbers are stored in a password-protected computer file. All family/child-related data (paper or electronic) are stored in a locked file cabinet in a locked office or on an encrypted computer. Any scientific reports, article submissions, or summaries of data will not include children/family names. Data will be presented in summary format that will preclude any personal identification. The planned assessments and intervention activities involve no more than minimal risks to participants. Although the children will be too young to provide verbal or written assent, we will monitor their behavior for signs of undue distress and ask parents to inform us if they feel their child is experiencing unusual levels of distress or discomfort. Research staff will end activities, when based on either their own judgment or the judgment of the child's parent, the activities are causing the child undue stress.

Plans to minimize risks to children:

To minimize the risk of an infant becoming stressed, the tasks will be short and play based to lend themselves to the attention span and interests of infants and their parents. The laboratory space is also designed to be infant friendly (carpeting, child-sized furniture, appropriate toys, etc.) and the infants will be allowed access to the parents and snacks at any time. Infants will be given time to warm up to the space and to the examiners with their parents present. Some unexpected stimuli (e.g., sound stick, tap on the shoulder, flashing light) will be designed to be consistent with the types of sensory experiences that are naturally occurring in the environment and are not aversive in nature.

To minimize the risk of an infant becoming stressed with application or removal of "sticky" electrodes for the heart rate monitors, we will provide sample electrodes for parents to use at home prior to coming to the testing session. We will also engage the infant in a game to distract the infant while placing electrodes. The electrodes will be covered after placement by the infants' clothing (e.g., shirt, socks) to minimize the infant becoming visually distracted by the electrodes and pulling at the electrodes. Pediatric electrodes designed for easy removal and using nonirritating materials will be used.

If an infant presents with an unusually fearful reaction and cannot be easily soothed or redirected (as determined by the examiner or the parent) during the physiological data collection, the developmental assessments, and/or home intervention, the item (or task) will be discontinued and resumed only once the infant gives behavioral assent and no longer appears stressed. If the infant does not assent or the parent or the examiner feels that continuing would stress the infant, the assessment/procedure/intervention will be discontinued.

Potential direct benefit to children:

All participants will receive the benefit of early identification of risk for developmental disabilities. By completing the FYIv3.1 when their child is 11 to 16 months of age, parents will be made aware of potential developmental problems that they may not have noticed until later. This may grant them earlier access to intervention and other services, which have been associated with improved developmental outcomes. We will provide appropriate referral information to all families whose children score at or above the 95th percentile on the FYIv3.1b, provided the parent provided contact information to us. We will keep updated contact information for the agencies that may be appropriate (e.g., Child Development Service Agencies, TEACCH, local service providers of speech therapy or occupational therapy).

Potentially, children may experience benefits from the novel intervention that we will be evaluating. The intervention uses a parent coaching model intended to improve infant outcomes in engagement, intentional communication and biobehavioral regulation. Although all participants will receive the PIE intervention, we do not yet know whether the children will experience any benefits.

6.1 Intervention

6.1.1 Description of Intervention

Parents and Infants Engaged is a parent-mediated intervention intended to improve engagement in parent-child dyads that include infants or young toddlers at elevated likelihood of a future diagnosis of autism spectrum disorder (ASD) or other neurodevelopmental disorders (NDs). Parent-child engagement is defined as an observable pattern of mutual focus, active participation, and reciprocity within an interactive context. PIE targets parent responsiveness to enhance parent-child engagement during family routines, and ultimately improve children's social, language, self-regulation, and cognitive outcomes. Within Parents and Infants Engaged, a coach addresses two domains in which early signs of NDs are often seen: Sensory Reactivity and Regulation (SR) and Prelinguistic Communication (PC). In the SR domain, the aim is to help parents recognize the sensory experiences afforded to the child, identify behavioral cues of a child's sensory experience, understand how parent responses to these cues can promote the child's regulatory abilities and engagement, and then practice effective response strategies. Similarly, the PC domain aims to help parents recognize their child's prelinguistic communicative acts, identify cues that children are communicating *intentionally*, understand how parent responses can promote more intentional communication and dyadic engagement, and then practice effective response strategies. Coaching occurs within the home, across varied daily routines.

Families are coached in either the SR or PC domain for their first 6 sessions (randomly assigned for the purpose of this trial), and then are coached in the other domain for an additional 6 sessions. Step one for coaching in each domain is to facilitate parental awareness and interpretation of infant sensory regulatory/prelinguistic communication behaviors. The second step shifts to incorporate observation and reflection on parent

responses to child behaviors; the parent is encouraged to experiment with adapting their responses based on what they know about their child as well as suggestions from the coach. Throughout each session, the coach uses reflective questioning and other strategies to foster parents' collaboration in identifying and using strategies attuned to the child's unique cues, and evaluating whether the strategies improve parent-child engagement. We expect that increasing the parent's awareness of the child's behaviors and their corresponding responses through reflective coaching will lead to increased responsiveness and sensitivity for the parent and thus a better capability to recognize the situations in which to implement their identified strategies. An additional aim is to empower parents to more independently identify and implement strategies that promote their child's engagement in the future, as their child's specific behaviors change.

Each session has four major components. During the **Introduction and Check-in**, the coach describes the purpose of the day's session, reviews content discussed in the previous session, and discusses with the parent the strategies they tried went. In **Video Review**, the coach uses a video of the parent and child (recorded at the prior session) to engage the parent in reflective observations of their child and themselves for about 20 minutes. The coach highlights at least 4 video scenarios to support parents in recognizing their child's cues and/or observing how they respond to their child and any subsequent changes in parent-child engagement. The focus of the video review reflections depends on the step of coaching and related coaching goals for the session. In Sessions 1 and 2, examples and reflections are designed to enhance parents' understanding of the child's sensory reactivity or prelinguistic communication cues. In Session 3-6, the coach promotes parents' understanding of how their responses to child cues impact the child's engagement. In **Live Coaching**, the coach and parent collaboratively brainstorm potential strategies for responding to the child's sensory reactivity or prelinguistic communication cues to help maximize their child's engagement within the current coaching domain. Then, the coach helps the parent notice their child's behaviors or reactions and opportunities to apply strategies, provides feedback to the parent, and facilitates reflection on effectiveness and modification of the chosen strategy. During **Family Action Planning**, the coach and parents collaboratively develop a written plan for implementing the strategies practiced in live coaching during the week ahead, including identifying the routines in which the strategies will be tried, when these will occur during the week, and how to address barriers if needed. Before ending the session, the coach videos a parent-child interaction during a routine identified by the parent and/or coach, choosing a different routine each week. This video is reviewed at the following session.

6.1.2 Method of Assignment/Randomization

Following the baseline assessment and final determination of study eligibility, as well as informed consent from eligible dyads, the study coordinator will contact the project methodologist with the ID number of dyad to be randomized to one of the two arms of the study. The project methodologist will randomize families of eligible infants (stratified for age < 14 months and ≥ 14 months) on a continuing basis, using the randomization function in RedCap. Dyads will be randomized such that parents will be coached on the Prelinguistic Communication domain of the Parents and Infants Engaged intervention first followed by the Sensory Reactivity domain (Arm 1), or to the Sensory Reactivity domain first, followed by the Prelinguistic Communication domain (Arm 2).

The project methodologist will have no contact with families and no knowledge of baseline assessment outcomes prior to randomization. Similarly, the project coordinator and assessment team will have no knowledge of the arm to which a dyad will be assigned at the time of the baseline assessment, given that randomization does not occur until after the baseline assessment has been completed (to ensure the infant meets all eligibility criteria for the trial).

Assessors will continue to be blinded to study arm assignment throughout the trial. However, the study coordinator, parents, and coaches, a selected group of research assistants, and study PIs will have knowledge of arm assignment due to their involvement in implementing the intervention and measuring the fidelity of implementation of the intervention.

6.1.3 Selection of Instruments/Outcome Measures

PRIMARY OUTCOME

1. Parent-infant dyadic engagement is the primary outcome for this study. We define dyadic engagement as an observable pattern of mutual focus, active participation, and reciprocal exchanges within a parent and child interaction.

We will collect data on this outcome at baseline, posttest 1 (after families have been randomly assigned to an intervention arm and coached in one of the two PIE intervention domains), and posttest 2 (after families have been coached in both of the PIE intervention domains).

The rationale for choosing dyadic engagement as the primary outcome is that parent coaching in each domain is designed to assist parents in engaging their child in positive interactions with them and increasing the length of these periods of engagement through supporting the infants in regulating their responses to sensory stimuli and/or responding sensitively to infants' prelinguistic communication cues.

This outcome will be evaluated using an adapted version of a parent-child engagement state coding system originally developed by Adamson et al. (2009) and adapted by Bottema-Beutel et al., (2018). Variations of the Adamson et al. engagement state coding have been Research assistants will be trained to reliability on coding dyadic engagement on videos that have been consensus coded by project staff overseeing coding of this variable. Videos for the study will comprise a ~20-minute video of parent-infant interactions that includes free-play, a semi-structured "What's in the box?" activity, snack time, and cleaning up after the snack. Following coding training, one out of every five coded videos will be randomly selected for independent coding, in order to assess the reliability of our measure of dyadic engagement data for the trial. Coders will not be aware of which videos are being coded for reliability purposes. Periodic booster training for research assistants coding dyadic engagement will occur to limit the risk of observer drift. In a previous study of preschoolers with autism, members of our research team maintained acceptable to excellent reliability on coding the relevant engagement states across timepoints, with ICCs ranging from .72 to .97.

Time required for study participants: 20 minutes at Baseline, Posttest-1 and Posttest-2.

OTHER INSTRUMENTS AND SECONDARY OUTCOME MEASURES

2. Parent responsiveness to infant sensory reactivity cues. [Measured via a project-developed rating tool.] This secondary measure is included to determine whether coaching in the sensory reactivity domain yields the expected specific effects on parents' responses to infant sensory reactivity cues. Parents will be rated on a 1-7 scale for their responsiveness to sensory reactivity for each of the 4 activities included in the parent-infant interaction session, using videorecordings of these sessions. A manual will be developed to describe the rating system and the level of responsivity associated with each of the 7 points on the scale. Research assistants will be trained to reliability by supervising staff. During rating of the project videos, one of 5 rated videos will be independently rated for reliability. Raters will be blind to study arm and timepoint of participants. We will code the videorecorded parent-infant interaction sessions described for our primary measure for this measure as well at Baseline, Posttest-1, and Posttest-2.

No additional time requirements for participants.

3. Parent responsiveness to infant prelinguistic communication cues. [Measured via a project-developed rating tool.] This secondary measure is included to determine whether coaching in the prelinguistic communication domain yields the expected specific effects on parents' responses to infant prelinguistic communication cues. Manualization, training and reliability procedures, as well as timepoints are identical to those described for the parent responsiveness to sensory reactivity measure.

No additional time requirements for participants.

4. Infant intentional communication. [Measured via a project-developed coding system.] The rationale for including this outcome measure is that parental responsive support of infant engagement will promote infants' increased use of intentional communication, previously found to predict later receptive and expressive language outcomes for preschoolers already diagnosed with autism (Yoder et al., 2015). Intentional communication acts are defined as acts that are directed toward a communication partner (in this case, the parent or other primary family caregiver present during the parent-infant interaction session) to convey a message, and include (a) vocalizations, (b) gestures, or (c) combinations of both vocalizations and gestures. A coding manual will be developed to describe the coding system and provide examples and nonexamples of Infant intentional communication acts. This measure will be coded from videos of the parent-infant interaction sessions. Research assistants will be trained to reliability by supervising project staff. One of every five coded videos will be randomly selected for independent coding by another research assistant. Coders will be blind to assigned arm of the intervention and to timepoint of the assessment. Members of our research team have successfully coded intentional communication acts in preschool children with autism with ICCs ranging from .84 to .92 across three timepoints. This measure will be coded from the videorecorded parent-infant interaction sessions described under our primary outcome, at Baseline, Posttest-1, and Posttest-2.

No additional time required for research participants.

5. Infant respiratory sinus arrhythmia (RSA). This measure was chosen as an index of

parasympathetic system functioning, and will be measured within a paradigm in which the infants are passively observing (a) an instrumental music video without social images, and (b) three on-minute vignettes of infant-directed speech, as an experimental analog of parent-infant interactions. We hypothesize we will see increased RSA levels during infant-directed speech, reflecting greater parasympathetic control and improved sensory response regulation, by Posttest 2. Data will be collected with the Firstbeat device, with 2 electrodes placed on the infant's chest, and covered with the infant's clothing. Records of interbeat intervals will be aligned with the video segments the infants viewed, edited using CardioEdit (Brain-Body Center, 2007) by a research assistant trained to reliability, and processed using CardioBatch (Brain-Body Center, 2007) to derive RSA. The research assistant who edits and processes the RSA data will be supervised by a research team member with prior experience in obtaining and processing RSA data. We have used the Child-Directed Speech paradigm in previous studies with toddler-to-preschool age children with autism and infant-to-preschool age children with no known developmental concerns (Watson et al., 2010, 2012). The internal consistency for the RSA measures during the three child-directed speech vignettes (Cronbach's alpha) was 0.84 for children with autism.

This measure will be collected at Baseline and Posttest-2, requiring ~6-10 minutes of participants' time.

5. Infant skin conductance level (SCL). This measure was chosen as an index of sympathetic system functioning, and will be measured within the above described infant-directed speech paradigm. We hypothesize we will see decreased SCL levels during infant-directed speech, reflecting less elevation of sympathetic activity and improved sensory regulation when observing infant-directed speech vignettes, by Posttest 2. Data will be collected using the Shimmer device; records of SCL will aligned with the video segments the infants viewed, and processed using Kubios. The research assistant who processes the SCL data will be supervised by a research team member with prior experience with collecting and processing SCL data.

This measure will be collected during the same procedure as used for RSA measurement, at Baseline and Posttest-2. No additional time required for participants.

6. The Mullen Scales of Early Learning provides 5 scales to assess development in children birth-68 months . Each scale (Gross Motor, Fine Motor, Visual Reception, Receptive Language, Expressive Language) yields a T-score, percentile and age equivalent. The MSEL scales have demonstrated good to strong internal consistency, test-retest reliability and concurrent valiidity; it has been widely used as a standardized measure of development across domains in studies of young children with NDs, including many previous studies by members of our team. Prior research indicates that receptive language may be improved distal to with improvements in parent-infant dyadic engagement and infant intentional communication. We will administer the Fine Motor, Visual Reception, Receptive Language, and Expressive Language Scales at Baseline to provide descriptive information across these developmental domain to characterize the developmental status of our sample. At Posttest-2, we will administer the Receptive and Expressive Language Scales only, as secondary outcome measures to determine whether the PIE intervention has distal effects on broader language outcomes of the infants.

In the age range for our infant participants, the estimated participant time required for the 4 scales of the MSEL at Baseline is 15-20 minutes. At Posttest-2, the estimated time to

administer the Receptive and Expressive Language Scales is 10 mintues.

7. Attention Following trials from the Joint Attention Protocol (Watson et al., 2003). One frequent behavioral characteristic of infants at elevated likelihood of later ND is that they have difficulty in responding to joint attention bids that require them to redirect their attention away from their current focus to a new object. Potentially, improvements in parent-infant dyadic engagement will, over time, yield improvements in response to joint attention as parents learn to use new strategies to effectively engage their infant, and infants have more experiences in reciprocal interactions with their caregivers. Such changes could signal infants' decreased dependency on parents observing and responding to their immediate focus of attention, and provide a larger variety of learning opportunities. The Joint Attention Protocol was developed and used in conjunction with an earlier study by members of our team as a measure that could be scored reliably during administration, and has demonstrated sound internal reliability, test-retest reliability, and concurrent validity when used with young children with autism (Nowell et al., 2018).

This measure will be collected at Baseline and Posttest-2. The estimated participant time required to administer 6 attention following trials is 2 minutes.

8. The Brief Observation of Social-Communication Change (BOSCC, Lord, Grzadzinski et al., 2017). In analyses with other samples screened with the FYIv3.1, our team has documented that the positive predictive value of the tool specifically for autism is around 30-40%, varying with the age at screening (unpublished data). Due to the nature of the items on the FYIv3.1, infants meeting the threshold for being at elevated likelihood for ND on the FYIv.3.1 will have parent-reported social-communication behaviors associated with autism. The BOSCC was designed to assess improvements in early social-communication skills that are usually impaired in young children with autism but also are known to change/improve over time. Multiple studies have provided evidence that the BOSCC can be scored with good interrater reliability and has good test-retest reliability and convergent validity with language and communication measures (e.g., Gengoux et al., 2019; Grzadzinski et al., 2016; Kitzerow et al., 2016); in addition, the BOSCC Social-Communication Total Score, which will be our measure, was found to have good internal consistency when applied to videoed interactions during both free-play (Cronbach's alpha = 0.88) and snack time (Cronbach's alpha = .87). Thus, we are using the BOSCC to examine whether these skills change significantly over the course of the full PIE intervention. For this study, we will use the 12-minute BOSCC interaction protocol during which an examiner interacts with the child, which will be videorecorded and scored later by trained research assistants blind to assignment arm and timepoint. As with other measures from videos, one of 5 scored videos will be randomly selected for independent scoring for reliability purposes. The research assistants working on this measure will meet regularly with the supervising staff (one of the authors of the BOSCC) to review scoring decisions to attentuate the risk of observer drift.

The BOSCC will be administered at Baseline and Posttest-2. The participant time required for this measure is ~13 minutes.

9. Sensory Processing Assessment for Young Children (SPA, Baranek, 1999a). In coaching parents to be sensitive to their infants' cues related to sensory reactivity and to respond in ways that support their infants' regulation of these responses, another potential distal outcome of the PIE intervention would be improvements in extreme patterns of sensory reactivity (i.e., diminished hypo- and/or hyper-reactivity). Use of the SPA as an

observational measure will provide us with the opportunity to assess whether any changes are observed by assessors who are blinded to the arm of the study to which families are assigned. The SPA is a play-based assessment that measures approach-avoidance to novel sensory toys, sensory seeking behaviors, and orienting responses across three sensory modalities, and is sensitive to maturational changes. It has good inter-rater reliability (ICC = .91 to .99 for different scales), discriminates different patterns of sensory response between children with autism and children with other developmental disabilities, and shows sensitivity to developmental changes (Baranek et al., 2007, 2013).

The SPA will be administered at Baseline and Posttest-2. The participant time required for this measure is ~15 to 20 minutes.

10. Sensory Experiences Questionnaire v. 2.1, (SEQ, Baranek, 1999b). As a complement to the SPA, we are using the SEQ to determine whether parents perceive improvements in their children's sensory reactivity patterns over the course of the full PIE intervention. The SEQ is a 43-item questionnaire for children 6 months to 6 years that measures responses to various sensory stimuli in the context of daily activities. Factor scores for hypo- & hyper-responsiveness and sensory seeking are compatible with the conceptual model of the SPA. The internal consistency is acceptable (Cronbach's α =0.80). It discriminates patterns unique to ASD and is sensitive to maturational changes (Baranek et al., 2006).

Parents will be asked to complete the SEQ at Baseline, Posttest-1, and Posttest-2, and completing it will require ~15 minutes.

11. Parents and Infants Engaged Intervention Rating Profile (PIE IRP; adapted from Witt & Martens, 1983 by our team for the PIE intervention). Parents will be asked to complete the PIE IRP at Posttest-2 as a measure of the social validity of PIE as implemented in this trial. The measure comprises 12 statements each rated on a 1-5 Likert scale by parents to indicate their level of agreement with the statement (e.g., "Reviewing and discussing videos of me interacting with my child was helpful." "I am able to recognize my child's sensory behaviors within routines.")

The estimated time required for parents to complete the PIE IRP is 5 minutes.

Summary of assessments and estimated participant time at each timepoint:

Baseline: total estimated time for parent-infant dyads is 80 minutes; an additional 15 minutes for parents only.

1. Parent-infant Interaction session - 20 minutes (Videos of this session will be used to measure Dyadic Engagement, Parent Responsiveness to Sensory Reactivity Cues, Parent Responsiveness to Prelinguistic Cues, and Infant Intentional Communication)
2. Child-Directed Speech Paradigm - 10 minutes (Will be used to collect respiratory sinus arrhythmia and skin conductance level measures).
3. Mullen Scales of Early Learning - 20 minutes. Visual Reception, Fine Motor, Receptive Language, and Expressive Language scales.
4. Attention Following trials - 2 minutes
5. Brief Observation of Social Communication Change - 13 minutes
6. Sensory Processing Assessment - 15 minutes
7. Sensory Experiences Questionnaire - 15 minutes (parents only)

Posttest-1: Total estimated time for dyads is 20 minutes; an additional 15 minutes for parents only.

1. Parent-infant interaction session - 20 minutes
2. Sensory Experiences Questionnaire - 15 minutes (parents only)

Posttest-2: Total estimated time for dyads is 70 minutes; an additional 20 minutes for parents only

1. Parent-infant interaction session - 20 minutes
2. Child-directed speech paradigm - 10 minutes
3. Mullen Scales of Early Learning Receptive and Expressive Language Scales - 10 minutes
4. Attention Following trials - 2 minutes
5. Brief Observation of Social-Communication Change - 13 minutes
6. Sensory Processing Assessment - 15 minutes
7. Sensory Experiences Questionnaire - 15 minutes (parents only)
8. PIE Intervention Rating Profile - 5 minutes (parents only)

6.1.4 Intervention Administration

PIE intervention schedule:

1. Introductory visit to meet family, outline the PIE intervention, review logistics, and record parent-chld video for first coaching session
2. Six weekly coaching sessions of ~one hour each in first PIE domain
3. [Break for Posttest-1]
4. Six weekly coaching sessions of ~one hour each in second PIE domain

PIE setting:

- Coaches will typically meet with families in their homes, but also could meet with them in another community setting based on a parent request and feasibility (e.g., the parent may want coaching related to managing a community outing routine, such as going to the grocery store accompanied by their infant).

People administering the intervention:

- The coaches for this trial will have Master's degrees in Speech-Language Pathology, Occupational Therapy, Early Intervention, or a related field, and prior experience working with young children with developmental disabilties and their parents.

PIE fidelity:

- Because the PIE intervention is newly developed, there is no existing fidelity of implementation measure. Thus, one product of the project will be a fidelity of implementation checklist for PIE coaches. The PIE intervention team (lead coach, additional coach(es), project PIs, and non-coaching therapists on the team) will collaborate to develop this checklist, as well as add to the PIE intervention manual, through weekly meetings in which PIE intervention goals and coaching strategies are discussed in the context of reviewing videos of coaching sessions. It is unlikely that the fidelity of implementation checklist will be finalized early enough in the project to use it for ongoing fidelity monitoring from the beginning of the trial. However, throughout the trial, each coach will video-record two coaching sessions in each of the PIE domains for the purposes of (a) potential review and feedback during the weekly meetings, and (b) scoring for fidelity of implementation once the fidelity checklist is finalized, and reliability in scoring the fidelity checklist has been established. These procedures allowing for ongoing refinement of the PIE intervention and elements considered to be indicators of the fidelity of implementation will result in products (expanded PIE manual and tested fidelity of implementation checklist) that will be essential for moving to an efficacy study, should the findings of this proof-of-concept study support that as a next step.

PIE training:

- The lead coach and a second coach read the PIE intervention manual along with Rush & Sheldon's (2011) book on coaching in early intervention. After reading this backgroud information, they will meet with the full intervention team to discuss questions and concerns. Then they will each pilot the PIE intervention with a family of an infant or toddler with developmental concerns who is not enrolled in the trial, prior to the enrollment of any trial participants. They will videorecord these sessions, and the PIE intervention team will review and discuss the videos during weekly team meetings, focusing on effective sharing of background information on each of the PIE domains, related additions needed to the PIE manual (e.g., handouts for parents), the process of reflective coaching specific to each domain, refinement of strategies used by the coaches, and problem-solving related to challenges identified by the coaches. This piloting process will constitute the training for the lead coach and the second initial coach.
- We anticipate that coaches will fluctuate across the course of this study, due to our plan to rely on PhD students who have Master's degrees and associated clinical/early intervention experience to serve as coaches. Training for subsequent coaches will include: (a) reading the PIE intervention manual, all coaching handouts, the Early Childhood Coaching Handbook (Rush & Sheldon 2011), and the PIE Fidelity checklist; (b) reviewing a video of a coaching session in the prelinguilstic communication domain and a video of a coaching session in the sensory regulation domain; (c) roleplaying a coaching session in each domain, recording a 10-minute video of the roleplay for review by the training coach; (d) shadowing a previously trained coach for two coaching sessions, one in each coaching domain; reviewing procedures with a trained coach for using tablet computer for coaching, and recording and storing coaching videos and other documents, with attention to data security; (d) conducting an initial coaching session in each PIE domain under the mentorship of a trained coach.

Intervention videos:

- All video files will be kept secured in the PIs laboratories at UNC-Chapel Hill and USC, identified by ID number, and archived on a secure network drive or on encrypted external hard drives. Video files will be clearly marked to identify whether the parent has given permission to use them for teaching/educational purposes. Portable computing devices, including the tablets used by the interventionists, will be encrypted, have a power-on password required, and an automatic log-off. Videos will be stored on tablets used by coaches only for the length of time required for use in coaching (typically one week for each video, except in cases where a session needs to be rescheduled to a later time). Upon completion of the study, the data will be archived on a secure server/in secure files in the Department of Allied Health Sciences at UNC project laboratory of the PI Watson and/or in the Mrs. T.H. Chan Professor of Occupational Science and Occupational Therapy in the USC laboratory of PI Baranek. De-identified data will be shared according to the Resource Sharing Plan, or other agreements negotiated with NICHD upon receipt of the grant.

6.1.5 Reaction Management

Proactively, we will provide appropriate referral information for accessing community early intervention services to all families whose infants' scores on the FYIv3.1b indicate they may be at EL-ND. If parent choose to pursue these services and the infant is determined to be eligible for public early intervention services governed by federal policies, the family will be assigned a service coordinator (as well as being offered other services based on the Individualized Family Service Plan, or IFSP). Because all of the participants in this trial will be in weekly contact with a project coach or other research staff member (e.g., the project coordinator who is scheduling assessment appointments), we will be able to monitor parent and infant reactions to the intervention or participation in the intervention trial. On a scheduled monthly basis, we will include an item on our full research team meeting agenda to inquire about any safety concerns related to participants, including stress reactions. In addition, coaches will be able to discuss any concerns they may have about reactions at the weekly intervention team meetings (which the PIs will attend). All staff interacting with participants will be informed that any urgent issues related to the health and safety of participants should be reported immediately to one of the PIs. We will maintain a list of community resources for parent of young children, including children with developmental concerns, for our catchment area, and share resources with parents as appropriate.

6.2 Assessments

6.2.1 Efficacy

The aims of the current proof-of-concept trial do not include an evaluation of the efficacy of the PIE intervention, and the design of the study does not include the necessary controls for an efficacy evaluation. The timing and procedures for assessments and the rationale for selecting them within the context of our study aims have been described elsewhere in this protocol (5.2.1 Primary outcome variables; 5.2.2 Secondary and Exploratory variable; 6.1.3

Selection of Instruments/Outcome Measures; Visit Schedule Table; Study Flow Chart).

6.2.2 Safety/Pregnancy-related Procedure

Not applicable to our study; although it is possible some parents may be pregnant, the study aims and procedures are unrelated to pregnancy and pose no additional risks than ordinary daily life in the event that a parent is pregnant.

6.2.3 Adverse Events Definition and Reporting

Adverse events are defined based on Standard Operating Procedures applicable to Investigators and clinical research team members conducting human subjects research at the University of North Carolina at Chapel Hill as follows:

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

Hospitalization: admission to the hospital for longer than 24 hours.

Serious Adverse Event: Serious adverse event means any event temporally associated with the subject's participation in research that meets any of the following criteria:
• results in death;
• is life threatening (places the subject at immediate risk of death from the event as it occurred);
• requires inpatient hospitalization or prolongation of existing hospitalization;
• results in a persistent or significant disability/incapacity;
• results in a congenital anomaly/birth defect; or
• any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

Reporting:

Dr. Watson (Lead PI) will conduct monthly case review meetings where the study team will report on active cases involved in the study. At the close of each case review, study personnel will be excused and Drs. Watson, Baranek, Crais, and Turner-Brown will discuss any data safety issues and/or any apparent adverse outcomes for participants identified during the case review. Dr. Watson will report unanticipated problems/adverse events in

accordance with UNC-Chapel Hill HRPP SOP # 19.0, and will halt continuation of study procedures that negatively affect participants. She will also report unanticipated problems or adverse events within the time frames stipulated in HRPP SOP # 19.5 (1 or 2 weeks, depending on the nature of the event) and take necessary corrective action. Dr. Watson will discuss/present any clinical/behavioral task issues that were identified with research personnel to ensure that everyone is informed about events and potential protocol changes. She will also arrange for trainings as needed. If data and/or safety issues come to the attention of Drs. Watson and/or Baranek between bimonthly meetings, each will intercede as described above.

6.2.4 Pharmacokinetics

Not applicable.

6.2.5 Biomarkers

Not applicable.

6.3 Study Procedures

6.3.1 Study Schedule

See Visit Schedule Table for a summary.

1. Screening

- Parents will complete the FYIv3.1b online or in paper form, in the setting of their choosing. This questionnaire will require 5-10 minutes.
- The study coordinator will contact parents of infants whose scores place them at elevated likelihood for later diagnosis of an ND by phone to provide screening results, screen further for study inclusion/exclusion criteria, describe the baseline assessment in the context of the larger study (for families who have not met any exclusionary criteria), and request verbal consent to participate in a baseline assessment with their infant. This phone call will take 15-30 minutes, depending on questions raised by the parent.

2. The baseline assessment visit will take place in the study's office in Carrboro, NC, as soon after the phone call and will last approximately 1 3/4 to 2 hours, allowing for introductions, completion of the written informed consent process, transitions from one assessment protocol to the next, breaks for the infant, and a brief conversation with parents regarding the infant's developmental assessment results and recommendations, if appropriate, for community services. Parents will also complete at questionnaire requiring an additional 15 minutes, at the location of their choice. The following assessments will be

completed:

- Parent-infant Interaction session - 20 minutes (Videos of this session will be used to measure Dyadic Engagement, Parent Responsiveness to Sensory Reactivity Cues, Parent Responsiveness to Prelinguistic Cues, and Infant Intentional Communication)
- Child-Directed Speech Paradigm - 10 minutes (Will be used to collect respiratory sinus arrhythmia and skin conductance level measures).
- Mullen Scales of Early Learning - 20 minutes. Visual Reception, Fine Motor, Receptive Language, and Expressive Language scales.
- Attention Following trials - 2 minutes
- Brief Observation of Social Communication Change - 13 minutes
- Sensory Processing Assessment - 15 minutes
- Sensory Experiences Questionnaire - 15 minutes (parents only; can be completed online, or in hardcopy form if parents prefer, from location of parent choice)

For children who meet final study eligibility criteria for the intervention trial based on baseline assessment results for the expressive and/or receptive language and sensory reactivity, the study coordinator will complete the written informed consent process at the end of the baseline assessment.

3. The assigned PIE intervention coach for each enrolled family will schedule an initial introductory visit with the family, which will include recording a 5-10 minutes video of parent-infant interaction to use in the first coaching session. This introductory visit will require a total of approximately 45-60 minutes.

4. Coaching in the first PIE domain for the family (randomly assigned) will take place in 6 weekly visits at the home of the dyad, lasting approximately one hour each.

5. Posttest-1 will occur after the conclusion of coaching in the first PIE domain at the study's office in Carrboro, NC. Total estimated time for dyads is 25-30 minutes, allowing for time for introductions and the infant to settle into the setting; parents will spend an additional 15 minutes completing a questionnaire at a location of their choice. The following assessments will be completed:

- Parent-infant interaction session - 20 minutes
- Sensory Experiences Questionnaire - 15 minutes (parents only; can be completed online, or in hardcopy form if parents prefer, from location of parent choice)

6. Coaching in the 2nd PIE domain will take place in 6 weekly visits at the home of the dyads, lasting approximately one hour each.

7. Posttest-2 assessments willl take place at the study office in Carrboro, NC, and will last approximately 1.5 to 2 hours, allowing for introductions, transitions between assessment activities, breaks for the infant, and a brief concluding conversation with parents regarding the infant's developmental assessment results and recommendations, if appropriate, for community services. Parents will also complete two questionnaires requiring an additional 15-10 minutes, at the location of their choice.

- Parent-infant interaction session - 20 minutes
- Child-directed speech paradigm - 10 minutes

- Mullen Scales of Early Learning Receptive and Expressive Language Scales - 10 minutes
- Attention Following trials - 2 minutes
- Brief Observation of Social-Communication Change - 13 minutes
- Sensory Processing Assessment - 15 minutes
- Sensory Experiences Questionnaire - 15 minutes (parents only, can be completed online, or in hardcopy form if parents prefer, from location of parent choice)
- PIE Intervention Rating Profile - 5 minutes (parents only, can be completed online, or in hardcopy form if parents prefer, from location of parent choice)

Families will be scheduled for baseline assessments as quickly as possible after the initial screening; we anticipate the study team will have the capacity to schedule and complete baseline assessments within 1 to 2 weeks after receiving the FYIv3.1b; however, family schedule preferences and constraints will be accommodated and may lengthen this time period. The total length of time from the baseline assessment (when they would consent to the intervention trial) through Posttest-2 would be a minimum of 16 weeks, assuming that no visits would be more than one-week apart. However, from our past experience with similar intervention trials, there will be some lengthening of the participation period for most dyads, due to needs to accommodate scheduling conflicts for both assessment and intervention visits. Thus, the total actual length of participation time from the FYIv3.1b completion through Posttest-2 is estimated to average ~22-25 weeks.

6.3.2 Informed Consent

1. Consent for screening (FYIv3.1b).

Both the mail and online version of the FYI will include a cover page that is essentially a fact sheet about the FYI and larger study. All information typically included in an informed consent form is described in the page,including confidentiality, risks, and benefits of the study. Thus, a parent who reads the page and submits the questionnaires will have given us their implied consent to use their FYI eligibility data. We have included a question: "would you be willing to be contacted about future research" as a consent to be notified about eligibility for the PIE intervention study. Families who return the FYI will also have the option to complete a "Subsequent Participation" form with their contact information, including telephone numbers.

2. Consent for baseline assessments.

The study coordinator will contact families of infants whose scores on the FYIv3.1b place them at elevated likelihood for an eventual ND diagnosis, to share screening results and ask if the parent is interested in learning more about the study. If the parent indicates interest, the study coordinator will explain the overall study, as well as the purpose and procedures for the baseline assessment visit, and ask if the parent is ready to give verbal consent for a baseline assessment. Infants who have met all the criteria to participate in baseline assessments must meet criteria for demonstrating communication delays and elevated patterns of sensory reactivity (hypo- and/or hyper-reactive) during the initial baseline assessments in order to meet fully eligibility criteria for the intervention phase of the study. Therefore, consent for the families will be obtained separately for the baseline

assessment visit and the intervention phase of the study (contingent on the infant meeting all inclusion criteria).

Upon arrival at the baseline assessment, a trained research staff member (study coordinator or one of the project assessors) will review the Informed Consent document for the baseline asssessment visit with the parent, describing the initial evaluation point-by-point, stopping frequently to ask if the parent has any questions or concerns, and to prompt the parent to review/restate information to ensure their understanding. The forms will be signed and dated by both the parent and the project staff representing the study. Copies of the signed consent forms will be given to the parent, along with a list of contact numbers if they have future concerns or questions. Parents will be reminded that they can withdraw participation from the study at any time by simply calling one of the contact persons, or telling one of the assessors if they decide to withdraw during the assessment session. As part of our study, families will be encouraged to pursue community services for their child. We will provide families with referral information regarding community service providers depending on the specific needs of their child. Additionally, some of the children involved in our study may already be receiving community services prior to their enrollment in our study. A release of information form will allow us to assist consenting families with their initial community-based referral as well as to pass along our assessment/intervention information to agencies with which consenting families are already working with.This form must be signed before assessments are conducted. The results of the original assessment will be shared with all families that participate in the initial assessment. For eligible families, the project coordinator will review the consent form for the intervention study and give parents the opportunity to enroll in the intervention study.

3. Consent for intervention study.

If the infant meets full eligibility criteria during the baseline assessment visit, a trained project staff member (study coordinator or an assessor) will review the informed consent document for participating in the intervention phase of the study at the end of the baseline visit, again stopping frequently to ask if the parent has any questions or concerns, and to prompt the parent to review/restate information to ensure their understanding. If a parent is ready to provide written consent for the intervention at the end of the baseline visit, then the form will be signed and dated by the parent and the project staff member, and a copy provided to the parent. Alternatively, parents can take the consent form home with them and return the forms by mail if they decide they want to participate in the study.

4. In addition to the procedures embedded in the consent process described above, including adequate time for parents' decision making, we have considered the possibility of coercion with reference to the incentives for study participation. The incentives are intended to offset the parents' time for assessment participation and to cover incidental expenses. The total amount of incentives is in-line with what an average NC wage earner would get for 4-5 hours of time, even without accounting for travel time. No incentives are planned for the in-home intervention sessions.

6.3.3 Screening

Parents will complete the FYIv3.1b online or in paper form, in the setting of their choosing.

This questionnaire will require 5-10 minutes.

The FYIv3.1b will be received by the project staff via RedCap (for online forms), by mail, or by pickup from healthcare providers' offices upon request, and scored immediately upon receipt.

The FYIv3.1b was developed to identify infants to elevated likelihood for later diagnosis of autism and other developmental conditions (e.g., attention deficit hyperactivity disorder; language delays/disorders; sensory processing disorders; global developmental delays). The screening cut-points on the FYIv3.1b were set in conjunction with a previous study for which we had access to diagnostic outcome information such that we capture about 1/3 of the infants who will go on to be confirmed as having a autism spectrum diagnosis while misclassifying less than 5% of the typically developing (TD) sample as at-risk. We know from previous studies using an earlier version of the FYI that many infants later diagnosed with other NDs also will have scores exceeding the threshold on the FYI (Turner-Brown et al., 2013).

If parents have provided consent for further contact and contact information in conjunction with completing the FYIv3.1b, the study coordinator will contact parents of infants whose scores place them at elevated likelihood for later diagnosis of an ND by phone to provide screening results, provide information about the study, and screen further for study inclusion/exclusion criteria. Specifically, in this phone call the study coordinator will screen for the following criteria:

Inclusion criteria:

- A parent or other primary caregiver of the infant is available for study participation, along with the infant.
- Family lives within the catchment area for the study.

Exclusion criteria

- Infant has a known genetic conditions (e.g., Down syndrome).
- Infant has a known significant uncorrected vision/hearing/physical impairments.
- Famiy who do not speak English as their primary language in the home (>50% of the time).

6.3.4 Recruitment, Enrollment and Retention

How participants will be identified:

- To identify infants at-risk for neurodevelopmental disorders, we will use a population-screening method based on birth records in North Carolina, mailing postcards to families of children in this age range within our catchment area; we will supplement recruitment by distributing postcards/flyers through physician's offices, public health clinics, and childcare programs, and via email and listserv announcements; we also will reach out to families of young children via social media groups that include parents of young children in our catchment area, and via booths at family-oriented local

fairs/festivals. All of these will be directed at providing parents with an opportunity to complete the FYIv3.1 for their 11- to 16-month-old infants.

How and where participants will be recruited:

- Participants will be recruited throughout the central region of North Carolina through two primary sources: (a) state birth registries (NC Vital records; 6 counties within 90 miles of Chapel Hill including Orange, Durham, Chatham, Alamance, Guilford, and Wake), and (b) primary care well-baby clinics — either through local pediatric practices or county health clinics, in rural and urban areas that represent wide demographics. Our team has experience and success with these methods over the past 15 years through other research studies. Families identified through birth registries will receive an informational postcard (via postal mail) asking the parent of the infant to complete the survey (FYI) online or to request a paper form, and return to the project's PO Box. Families identified through pediatric practices and health clinics will be given an informational postcard at the time of their well-baby visits by office staff at those clinics. They may also fill the FYI out online or as a paper form and return to the project's PO Box. Filling out the form constitutes consent for the initial screening (based on our previous IRB approved procedures). For recruitment via listservs, the listserv message will include a link to the online FYIv3.1b as well as contact information for the project (email, phone) through which parents can request a hard copy of the FYI. Finally, for booths at local family-oriented fairs and festivals,

Likelihood we will have access to the targeted number of participants:

- Based on previous studies with similar methodologies and catchment areas, we estimate that the familes of 32,000 infants will have the opportunity to complete the FYIv3.1 over the course of the project, with an overall return rate of ~15%, yielding 4800 completed FYIs. We anticipate that 5% of these infants (N=240) will score at risk on the FYI (i.e., risk scores ≥ 95th %ile based on the FYIv3.1 normative data). Of those, 35% will be eligible for the assessment phase of the study and agree to the developmental assessment at UNC (N=84), and 57% of these will meet full inclusion criteria (N=49). Of those, 90% will consent to randomization, yielding approximately 44-45 families to randomize into the intervention study. The inclusion enrollment table provides the breakdown by sex and ethnicity given the North Carolina demographics, adjusted for expected attrition for non-English speaking families (i.e., we have reduced Hispanic enrollment by 1/3 of census figures). [NOTE: Current census demographics are: 64.7% White (not Hispanic); 22.0% Black/African American; 2.5% Asian; 8.7% Hispanic/Latino*; 2.0% More than one race; 0.1% Native Hawaiian/Pacific Islander; 1.5% American Indian/Alaska Native. Births in the 6 county catchment area numbered 26,814 in 2014 and birth rates have increased since then. We will broaden the catchment area to adjacent urban areas (e.g., Winston-Salem; Fayetteville) as needed to yield the target sample.]

Protection of privacy of potential subjects during recruitment:

- Postcards about the study will be mailed to families on a one-time basis when the children are between 11 and 16 months of age. These cards will be sent to families based on birth records alone, with no prior knowledge of how the infants will score on

the FYI. The postcards will give a web address to which parents can go to complete the FYIv3.1; in addition, families will be provided an email address and phone number, either of which can be used to request that a hard copy of the FYIv3.1 be mailed to them. The FYIs will be returned by parents, unscored, in a postage-paid self-addressed envelope, or will be completed online. FYIs will also be available at pediatric practices and health clinics along with postage-paid self-addressed envelopes.The FYIs will be identified with the potential participants' assigned ID numbers rather than with names. Agreement to subsequent contact and contact information (names, addresses, phone numbers) will be collected on a separate form from the FYI. This information will be stored in a separate file from the FYI results, and linked via the participant ID number. For any FYIs flagged due to a child meeting the predefined criteria (risk scores at or above the 95th %ile), the Project Coordinator will retrieve the contact information using the participant ID and initiate contact with the family by phone. In the event that the family does not answer and the call goes to voicemail, the Project Coordinator will leave a message that she has called along with her phone number, but will not leave any information pertaining to the FYI results.

How potential participants will be contacted:

- Completed FYIs will be scored and screened for risk status. Infants who score ≥95th %ile risk score will be flagged, and those families will receive a phone call informing them of the results of the screening (by a qualified/trained project coordinator), and screening the child and family for addtional inclusion and exclusion criteria is they are interested in potentially participating in the study. Those who have continued to meet eligibility criteria that can be assessed through the FYIv3.1b and the phone call will be invited for a more comprehensive baseline assessment. A maximum of 4 attempts will be made to contact a family: an initial phone call, a follow-up phone call if there is no response to the initial call after one week, an email (if the parents provided an email address in their contact information), and finally a mailed letter. The goal in the first three attempts will be to have a phone conversation with one of the child's parents, to inform them about the child's score on the FYI, to offer resource information about the public early intervention program, and to determine whether the child/family are eligible to participate in the Baseline assessment. If we do not get a response to the first three attempts, we will include information about the child's screening results and contact information for the regional Child Development Service Agency that would serve the family in the letter, as well as contact information for the project should the parents wish to discuss the screening results or potentially consider consenting to an initial evaluation at that point. If we get no response from the parents after these 4 attempts, we will assume the parents have declined enrollment in the study.

Who will do the recruiting:

- Recruitment materials (flyers, mailings ,etc.) will be prepared by study staff and volunteers, who also will distribute recruitment materials to health care facilities, childcare programs, on social media, and at local fairs/festivities. At local fairs and festivals, study staff will use tablet computers to provide parents of children in the age range access to an electronic version of the FYIv3.1b. Phone contacts with parents of children who score at-risk for the FYIv3.1, phone screening for exclusion criteria, explanation of the study, mailing of study information and consent forms, and the in-

person informed consent process will be the responsibility of the Project Coordinator.

6.3.5 Study Visits

1. The baseline assessment visit will take place in the study's office in Carrboro, NC, as soon after the phone call and will last approximately 1 1/2 to 2 hours. Parents will also complete at questionnaire requiring an additional 15 minutes, at the location of their choice. The following assessments will be completed:

- Parent-infant Interaction session - 20 minutes (Videos of this session will be used to measure Dyadic Engagement, Parent Responsiveness to Sensory Reactivity Cues, Parent Responsiveness to Prelinguistic Cues, and Infant Intentional Communication)
- Child-Directed Speech Paradigm - 10 minutes (Will be used to collect respiratory sinus arrhythmia and skin conductance level measures).
- Mullen Scales of Early Learning - 20 minutes. Visual Reception, Fine Motor, Receptive Language, and Expressive Language scales.
- Attention Following trials - 2 minutes
- Brief Observation of Social Communication Change - 13 minutes
- Sensory Processing Assessment - 15 minutes
- Sensory Experiences Questionnaire - 15 minutes (parents only; can be completed online, or in hardcopy form if parents prefer, from location of parent choice)

For children who meet final study eligibility criteria for the intervention trial based on baseline assessment results for the expressive and/or receptive language and sensory reactivity, the study coordinator will complete the written informed consent process at the end of the baseline assessment.

2. The assigned PIE intervention coach for each enrolled family will schedule an initial introductory visit with the family of 45-60 minutes. Topics for discussion will be:

- What do we mean by coaching?
- Why are we doing these sessions?
- How will coaching work?

The coach also will complete the PIE Routines Questionnaire with the parent, as a basis for discussing what the usual family routines are involving the infant, and what goals the parent may have for improving the infant's participation in these routines.

At the end of the session, the coach will record a ~10-minute video of the parent interacting with the infant for use in the first coaching session.

4. Coaching in the first PIE domain for the family (randomly assigned) will take place in 6 weekly visits at the home of the dyad, lasting approximately one hour each. The agenda for each visit will include:

- Check-in and introduction to the session
- Review of selected scenarios in the video of parent-infant interaction from the prior session, to support parents understanding of their infant's level of engagement,

communicative or sensory reactivity cues of the infant and how they are related to the infant's engagement, and how parent's response strategies impact the infant's engagement
- Live coaching - coach will identify with parent what response strategies they will use to try to increase the infant's engagement, provide feedback to the parent during and after their interaction with the infant about what they observe, and elicit parent's reflections on the interaction and how strategies might be changed, expanded or enhanced.
- Family action planning - parent and coach complete a written plan for the coming week of response strategies the parent will consciously use, and the routines in which the response strategies will be used.
- Coach records a ~10-minute video of a parent-infant interaction to use in the next coaching session.

5. Posttest-1 will occur after the conclusion of coaching in the first PIE domain at the study's office in Carrboro, NC. Total estimated time for dyads is 25-30 minutes; parents will spend an additional 15 minutes completing a questionnaire at a location of their choice. The following assessments will be completed:

- Parent-infant interaction session - 20 minutes
- Sensory Experiences Questionnaire - 15 minutes (parents only; can be completed online, or in hardcopy form if parents prefer, from location of parent choice)

6. Coaching in the 2nd PIE domain will take place in 6 weekly visits at the home of the dyads, lasting approximately one hour each.

- Check-in and introduction to the session
- Review of selected scenarios in the video of parent-infant interaction from the prior session, to support parents understanding of their infant's level of engagement, communicative or sensory reactivity cues of the infant and how they are related to the infant's engagement, and how parent's response strategies impact the infant's engagement
- Live coaching - coach will identify with parent what response strategies they will use to try to increase the infant's engagement, provide feedback to the parent during and after their interaction with the infant about what they observe, and elicit parent's reflections on the interaction and how strategies might be changed, expanded or enhanced.
- Family action planning - parent and coach complete a written plan for the coming week of response strategies the parent will consciously use, and the routines in which the response strategies will be used.
- Coach records a ~10-minute video of a parent-infant interaction to use in the next coaching session.

7. Posttest-2 assessments willl take place at the study office in Carrboro, NC, and will last approximately 1.25 hours. Parents will also complete two questionnaires requiring an additional ~20 minutes, at the location of their choice.

- Parent-infant interaction session - 20 minutes
- Child-directed speech paradigm - 10 minutes

- Mullen Scales of Early Learning Receptive and Expressive Language Scales - 10 minutes
- Attention Following trials - 2 minutes
- Brief Observation of Social-Communication Change - 13 minutes
- Sensory Processing Assessment - 15 minutes
- Sensory Experiences Questionnaire - 15 minutes (parents only, can be completed online, or in hardcopy form if parents prefer, from location of parent choice)
- PIE Intervention Rating Profile - 5 minutes (parents only, can be completed online, or in hardcopy form if parents prefer, from location of parent choice)

Families will be scheduled for baseline assessments as quickly as possible after the initial screening; we anticipate the study team will have the capacity to schedule and complete baseline assessments within 1 to 2 weeks after receiving the FYIv3.1b; however, family schedule preferences and constraints will be accommodated and may lengthen this time period. The total length of time from the baseline assessment (when they would consent to the intervention trial) through Posttest-2 would be a minimum of 16 weeks, assuming that no visits would be more than one-week apart. However, from our past experience with similar intervention trials, there will be some lengthening of the participation period for most dyads, due to needs to accommodate scheduling conflicts for both assessment and intervention visits. Thus, the total actual length of participation time from the FYIv3.1b completion through Posttest-2 is estimated to average ~22-25 weeks.

6.3.6 End of Study and Follow Up

Coaches will complete an exit interview for the intervention with families at the end of their last coaching session. Parents also will be asked to complete the "Intervention Rating Profile" for the PIE intervention at the time of the Posttest-2 assessment.

At the end of the Posttest-2 assessment, the assessment coordinator (and one or more other assessors as appropriate) will provide information to the family on the child's developmental status based on the standardized assessments conducted, and will provide parents with a written summary that they can take home with them.

Parents who wish to discontinue participating in the intervention will be invited to continue participating in any remaining scheduled assessments. Their reason(s) for discontinuing the intervention will be recorded if the parents is willing to share, and if the reason suggests a possible adverse event, the study coordinator will bring this to the attention of the PIs for review.Similarly, if a parent wishes to withdraw from the entire study, the study coordinator will record the reason if provided, and notify the PIs immediately if the reason indicates a possible adverse event.

Parents will be invited to contact the study coordinator following the end of their study participation if they have questions or concerns related to the study, or if they are seeking assistance in finding community services for their child.

6.3.7 Removal of Subjects

Participants may withdraw voluntarily at any time; this option will be covered in the consent process and study staff will remind parents that they have that option if they express reluctance to continue their study participation at any point.

We do not anticipate any situations in which the study staff would make a decision to remove participants from the study, given the low level of risk associated with the study procedures.

6.4 Statistical Method

6.4.1 Statistical Design

The study is designed as a randomized comparative trial with two phases. For Study Phase 1, dyads will participate in baseline assessments; then eligible, consenting families will be randomized, stratifying by child age, to one of two treatment arms. Arm1 families will participate in initial coaching on the PIE sensory reactivity (SR) domain, and Arm2 families will participate in initial coaching on the PIE prelinguistic communication (PC) domain. Families will participate in 6 weekly coaching sessions in their respective treatment arms, and return for Posttest-1. For Study Phase 2, dyads in Arm1 will receive 6 weekly coaching sessions on the PC domain, and dyads in Arm2 will receive 6 weekly coaching sessions on the SR domain. Then families will return for Posttest-2.

Comparisons of dyads assigned to Arm1 and Arm2 at Posttest-1 will allow us to estimate the separate effects of the two domains of PIE coaching, as dyads will have only been coached in one domain (responding to prelinguistic communication cues or sensory reactivity cues) prior to Posttest-1. At Posttest-2, we will get estimates of the additive effects of coaching in the second PIE domain, and be able to evaluate whether there are any effects of the order of coaching by comparing dyads in Arm1 to those in Arm2.

For analyses, we will utilize repeated measure analyses within a mixed modeling framework, to assess time and tx order effects, while accommodating missing data and optimally utilizing all available data.

6.4.2 Sample Size Considerations

Assuming recruitment of 44 infant-parent dyads and allowing for a 9% (n=4) dropout rate, which is consistent with high retention rates (> 95%) in our prior intervention studies, 40 dyads (20 per treatment arm) will have complete data for analyses. Assuming a conventional type I error rate of .05, and intercorrelations among the repeated measures from .3 to .7, the magnitude of treatment group effects detectable with a .80 statistical power will range from f=.37 to .42, respectively, which are large standardized effects. The magnitude of time effects and time-by-treatment arm interaction effects detectable with a .80 power will range from .27 to .18, also respectively, which are medium-sized standardized effects. Thus, the study is underpowered to detect any but large differences

between the treatment arms and medium-sized or larger effects on time and time-by-treatment arm interactions. More important than the statistical comparisons, though, the analyses will yield key descriptive characterizations of the treatment-arm effects at the two posttest points (i.e., means, medians, proportions, and variances) on key outcomes, as well as effect size estimates that can be used in planning a larger scaled efficacy trial of the PIE intervention.

6.4.3 Planned Analyses

Data will be analyzed using an intention-to-treat analytic approach. Depending on patterns of attrition or numbers of dyads participating in fewer than the planned 6 coaching sessions in each of the two PIE domains, we may additionally employ some post-hoc analytic approaches (e.g., comparisons of treated participants in each arm; including a covariate for number of sessions) to inform our understanding of the outcomes in this proof-of-concept study. The study outcomes based on the planned intention-to-treat analyses will be reported, with supplemental post hoc analyses reported if appropriate/informative.

Analyses will address one primary objective and three secondary objectives:

Primary:

1. Estimate the separate and combined effects of the two PIE intervention domains on dyadic engagement (primary outcome).

Secondary

2. Estimate the separate and combined effects of the two PIE intervention domains on infant intention communication.

3. Evaluate the *differential* changes in parent responsiveness following coaching on two individual Parents and Infants Engaged (PIE) intervention domains — responses to variable infant (a) sensory reactivity or (b) prelinguistic communication — as well as *cumulative* changes in parent responsiveness following coaching on both PIE domains.

4. Determine the extent to which (a) autonomic indices of infant self-regulation and (b) language, sensory reactivity patterns, response to joint attention, and social-communication skills change over the course of the PIE intervention. .

Overall analytic procedures:

All data will be cleaned and inspected for outliers, missing data and distributional irregularities. Although general linear modeling methods are robust to minor violations of distributional assumptions, appreciable departures from normality can compromise statistical tests and estimators. Where error distributions potentially deviate from normality or heteroscedasticity is suspected, the tests of the contrasts described below will be conducted using exact (resampling-based) nonparametric methods.

We will complete planned analyses of study outcomes using repeated measures analyses within a mixed modeling framework, to assess time and tx order effects, while

accommodating missing data and optimally utilizing all available data.

Although we are performing multiple statistical tests across outcomes and hypotheses in addressing the three specific aims, in this project is more important to avoid overlooking statistical signals of effectiveness of the novel intervention approach (type II errors), than avoiding false assertions of effectiveness (type I errors). We believe it is premature, therefore, to employ conservative adjustments to the type I error rates in statistical tests, which would compromise the power of statistical tests to detect such signals.

6.4.3.1 Primary Analyses

The primary objective of this study is to examine whether the novel PIE intervention transforms parent-infant transactions over time as intended, thereby facilitating increases in the time infants spend in dyadic engagement with their parents. We will also evaluate whether dyadic engagement outcomes differ based on whether parents are coached first in the sensory reactivity domain followed by coaching in the prelinguistic communication domain, or are coached in the opposite order.

Specifically, we will estimate the separate and combined effects of the two PIE intervention domains on dyadic engagement (primary outcome). H1a: At Posttest-1, dyads coached in either PIE domain will exhibit moderately more dyadic engagement compared to Baseline (Cohen's d ≥ .40). H1b: At Posttest-2, dyads in both study arms will show additional small to moderate increases in dyadic engagement compared to Posttest-1 (Cohen's d ≥ .25).

Our primary analysis will be conducted to explore a priori contrasts of interest within using repeated measures within a mixed modeling framework. Of key interest will be the contrast of Baseline to Posttest-1 scores and the contrast of Baseline to Posttest-2 scores (time effect). In addition, the model will include terms for treatment arm effects and treatment arm-by-time interactions. A time effect will indicates growth in the outcome from baseline to the posttest point, a zero or negligible time effect indicates stability, and a negative time effect suggests a drop in scores. A non-negligible treatment arm effect indicates that the two treatment arms differ on the outcome; while a non-negligible interaction coefficient suggests that the magnitude of change from baseline to the posttest point are not equivalent for members of the 2 treatment arms. Since the primary outcomes are proportions, arc sin transformations of these proportions will be performed before entering them into the models.

6.4.3.2 Secondary Objectives Analyses, if applicable

Secondary Objective Analyses

Objective 2. Estimate the separate and combined effects of the two PIE intervention domains on infant intention communication.

H2a: At Posttest-1, infants in both groups will show no more than modest gains in intentional communication (Cohen's d < .25).

H2b: At Posttest-2, infants in both groups will show moderate increases in intentional communication compared to Baseline (Cohen's d ≥ .40).

Analyses: This outcome variable involves counts of infant intentional communication attempts. We expect the average number of counts to be sufficiently large (eg. ≥ 8) that a normal approximation to a Poisson error distribution will be appropriate; however, if not, Poisson or negative binomial regression methods, or nonparametric approaches may be employed. The analyses for Objectives 2 and 3 will use the same framework as for our primary Objective #1, that is, to evaluate a priori contrasts of interest within a repeated measures mixed modeling framework. We will examine the contrast of Baseline to Posttest-1 scores and the contrast of Baseline to Posttest-2 scores (time effect). In addition, the models will include terms for treatment arm effects and treatment arm-by-time interactions.

Objective 3. Evaluate the differential changes in parent responsiveness following coaching on two individual Parents and Infants Engaged (PIE) intervention domains — responses to variable infant (a) sensory reactivity or (b) prelinguistic communication — as well as cumulative changes in parent responsiveness following coaching on both PIE domains.

H3a: At Posttest-1, parents in both intervention arm will show increases in responses attuned to their infants' behaviors compared to Baseline, with parents coached in the sensory reactivity domain showing more responses attuned to infants' sensory reactivity, and parents coached in the prelinguistic communication domain showing more responses attuned to infants' signals of attention focus and communicative intent.

H3b: At Posttest-2 (after coaching in both PIE domains), there will be no between-arm differences in parent responses attuned to infant sensory reactions or prelinguistic communication leads, due to increases in parent responsiveness to the newly coached domain of infant behaviors.

Analyses: See analyses for Objective 2.

Objective 4. Determine the extent to which autonomic indices of infant self-regulation change over the course of the PIE intervention.

H4a: From Pretest to Posttest-2, infants will show limited changes in autonomic indices during exposure to nonsocial stimuli (Cohen's d <.25), but will show moderate-sized increases in respiratory sinus arrhythmia (RSA) and decreases in skin conductance levels (SCL) during exposure to child-directed speech (Cohen's d ≥ .40).

H4b: Infants will demonstrate small improvements in language, sensory reactivity patterns, response to joint attention, and social-communication skills over the course of the PIE intervention.

Analyses: The models for these analyses will use the repeated measures mixed modeling framework, as for Objectives 1, 2 and 3, except that the effects will be examined only at Posttest-2 (given that these measures will not be taken at Posttest-1). The models will include terms for treatment arm effects and treatment arm-by-time interactions.

6.4.3.3 Analysis of Subject Characteristics

Baseline characteristics will be analyzed by study arm as follows:

1. Child age - corrected age in months - mean, SD, range
2. Child sex - male, female - numbers in each category
3. Chld race, as identified by parents - White, Black, More than one race, Other - numbers in each category
4. Parent self-identified race - White, Black, More than one race, Other - numbers in each category
5. Child ethnicity, as identified by parents - Latino/Hispanic, Non-Latino/Non-Hispanic - numbers in each category
6. Parent self-identified ethnicity - Latino/Hispanic, Non-Latino/Non-Hispanic - numbers in each category
7. Parent education - level of education of parent enrolled in the study - numbers of parents with highest education level: < high school: completed high school; completed 1-2 year post high school certificate or degree program or some college; hold 4-year college degree (Bachelor's level); hold graduate or professional degree (Master's, PhD, MD, JD).
8. Child scores on the Mullen Scales of Early Learning - Visual Reception and Fine Motor T-scores - mean, SD, range
9. Child scores on the MacArthur Communication Development Inventory - words understood, words spoken, gestures - mean percentile score, SD, range
10. Parent Stress Scale - total scale score - mean, SD, range

For each of these baseline characteristics, comparisons will be made between dyads assigned to the two study arm to evaluate baseline equivalence of the arms on non-outcome characteristics.

6.4.3.4 Interim Analysis

We do not plan for interim analyses.

6.4.3.5 Health economic evaluation, if applicable

Not applicable.

6.4.3.6 Other

6.4.4 Subsets and Covariates

Models will initially be run without covariates. If any baseline characteristics differ significantly between the two study arms, we will consider rerunning models with covariates if there is a conceptual basis for the covariate potentially confounding the study outcomes.

6.4.5 Handling of Missing Data

Under the ITT framework, all research families' available data will be analyzed, even if incomplete. Full information maximum likelihood estimation, which fully utilizes all available data even if incomplete, will be used in analyses wherever possible. This approach yields correct statistical conclusions in the presence of missing data, as long as the data can be considered "missing at random (MAR)" (Little & Rubin, 2019). The MAR assumption implies that missing data elements can be treated as randomly missing as long a covariates relevant to the reasons (technically probability of being missing) are included in the models. Alternatively, if sample sizes are insufficient to support full information maximum likelihood estimation, then multiple imputation (MI), which is asymptotically equivalent, may be employed (Little & Rubin, 2019; Shafer, 1997).

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Incentives

- Families participating in the study will receive a small monetary incentive to participate. We have budgeted for a 20 dollar gift certificate for the first assessment (Baseline), 25 dollars for the second assessment (Posttest-1), and 50 dollars for the third (Posttest-2). We will also provide families with a 10 dollar gas card at each assessment visit.
- Families will receive the specified incentive at each assessment visit. If a family withdraws from the study they will not receive the subsequent incentive(s).
- Both children and their parents will participate in our study. The incentive payments will be made to the parents.
- Potential for coercion: The incentives are intended to cover the parents'/guardians' time for study participation, incidental expenses and for travel (gas card) for each visit. The incentives increase slightly to increase retention of the sample to the conclusion of the study. The participants will receive 95 dollars in incentives for approximately four hours of assessment. According to data released in 2016 by the NC Department of Commerce, the average hourly wage in NC is 21.24. Thus the incentive offered for assessment visits, considering travel time, is in-line with what an average wage-earner would get for this amount of time. No incentives are planned for the in-home intervention sessions.
- Privacy considerations: We will not collect Social Security Number information for the purposes of offering these incentives.
- Costs to be borne by the participants: The only potential costs to participants related to study participation will be any missed employment compensation due to their participation in home intervention sessions and assessment visits. Additionally, the gas cards may not fully compensate

all participants for their travel to the assessment site, depending on the distance they will travel and the fuel efficiency of their vehicle.
- Alleviating potential costs to participants: A postage paid envelope will be provided with the any hard copies of the FYI or other assessment materials for families to return the documents at no cost to them; a similar envelope will be provided to families to return consent for intervention forms if these are not signed at the study offices.

Informed Consent:

- The informed consent process is described in detail in section 6.3.2 of this protocol.
- Completion of the FYIv3.1b is considered to entail implied consent for use of the data. Both the mail and online version of the FYI will include a cover page that is a fact sheet about the FYI and larger study. All information typically included in an informed consent form is described in the page, including confidentiality, risks, and benefits of the study. It is our understanding that a parent who reads the page and submits the questionnaires give us their consent to use their data. Only families who answer "yes" to the question "would you be willing to be contacted about future research" will be contacted in the event their child scores at-risk on the FYI.
- Written informed consent will be obtained for the baseline assessment and for the intervention (consent to be obtained separately for baseline assessment and intervention, because some infants will not meet criteria at the baseline assessment for inclusion in the intervention trial).
- Consent documents are attached, including (a) the cover letter for the FYIv3.1b; (b) the consent form for the baseline assessment, and (c) the consent form for intervention.
- The child participants will not provide written assent due to their young age (11-16 months old at study entry) and related inability to understand the study purpose or procedures.

Collection of identifiers and sensitive information; confidentiality

- We will collect names, mailing/street addresses, telephone numbers, and email addresses for the purposes of contacting families about the study.
- We will collect full face video images of parents and children for the purpose of measuring study outcomes.
- Identifiers coded with a linkage file will be stored electronically in a different folder from the research data collected on participants. Access to the folder with the linkage file will be restricted (via electronic permission settings) to the MPIs and the Study Coordinator. The Study Coordinator will provide the necessary contact information to the interventionists for the respective families assigned to each interventionist.

- Screening measures and protocols from the developmental assessments will be stored in a locked file cabinet in a locked office and identified only by dyad ID number. Any scientific reports, article submissions, or summaries of the data will not include names. Additionally, individual data that might possibly identify any one child or parent will not be presented; data will be presented in summary format that will preclude any personal identification. In some cases, parents may give permission to use short segments of video for teaching/educational purposes. All videos will be kept secured in the PI's laboratory, identified by ID number, and archived. Video files will be clearly marked to identify whether the parent has given permission to use them for teaching/educational purposes. We will not share identifiable data with any other party (such as a care provider or physician) without written consent from the parent/guardian. However if a parent/guardian chooses to share the written report that we provide to them, they will

be made aware that this information may then become part of their child's record with that institution, which may provide Insurance companies with access to that information.
- Electronic data will be stored on a secure and encrypted network (REDCap) that requires password access.
- Portable computing devices will be encrypted, have a power-on password required, and an automatic log-off.
- The primary potential for deductive disclosure will come from our videotaping of research participants, which is essential for several aspects of the study protocol. Because the videotapes will have full face images of children and their parents, and because first names will be used often in the course of interactions captured on videotapes, the identity of participants could be deduced by someone watching the videotapes. We, therefore, will take careful measures to protect the security of the videotapes.
- Study personnel will have access to physical data (paper forms, DVD, external hard drives) that will be housed in the PIE office in locked cabinets. Staff will be required to sign out/in any form of these data (information recorded in dyad's individual paper file or on DVD) in a notebook. All electronic data will be available on a secure network drive that is password protected and encrypted (REDCap, School of Medicine shared drive, UNC Office 365 suite of secure cloud applications). The deidentified data will be available through the secured network and the identifying match will be housed separately. Access to the data files will be restricted, based on the role of the research team member. For example, members of the assessment team will not have access to data related to the intervention, in order to preserve their "blindness" to the randomized group assignment of study participants.

Privacy

- Phone interviews in the PIE office will be conducted behind closed doors.
- Assessments will be conducted in a private suite.
- No mailed information will include any indication of child/parent status that is visible on the exterior of the envelope.
- Coaching sessions will take place in the family's home, scheduled at the convenience of the parent.

7.2 Institutional Review Board (IRB) Review

The study will undergo review and approval by the UNC-CH IRB, with the application submitted through the online application system (IRBIS).

Modifications will be submitted for UNC-CH IRB review through the online system, and IRB approval will be secured before modifications are implemented.

Reportable events and unanticipated problems under the purview of the IRB will be reported following UNC-CH Standard Operating Procedures.

7.3 Subject Privacy, Confidentiality & Data Management

See section 7.1 for the protocol related to participant privacy and confidentiality and data security.

Data will be entered and stored in RedCap. Parent report measures will be entered directly into RedCap by participants, unless the participants request to complete hard copies of these measures instead.

Other data will be entered into RedCap by trained research assistants who will be granted limited access to the RedCap site consistent with their data entry role. One research assistant will enter the data initially, and a second research assistant will independently check the data entry for errors.

Access to names, home addresses, email addresses, and phone numbers entered into RedCap will be restricted to the data manager, project PIs, and study coordinator; the project PIs or study coordinator may provide temporary access to this information for other study staff if needed to complete an assigned task.

Data entry records will be identified by each participating dyad's unique ID number.

7.4 Deviations/Unanticipated Problems

A log of protocol deviations will be maintained through active data collection. Any protocol deviation that harms a partcipant or places others at increased risk of harm will be reported to the IRB per UNC-CH SOP 1401.

Reportable deviations or unantcipated problems will be reported to the IRB through the online reporting system within two weeks of the PIs becoming aware of the problem.

Any protocol deviation that is made to eliminate an immediate hazard to a participant without IRB approval will be subsequently reported to the IRB per UNC-CH SOP 1401.

Any unanticipated event that involves risk to a participant or others will be reported to the IRB per UNC-CH SOP 1401. For this purpose, unanticipated events are defined as follows (from UNC-CH SOP 1401):

1. Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO): Any incident, experience, or outcome that

    1. 4.5.1 is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

2. 4.5.2 is related or possibly related to a participant's participation in the research; and

3. 4.5.3 is serious or 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.

7.5 Data Collection

Data collection information has been previously detailed in sections 5.2, 6.1.3, 6.3.5, and in the Visit Schedule Table.

Data will be securely archived in RedCap.

The linkage file will be maintained until videos of the dyads have been destroyed. Access will be restricted to the study PIs or other research staff they designate, based on need to access the linkage files.

Videos of dyads will be destroyed before the child reaches the age of 18.

7.6 Data Quality Assurance

All research staff will complete training in human subjects research ethics.

Each research staff member will be trained to complete activities related to their role(s) on the project by a qualified trainer, with ongoing oversight. In addition to key personnel (MPIs and Co-Is, including study methodologists/statisticians), project roles will include a study coordinator (with overall responsibility for recruitment, enrollment, informed consent, scheduling visits, data storage, data entry, and training and supervision of RAs involved in these activities), lead coach (responsible for training and oversight of project coaches), an assessment coordinator and assessment team leads (responsible for organizing and providing assessor training and leading individual assessment visits), and coding team leaders (responsible for training RAs and monitoring and maintaining their reliability for measures involving coding/rating/scoring of videos).

The lead coach, assessment coordinator, and coding team leaders will each ensure that team members fulfilling roles under their purview have completed all required training steps and met criteria for fidelity in administering assessments, implemeting intervention, and/or reliability in scoring/rating/coding as required for the purpose of data quality.

To simplify the process of reliable coding/rating of measures taken from videos, all activities related to one measure will be focused either at UNC-CH or at USC, to minimize the need for cross-site training on coding or rating the same measure.

For measures that are not entered directly into RedCap by parents, data will be entered by

one research assistant and independently check for accuracy by another research assistant. Verification that data entered for a participant's measure have been checked will be recorded within RedCap.

Prior to analysis, data will be cleaned and any inconsistencies will be addressed.

7.7 Study Records

Study records include:

Completed FYI3.1b

Short Demographic Questionnaire (completed in conjunction with the FYI3.1b)

Contact information for parents who complete the FYI3.1b

Long Demographic Questionnaire (completed by participants who consent to baseline assessments)

MacArthur Communication Development Inventory (baseline)

Parent Stress Scale (baseline)

Sensory Experiences Questionnaire (baseline, Posttest-1, Posttest-2)

Mullen Scales of Early Learning

- Visual Reception Scale (Baseline)
- Fine Motor Scale (Baseline)
- Receptive Language Scale (Baseline, Posttest-1, Posttest-2)
- Expressive Language Scale (Baseline, Posttest-1, Posttest-2)

Parent-Child Interaction Session (Baseline, Posttest-1, Posttest-2)

- Videos of session
- Dyadic Engagement (coded from videos, using Observer software)
- Parent Responsivity to Child Sensory Reactivity Cues (rated from videos)
- Parent Responsivity to Child Prelinguistic Communication Cues (rated from videos)
- Child Intentional Communication (coded from videos, using Observer software)

Child-Directed Speech Protocol (Baseline, Posttest-2)

- Videos of session
- Gazepoint records (eye-tracking during child-directed speech protocol)
- Firstbeat records (interbeat-interval)
- Shimmer records (skin conductance levels)

Brief Observation of Social Communication Change (Baseline, Posttest-2)

- Videos of session
- Scoring protocols completed from videos

Sensory Processing Assessment (Baseline, Posttest-2)

- Videos of session
- Scoring protocols

Response to Joint Attention Scoring protocols (Baseline, Posttest-2)

Developmental reports for children (Baseline, Posttest-2)

PIE Coaching fidelity videos

PIE Coaching fidelity scoring protocols

Videos of parent-infant routines used for coaching

PIE Coach session plans

PIE Family action plans

Interview notes from final coaching session exit interview

PIE intervention rating profile

7.8 Access to Source

Source documents include:

Documents created when participating parents complete measures within RedCap

- Accessible in RedCap to study staff with roles of study coordinator, data manager, statistician, PI, data downloader (this role will only have access to deidentified data)
- Data created directly in RedCap upon entry

Documents created when participating parents complete hard copy versions of parent-report measures

- Accessible to study staff with roles of study coordinator, data manager, data entry (this role will enter data based on dyad unique ID without access to direct identifiers), statistician, PI, data downloader (this role will only have access to deidentified data)
- Data entered into RedCap from hard copies by data entry staff (research assistants)

Scoring protocols for measures administered during assessment visits

- Accessible to study staff with roles of assessment coordinator, assessment team lead,

assessor, study coordinator, data manager, data entry (this role will enter data based on dyad unique ID without access to direct identifiers), statistician, PI, data downloader (this role will only have access to deidentified data)
- Data created by assessors on hard copy protocols used during assessment visits
- Data entered into RedCap by data entry staff (research assistants)

Videos of parent-infant interaction sessions

- Accessible to study staff with roles of assessment coordinator, assessment team lead, assessor, study coordinator, video-downloaded/editor (research assistant), coding team leader, coder (research assistant), PI
- Data created by coding/rating from videos, in either Excel files or using Observer (generating an odf file within the Observer software)
- Data entered into RedCap by data entry staff (research assistants) or by exporting from Observer into Excel, uploading Excel files into RedCap

Fidelity videos of coaching sessions

- Accessible to study staff with roles of lead coach, coach, coding team leader, coder (research assistant), PI
- Data created by scoring fidelity of coach using coaching fidelity protocol
- Data entered into RedCap by data entry staff (research assistants)

7.9 Data or Specimen Storage/Security

See sections 7.1 and 7.3

7.10 Retention of Records

Data will be securely archived in RedCap.

The linkage file will be maintained until videos of the dyads have been destroyed. Access will be restricted to the study PIs or other research staff they designate, based on need to access the linkage files.

Videos of dyads will be destroyed before the child reaches the age of 18.

Once video files have been destroyed, the linkage file will also be destroyed, and the archived dataset will be reviewed to confirm that all personally identifiable information has been removed.

The deidentified dataset will be retained indefinitely.

Destruction of records require approval by one of the project PIs.

7.11 Study Monitoring

Monitoring of this study is the responsibility of the MPIs. (see section 7.12).

7.12 Data Safety Monitoring Plan

The protocol in this study presents minimal anticipated risk to participating children or families. The UNC IRB will maintain ethical and regulatory oversight of the study. Dr. Linda Watson and Dr. Grace Baranek (MPIs) will be jointly responsible for the safety of participants and for the validity and integrity of the data on a daily basis. They will ensure that:
• only subjects who meet the study eligibility criteria are enrolled,
• the informed consent process will be conducted appropriately and that informed consent will be obtained prior to proceeding with any study procedures
• data will be collected and analyzed as specified in the protocol,
• unanticipated problems and adverse events will be reviewed promptly and reported to the UNC IRB as required,
• privacy and confidentiality of subjects will be maintained
• withdrawals are documented.

Dr. Watson (Lead PI) will conduct monthly case review meetings where the study team will report on active cases involved in the study. At the close of each case review, study personnel will be excused and Drs. Watson, Baranek, Crais, and Turner-Brown will discuss any data safety issues and/or any apparent adverse outcomes for participants identified during the case review. Dr. Watson will report unanticipated problems/adverse events in accordance with UNC-Chapel Hill HRPP SOP # 19.0, and will halt continuation of study procedures that negatively affect participants. She will also report unanticipated problems or adverse events within the time frames stipulated in HRPP SOP # 19.5 (1 or 2 weeks, depending on the nature of the event) and take necessary corrective action. Dr. Watson will discuss/present any clinical/behavioral task issues that were identified with research personnel to ensure that everyone is informed about events and potential protocol changes. She will also arrange for trainings as needed. If data and/or safety issues come to the attention of Drs. Watson and/or Baranek between monthly meetings, each will intercede as described above.

7.13 Study Modification

Modifications to the study will be submitted to the IRB for approval prior to implementing changes (except in the case of any unanticipated changes required for immediate safety of participants or others).

The study coordinator will update project documents accordingly following approval of the

modification.

7.14 Study Discontinuation

We do not anticipate any conditions under which the study would be discontinued, in light of the limited risks it poses to participants.

7.15 Study Completion

The initial funding period for this study is 2 years, starting August 1, 2017. We anticipate that completion of the study will require a longer period of time, however, and will renew our IRB application/approval throughout the duration of the study. We will notify the IRB when the study is closed.

7.16 Conflict of Interest Management Plan

Study investigators and staff will comply with all UNC-CH procedures for managing conflicts of interest and potential conflicts of interest, including completing required conflict of interest reporting in conjunction with each annual renewal of our IRB approval.

7.17 Funding Source

This study is funded by a grant from NICHD R21 HD091547.

7.18 Publication Plan

The MPIs hold primary responsibility for publishing the results of this study.

Results will be reported in clinicaltrials.gov as required by our NIH funding.

We plan to submit a manuscript for peer review reporting the results for primary and secondary outcomes in this study as soon as possible after all data processing, coding, entry, cleaning and analysis have been completed.

Appendices

Appendix #	Title	Section	Topic
1	FYI parent letter online	6 Methods	6.3.4 Recruitment, Enrollment and Retention
2	FYI parent letter hard copy	6 Methods	6.3.4 Recruitment, Enrollment and Retention
3	Parent flyer	6 Methods	6.3.4 Recruitment, Enrollment and Retention
4	Flyer for healthcare providers	6 Methods	6.3.4 Recruitment, Enrollment and Retention
5	Information sheet	6 Methods	6.3.4 Recruitment, Enrollment and Retention
6	FYI postcard	6 Methods	6.3.4 Recruitment, Enrollment and Retention
7	Letter template for children who meet FYI criteria but unable to contact	6 Methods	6.3.4 Recruitment, Enrollment and Retention

8	Posttest-2 report template	6 Methods	6.3.6 End of Study and Follow Up
9	FYIv3.1b parent letter with consent information	7 Trial Administration	7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization
10	Baseline Assessment Consent	7 Trial Administration	7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization
11	Intervention Study Consent	7 Trial Administration	7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization
12	Study Flow Chart	7 Trial Administration	7.18 Publication Plan
13	Visits Table	7 Trial Administration	7.18 Publication Plan

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