Therapeutic Intervention Supporting Development from the Neonatal and Infant Critical Care Unit to 6 months for Infants Post Hypoxic-Ischemic Encephalopathy

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Study Title

Therapeutic Intervention Supporting Development from NICU to 6 months for Infants Post Hypoxic-Ischemic Encephalopathy

Objectives

Primary Objective: Feasibility Aims

1. Is it feasible to complete 1 baseline survey, 1 assessment and 2 parent/therapist collaborative sensorimotor intervention (SMI) sessions with infants with moderate or severe hypoxic-ischemic encephalopathy (HIE) or neonatal encephalopathy (NE) prior to discharge from the Newborn and Infant Critical Care Unit (NICCU)?
2. What proportion of parents complete ≥80% of the recommended SMI intervention?
3. What proportion of parents complete 100% of the baseline survey and 3 assessment visits?

Secondary Objectives

4. Is it feasible to evaluate the impact of brain lesion location on response to the SMI intervention?

Design and Outcomes

The purpose of this clinical trial (CT) is to evaluate the feasibility and begin to evaluate the effect of early sensorimotor intervention (SMI) for infants with HIE or NE. Twenty infants with HIE or NE and their parent will receive the therapeutic intervention that is typically provided in the NICCU and community (standard care), but infants in this study will receive an additional 2 SMI intervention sessions in the Children's Hospital of Los Angeles (CHLA) NICCU and 8 SMI intervention sessions in the home, at CHLA or at the University of Southern California (USC) Health Sciences Campus over the first 6 months of life. They can also occur via telehealth. These 10 sessions will consist of supporting parents to provide their infants with **daily** opportunities for positive sensory experiences and therapeutic play to enhance development.

- To determine feasibility (Aim 1 and 2), timing and participation in the SMI intervention sessions will be reported.
- To assess fidelity and adherence (Aim 2), parents will be asked to complete a log of their child's activities one day per week, randomly selected, for the 26 weeks from baseline to the end of intervention.
- To assess fidelity of the assessment schedule (Aim 3), parents will be asked to participate in developmental assessments at baseline, NICCU discharge, 3 months of age and 6 months of age. The assessments will include: Test of Infant Motor Performance at NICCU discharge and 3 months of age; the Bayley Scales of Infant and Toddler Development 4th edition at 6 months of age; and the Maternal Confidence Questionnaire, Parenting Stress Index, and Sensory Profile 2 at baseline and/or NICCU discharge, and 3 and 6 months of age.
- To characterize the participants (Aim 4), infants will have medical and

sociodemographic data collected from parents and electronic medical records, including the discharge summary from the NICCU, brain imaging, neurology reports, and reports from the High-Risk Follow Up Clinic. Parents will also be asked to self-report medical needs between assessment visits, use of daycare, and access to community therapy services using standardized questionnaires.

- To identify infants at high risk of cerebral palsy (Aim 4), infants will be assessed using Prechtl's General Movement Assessment at NICCU discharge and at 3 months and using the Hammersmith Infant Neurological Exam at 3 and 6 months of age.
- To assess the feasibility of evaluating the impact of brain lesion location on response to intervention (Aim 4), data from the magnetic resonance imaging (MRI) scan that is provided to all infants with HIE post therapeutic hypothermia or NE at CHLA will be analyzed to characterize the degree of HIE brain injury or NE and involvement of specific motor regions of the brain.

Interventions and Duration

All infants will receive the therapeutic intervention that is typically provided (standard care) in the CHLA NICCU and community, and infants in this trial will receive an additional 2 SMI intervention sessions in the CHLA NICCU and 8 SMI intervention sessions in the home, at CHLA, or at the University of Southern California (USC) Health Sciences Campus over the first 6 months of life at 1, 3, 5, 8, 11, 15, 20, 26 weeks post NICCU discharge. They can also occur via telehealth. If the infant is referred by a local NICU, they will omit the 2 SMI intervention in at CHLA. These 10 1-hour sessions will be provided by a licensed physical or occupational therapist and will consist of supporting parents to provide their infants with **daily** opportunities for positive sensory experiences and therapeutic play to enhance development. If the infant is at CHLA at 2 weeks after therapeutic hypothermia, the sessions can be done at CHLA or via telehealth until the child is discharged home.

Sample Size and Population

Twenty infants with HIE or NE and their parents (dyad) will participate in this clinical trial.

STUDY TEAM ROSTER

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1 STUDY OBJECTIVES

1.1 Primary Objective

Primary Objective: Feasibility Aims

1. Is it feasible to complete 1 baseline survey, 1 assessment and 2 parent/therapist collaborative SMI intervention sessions with infants with moderate or severe HIE or NE prior to NICCU discharge?
   H1: ≥80% of eligible infants will enroll and complete 1 baseline survey, 1 assessment and 2 intervention visits.
2. What proportion of parents complete ≥80% of the recommended SMI intervention?
   H2a: Parent/infant dyads will complete at least 8 of 10 recommended visits with the therapist.
   H2b: Parents will report daily completion of interventions on 80% of randomly sampled days.
3. What proportion of parents complete 100% of the baseline and 3 assessment visits?
   H3a: Parent/infant dyads will complete the baseline and 3 assessment visits.

Secondary Objectives

4. Is it feasible to evaluate the impact of brain lesion location on response to intervention?
   H4: ≥50% of enrolled infants will have an MRI with tractography and cortical volume measurement post therapeutic hypothermia.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Hypoxic-ischemic encephalopathy (HIE) is a form of newborn brain injury due to a lack of oxygen (hypoxia) or blood flow (ischemia) to the brain, which results in a high incidence of moderate-severe disability. Worldwide, HIE is estimated to affect more than 1 million infants born annually.[1] Over 85 percent of infants with HIE now survive to discharge from the Neonatal Intensive Care Unit (NICU).[2] Currently, therapeutic hypothermia is standard of care, which has improved survival rates but not the incidence of moderate-severe disability or cerebral palsy.[3] In a review of 7 major randomized controlled trials of therapeutic hypothermia for HIE, at 18 to 24 months after hypothermia, an average of 26% of children had a major neurodevelopmental impairment (range 14-35%), 25% had a significant cognitive impairment (range 23-30%), and 23% developed cerebral palsy (range 13-32%).[4] These neurodevelopmental disabilities do not resolve with time as moderate to severe disability at 18 months is highly correlated with outcome at 6-7 years of age.[5]

Study Rationale

A ***critical gap*** is that there are no clinical trials that have targeted rehabilitation to support infants with HIE prior to the onset of motor delay with the goal of reducing

severity of disability. Therapeutic hypothermia works in the acute phase of brain injury by mitigating secondary energy failure to rescue dying neurons, without a clear role in inducing positive neuroplasticity.[6] Therefore, infants with HIE may benefit from close developmental surveillance and sensorimotor intervention (SMI) to induce positive neuroplasticity and optimize developmental outcomes. In addition, parents of infants with HIE may benefit from anticipatory guidance to promote global development and extensive education on how to incorporate play-based interaction into their daily routine to induce positive neuroplasticity and optimize developmental outcomes.

In clinical practice, logistical barriers prevent infants with HIE from receiving early developmental intervention. The infants are usually discharged within 3 to 7 days after completing therapeutic hypothermia, so the timeline for assessment of the infant's neurodevelopment and the opportunities for parent training, positive sensory experiences, and anticipatory guidance in the NICU are limited. In addition, while therapeutic intervention provided in the NICU is typically covered by medical insurance, post discharge infants' developmental interventions are generally supported by Early Intervention under the Individuals with Disabilities Education Improvement Act.[7] However, current policy provides significant barriers to beginning intervention within days of discharge from the NICU leaving parents with limited resources to support development in their infant at high risk of developing cerebral palsy.[8] A "wait and see" approach is commonly used resulting in delays in referral for assessment or therapeutic intervention until consistent signs of delay are present.[9] With the wide range of "typical" onset of motor skills, many infants are not referred for intervention until they are not sitting at 9 to 12 months, missing a peak opportunity to prevent delays by intervening early.

Therapeutic intervention provided immediately and consistently after HIE and prior to the onset of developmental delay may prevent or substantially reduce the severity of delay reducing overall cost of care. The proposed intervention blends a therapist-supported, parent-delivered sensorimotor intervention (SMI) that begins in the CHLA NICCU and builds on developmental opportunities once discharged and continuing through the first 6 months of life. The CHLA NICCU phase serves to support the infant and parent in building a relationship, helps to identify ideal times of interaction, and empowers the family to engage in positive sensory experiences with their infant.[10] Once discharged home, training the parent to provide 20 minutes of developmentally appropriate play activities using a variety of strategies to address key principles of the intervention is feasible. Parents describe embedding learned skills into their daily caregiving once they have been supported in their implementation.[11,12] In contrast, parents without this support report it being difficult to add new routines. Thus, it is critical that intervention starts as early as possible to support the parents' adherence to the intervention principles and dose of intervention while supporting the child's interest in social and cognitive enrichment provided during play.[13,14]

The SMI is based on two evidence-based approaches: SENSE (Supporting and Enhancing NICU Sensory Experiences)[10,15] and SPEEDI (Supporting Play, Exploration, and Early Developmental Intervention).[16] While past studies and an ongoing large

clinical trial at 2 sites [PI Dusing, SMI[12], NCT03518736)] are measuring the efficacy of this type of SMI intervention for infants born preterm, infants with HIE are at high risk of developing cerebral palsy, yet have been excluded from this ongoing work to reduce heterogeneity of the sample. This study addresses this gap in the research literature.

3 STUDY DESIGN

The purpose of this clinical trial (CT) is to evaluate the feasibility and begin to evaluate the effect of early sensorimotor intervention (SMI) for infants with HIE. Twenty infants with HIE and their parent will receive the therapeutic intervention that is typically provided in the CHLA NICCU and community (standard care), but the infants will also receive an additional 2 SMI intervention sessions in the CHLA NICCU (unless referred by local NICU) and 8 SMI intervention sessions in the home, at CHLA, or at the University of Southern California (USC) Health Sciences Campus over the first 6 months of life. They can also occur via telehealth. These 10 sessions will consist of supporting parents to provide their infants with daily opportunities for positive sensory experiences and therapeutic play to enhance development. Infants will be assessed by masked assessors at baseline, at NICCU discharge, and at 3 months and 6 months of age using standardized developmental and neurological assessments, parent-report measures via questionnaires, and medical records.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

To be eligible to participate, an individual must meet all of the following criteria:

1. One adult parent/legal guardian has provided signed and dated informed consent form agreeing to the child's participation and the parent's own participation. If a parent/legal guardian is providing consent for a child's participation and a different adult caregiver will be participating, the other adult caregiver must consent to their own participation
    a. A parent/legal guardian must be willing to also be enrolled in the study and be legally able to consent to their own participation in the research (18 years or over). Parents/legal guardians who are under 18 years and remain in the care of their parents are likely to have a different level of caregiving and support than those who are adults which may impact the delivery of the intervention and assessment visits. If one parent is over 18 years, that parent can participate.
    b. Inclusion criteria for the adult is that they will be a caregiver for the enrolled infant
    c. Stated willingness to comply with all study procedures and availability for the duration of the study
2. Infants with HIE based on the modified Sarnat Exam on admission[17] and has started to receive therapeutic hypothermia for 72 hours.[18] Or infants with neonatal encephalopathy.
3. Cared for in the Newborn and Infant Critical Care Unit (NICCU) at Children's Hospital Los Angeles (CHLA) or by referral from other local NICUs.
4. Family lives within 60 miles of CHLA.

4.2 Exclusion Criteria

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

1. Infant born preterm.
2. Infant with congenital anomalies, chromosomal or microarray abnormalities.
3. Infant with microcephaly.
4. Infants who have been redirected for comfort care.
5. Infants who are medically unstable.

4.3 Study Enrollment Procedures

- The medical records of all infants with HIE or NE at the CHLA NICCU will be screened for eligibility, i.e. searching for infants who had a diagnostic/ICD-10 code associated with HIE, including neonatal encephalopathy, birth depression, intrapartum asphyxia.
- Parents of eligible infants will be taken to a private space, provided information about the study, and asked to consent to the study. Documentation of reasons for ineligibility and for non-participation of eligible candidates will be completed using a screening log in REDCap.
- Once consented, infants will receive standard care plus sensorimotor intervention (SMI). If referred by other local NICU, infants will follow the same procedure of consenting within 72 hours of discharge.

4.4 Withdrawal Criteria

- Participants are free to withdraw from participation in the study at any time upon request. The reason for participant discontinuation or withdrawal from the study will be recorded in the participant tracking records in REDCap. Participants who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.
- Significant study intervention non-adherence (Losing touch with the family / missing more than 5 visits without contacting the research team.)
- Infants who become medically unstable prohibiting participation in more than 1 assessment or 3 days of intervention will be dropped from the study.
- If any clinical adverse event (AE), or other medical condition (i.e. Acute Fractures, Cancer, etc) or situation occurs such that continued participation in the study would not be in the best interest of the participant or they will be unable to participate fully.
- Participant unable to be reached.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Standard care intervention provided to infants. Intervention will begin after an infant has met the following conditions: extubated and weaned to respiratory support that is ≤ 2 L per minute canula flow, not requiring vasopressors, and no diagnosis of status epilepticus for ≥24 hours. Infants will receive standard care in their respective NICCU and community. Typical service in the NICCU will include routine medical care, physical, occupational, or speech therapy assessments and referral to the infant's local Early Intervention program as deemed necessary by the medical team. All infants will be referred to the High-Risk Newborn Follow-Up Clinic per current clinical policy.

SMI intervention. Infants will receive 2 SMI intervention sessions in the CHLA NICCU (omitted if infant referred from other NICU) and 8 SMI intervention sessions in the home, at CHLA or at the USC Health Science Campus (parent choice) at 1, 3, 5, 8, 11, 15, 20, 26 weeks post NICCU discharge. They can also occur via telehealth. These intervention sessions will be provided by licensed occupational and physical therapists and are considered best practice therapeutic interventions. The 2 intervention sessions in the NICCU will consist of collaborating with parents to recognize their infant's cues to engage in interaction, readiness for sensory exposures, and anticipatory guidance on the transition to home.[10] The 8 intervention sessions in the home will focus on supporting the parents to read their infant's cues to identify the ideal times for interaction and provide 20 minutes of daily intervention addressing four key principles:[12,16] encourage 1) self-initiated movement, 2) movement variability, 3) visual and manual object interaction, and 4) social interaction. Parents are encouraged not to impose movement on the infant but to encourage movement through environmental enrichment. If the infant is at CHLA at 2 weeks after therapeutic hypothermia, the sessions can be done at CHLA or via telehealth until the child is discharged home.

Education and interventions in the NICCU setting will be supported by standard written parent education materials and access to videos via a website. Refer to NICCU SMI Parent Activities. The aim of education centers around connecting parents to their infants, helping them understand how to read and respond to their infant's cues, identifying the important influence of the sensory environment, and to drive parents to engage in specific amounts of positive, evidence-based, developmentally appropriate sensory exposures each day. Log sheets are provided to track the sensory experiences that parents do with their infants. The higher frequency of visits shortly after NICCU discharge are designed to support parent's questions and the rapid developmental changes seen in this period. A website is available to provide video-based examples of play activities to parents. Handouts with anticipatory guidance on general wellness information such as sleep strategies, calming, and parent self-care will also be provided at these early visits. The intervention supports sensorimotor development and parent engagement and increased opportunities for motor and cognitive based play and interaction.

Parents will be provided with a SPEEDI Home Activity Guide and Log including multiple stages of difficulty for each activity to encourage progression of the activities and access to a website with video examples of each activity. Refer to Home SMI Parent Activities. Parent are encouraged to gradually advance the stages of difficulty for the activities to provide their infant with the "Just Right Challenge." While specific activities are provided, they are designed to support use of the principles in daily play sessions and to encourage parents to think creatively about how they can expand the infant's experiences while supporting their learning. We plan for a therapist and parent to meet every 2-6 weeks in person to collaborate to re-assess the infant's new skills and determine which stage or duration of each activity is the "Just Right Challenge" for the infant.

Fidelity of the therapist and parent delivered intervention has been assessed in our preliminary work to be excellent,[15,16,19] and we will use the same fidelity measures in the proposed study.

5.2 Handling of Study Interventions

Refer to NICCU SMI Parent Activities for details of NICUU intervention.
Refer to Home SMI Parent Activities for details of home, CHLA or USC intervention.

5.3 Concomitant Interventions

The alternative to participation is not to participate. No participant is asked to change their standard medical and therapeutic care. So, there is not an alternative treatment option.

5.4 Adherence Assessment

Parent-infant dyads who participate in less than 70 percent of the planned intervention sessions will be considered as not being adherent.

6 STUDY PROCEDURES

6.1 Schedule of Assessments

Assessment	Screening	Baseline, Enrollment, Randomization: (Baseline survey)	NICCU Intervention (2 sessions)	NICCU Discharge Assessment (A1)	Home Intervention (6 sessions)	3-month Assessment (A2)	Home Intervention (2 sessions)	6-month Assessment (A3)
Informed Consent Form	X							
Inclusion/Exclusion Criteria	X							
Medical History (medical reports)	X	X		X		X		X
Enrollment/Randomization		X						
Maternal Confidence Questionnaire		X		X		X		X
Analysis of Neuroimaging Data				X				
Test of Infant Motor Performance				X		X		
Bayley-4								X
General Movement Assessment				X		X		
Hammersmith Infant Neurological Examination						X		X
Activity log (weekly)			X	X	X	X	X	X
AHEMD-IS Inventory				X		X		X
Demographics				X				
Parent Stress Index-Short Form				X		X		X
Rehabilitation Services Questionnaire				X		X		X
Sensory Profile 2				X		X		X
Adverse events		X	X	X	X	X	X	X

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Screening

The medical records of all infants with HIE admitted to the CHLA NICCU will be screened for eligibility by study staff. Parents/legal guardians of eligible infants will be provided with a recruitment flyer by NICCU staff or the study team that is also NICCU staff. The study will be explained to the parent/legal guardians and they will have an opportunity to consider their interest in learning more.

Consenting Procedure

If the parent/legal guardian wishes to hear more about the study a study team member who has completed the NIH GCP training and has been trained to obtain consent without coercion will meet with the parent in the NICCU or a quiet meeting area to review the consent form. Parents will be provided an opportunity to ask any questions and as much time as needed to review the consent and discuss it with family and friends. Once all the parent/legal guardian questions are answered they will be asked to sign the consent if they would like to consent to their infant and themselves participating in the study. Only one parent will be required to sign the consent form, however space will be provided for 2 parents to sign the consent agreeing to their own participation as in the past in some instances both parents have expressed interest in participating. Although we will target the parent who will be home with the infant most after NICCU discharge to fully participation in the study, if both parents sign the consent they can both participate in the intervention and assessment visits.

The consent process can be done in person, via phone or via teleconferencing. Parents who choose to participate will sign the consent using REDCap. REDCap will be used to store the consent form. Documentation of reasons for ineligibility and for non-participation of eligible candidates will be completed using a screening log in REDCap.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment is defined as the date that the parent/legal guardian agrees to participate and signs the consent form.

- Once consented, infants will be assigned to standard care plus sensorimotor intervention (SMI). If referred by other local NICU, infants will follow the same procedure of consenting and randomization within 72 hours of discharge.

General Assessment Information

All infants enrolled in the study will participate in the same assessment schedule. An assessor blinded to previous assessments will conduct all assessments. Inter-rater reliability on 10% of the visit will be assessed through scoring of videotaped

assessments. Given the high risk of cerebral palsy in this population, outcome measures described as "Highly Recommended" by the NINDS Common Data Elements for Cerebral Palsy were used for each domain.

The assessors will not discuss intervention with the interventionist. Some assessments will be videotaped and scored via video by coders.

For standardized assessments completed in the CHLA NICCU (Test of Infant Motor Performance, General Movement Assessment), they will be completed by a trained, licensed occupational or physical therapist with privileges in the CHLA NICCU and experience handling infants who are medically fragile.

If parents request information from the standardized assessments, the scores of the Test of Infant Motor Performance and Bayley Scales of Infant and Toddler Development can be provided. The PI will share the information with the participant via phone.

Description of All Assessments (alphabetical order)

Activity log. Parents will be asked to complete a log of their child's activities across one day per week, randomly selected, for the 26 weeks from baseline to the end of intervention. Parents who have a smartphone will be offered a free, custom designed smartphone app and will be sent an alert to complete the log reflecting activity in the last 12 hours.[20] Parents without a smartphone or who prefer email will be sent an email to a REDCap survey to complete the log.

Affordances in the Home Environment for Motor Development Infant Scale (AHEMD-IS) Inventory: AHEMD is a standardized questionnaire used to quantify access to types of toys or environments in the home. Parents complete this questionnaire at NICCU discharge, and when the infant is 3 months and 6 months of age, via REDCap.

Bayley Scales of Infant and Toddler Development, 4th edition (Bayley-4). The Bayley-4 is a therapist-administered, primary outcome measure. The Bayley-4 is a valid and reliable norm-referenced test designed to assess multiple developmental domains including cognition and motor abilities of infants between 1 to 42 months.[21] The Bayley-4 test-retest reliability is provided within each age bracket for each subtest domain (.67-.94), and test content demonstrated good validity. The Bayley-4 will be completed at 6 months of age.

Demographics: Parents will complete demographic and social history using forms F2197_Demogrphics and F2198_Social Status from the CDE using REDCap at NICCU discharge.

General Movement Assessment (GMA). The GMA is a therapist-administered measure for the early detection of cerebral palsy to characterize the participants. The

GMA was developed to distinguish between infants with and without motor dysfunction and predict which infants may have future motor delays.[22,23] All infants will be assessed using the GMA at NICCU discharge and at 3 months of age.[22] At NICCU discharge, the GMA will be scored by a certified assessor as general movements that are: normal, poor repertoire, cramped-synchronous, chaotic, or hypokinesis. Cramped-synchronous movements are highly predictive of cerebral palsy. At 3 months of age, the GMA will be scored by a certified assessor as normal fidgety, abnormal fidgety, or absent fidgety. Absent fidgety movements are highly predictive of cerebral palsy.

Hammersmith Infant Neurological Exam (HINE). This is a therapist-administered measure for the early detection of cerebral palsy to characterize the participants. The HINE is a standardized and scoreable neurological exam used as part of a comprehensive clinical profile to diagnose cerebral palsy.[24,25] The HINE will be assessed at 3 and 6 months. Infants who score less than 57 at 3 months or 63 at 6 months will be considered as having an abnormal HINE score.

Maternal Confidence Questionnaire (MCQ). The MCQ consists of 14 questions, and aims to assess maternal confidence in parenting. It has fair test-retest reliability (0.69) and good internal consistency with Cronbach's alpha between 0.86 to 0.93. Parents complete this questionnaire at baseline, NICCU discharge, and when the infant is 3 months and 6 months of age, via REDCap.

Medical Record Review / Medical Updates. A combination of medical records and parent interview will be used to describe the medical history of enrolled participants using the F2203_Medical History and F2207_Surgical and Hospitalization History. While infants are in the NICCU the medical record will be used exclusively (baseline and NICCU discharge assessments). After NICCU discharge parents will be asked to complete these forms via REDCap when the infant is 3 and 6 months of age. Parents will be asked for HIPAA authorization for the research team to attain the following medical records to describe the participants: NICCU discharge summary and neurology, neuroimaging and High-Risk Infant Clinic reports through 2 years of age.

Neuroimaging Data Collected as Part of Routine Clinical Care. Neonates will undergo magnetic resonance imaging (MRI) using a standardized MRI protocol, which was developed for use across sites and MRI platforms as part of the NIH-funded phase III High-dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) Trial. This protocol includes: structural T1- and T2-weighted MRI scans, Diffusion Tensor Imaging (DTI) and MR Spectroscopy. Data from the participants will be processed offline by a single investigator (JLW) who is masked to the infant's history and clinical course. The locus and degree of brain injury will be scored using the Washington University HEAL scoring system. Additionally, regions of interest (ROIs) will be placed in the ventrolateral thalami, posterior putamen and corticospinal tract at the level of the midbrain (cerebral peduncles), posterior limb of the internal capsule and corona radiata and used to extract fractional anisotropy (FA), axial (AD) and radial diffusivity (RD). Together these data will be used to

characterize the degree of HIE brain injury and involvement of the corticospinal tract and deep gray nuclei (thalami, putamen). These variables will be tested as potential moderators of treatment effects in future studies.

Parent Stress Index- Short Form: This measure will be completed via REDCap to consider if the intervention adds stress to families lives. While not directly related to the aims of the study this measure is important to making future clinical recommendations. The Parenting Stress Index—Short Form was used as a self-report instrument to measure level of stress directly associated with the parenting role. The PSI-SF measures stress directly associated with the parenting role. The PSI-SF consists of 36 statements, and parents respond to each statement using a 5-point scale to indicate the degree to which that item has been disturbing to them in the past week. This instrument yields scores for several factors in addition to a Total Stress score. The Total Stress score, utilized is a composite score of the subscale scores. Parents who obtain a Total Stress score above a raw score of 90 are considered to be experiencing clinically significant parenting stress. Internal consistency reliability for the composite Total Stress is reported by the author to be .91. Stability of the instrument was assessed by test-retest after a 6-month interval and yielded an alpha of .84 for the Total Stress. The PSI-SF has recently been validated by independent research efforts. Parents complete this questionnaire at NICCU discharge, and when the infant is 3 months and 6 months of age, via REDCap.

Rehabilitation Services Questionnaire: The F2201_Rehabilitation_Therapies_ Episodes_Care form CP version 1.0 will be used to collect the CDE related to rehabilitation services including Early Intervention services via REDCap. This form will be completed at all visits. The total number of non-study related sessions of Physical Therapy, Occupational Therapy, and Speech Therapy services in either the NICCU, Early Intervention or and outpatient setting will be calculated for the time between each assessment visit.

Sensory Profile 2. The Sensory Profile 2 (short form) is a questionnaire of the infant's sensory system.[26] It is used in clinical practice and research and has good test-retest reliability (α=0.81-0.90), validity, and internal consistency (α =0.83). Summary scores for Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Auditory Filtering, Under Responsiveness/Seeks Sensation, Low Energy/Weak, and Visual/Auditory Sensitivity were used as outcomes. Parents complete this questionnaire at NICCU discharge, and when the infant is 3 months and 6 months of age, via REDCap.

Test of Infant Motor Performance (TIMP). The TIMP is a therapist-administered, primary outcome measure. The TIMP is a standardized test for assessing neuromotor development of infants between 34 weeks post menstrual age and 4 months.[27,28] The TIMP is reliable and sensitive to changes in motor performance with increasing age and skill. The TIMP has been used in clinical trials and is considered to be an excellent discriminative, evaluative, or predictive instrument for at risk infants. The TIMP will be completed at NICCU discharge and at 3 months of age.

Baseline survey: Baseline survey in the CHLA NICCU as soon as infants are enrolled in the study and before they start intervention.

1. Medical Record Review by the study team
2. Maternal Confidence Questionnaire by parents, entered directly into REDCap.

6.2.3 Assessments

Assessment #1: Before NICCU discharge or within the first week after NICCU discharge but before starting intervention in the home, at CHLA, or at USC.

1. Medical Record Review by the study team
2. Test of Infant Motor Performance
3. General Movement Assessment
4. Neuroimaging data collected as part of routine clinical care
5. Parent surveys, entered directly into REDCap
    a. Affordances in the Home Environment for Motor Development Infant Scale (AHEMD-IS) Inventory
    b. Demographics
    c. Maternal Confidence Questionnaire
    d. Parent Stress Index- Short Form
    e. Rehabilitation Services Questionnaire
    f. Sensory Profile 2
6. Collect Activity log from parents
7. Adverse events. Refer to section 7.3 for further details.

Assessment #2: at 3 months of age.

1. Medical Record Update by parents
2. Test of Infant Motor Performance
3. General Movement Assessment
4. Parent surveys, entered directly into REDCap
    a. Affordances in the Home Environment for Motor Development Infant Scale (AHEMD-IS) Inventory
    b. Maternal Confidence Questionnaire
    c. Parent Stress Index- Short Form
    d. Rehabilitation Services Questionnaire
    e. Sensory Profile 2
5. Collect Activity log from parents
6. Adverse events. Refer to section 7.3 for further details.

6.2.4 Final Assessment and Criteria for discontinuing study intervention.

Final Assessment: Assessment #3 at 6 months of age

1. Medical Record Update by parents
2. Bayley Scales of Infant and Toddler Development, Edition 4
3. Parent surveys, entered directly into REDCap
    a. Affordances in the Home Environment for Motor Development

Infant Scale (AHEMD-IS) Inventory
   b. Maternal Confidence Questionnaire
   c. Parent Stress Index- Short Form
   d. Rehabilitation Services Questionnaire
   e. Sensory Profile 2
4. Collect Activity log from parents
5. Adverse events. Refer to section 7.3 for further details.

Criteria for discontinuing study intervention.

1. Participants will discontinue intervention if the parents report a change in medical status that makes the child ineligible based on exclusion criteria.
2. Intervention will be discontinued if participants experience moderate or worse adverse events which results in a change in availability to complete the intervention
3. A participant may always be removed from intervention whenever the participants' family wishes and alerts the PI.

7 SAFETY ASSESSMENTS

7.1 Known Potential Risks

- There is minimal risk associated with participating in this study for infants and parents.

- Children may be tired or a little fussy during or after the assessment or intervention study visits.
  - To mitigate this risk: The team includes experienced medical professionals and researchers who are trained to provide care in the NICCU, home, at CHLA, and at USC. All infants in the NICCU, home, at CHLA, or at USC will remain on any cardiac, respiratory, or oxygen monitors or supports. As part of the intervention, parents will be empowered to read their babies cues to anticipate the infants' level of fatigue and response by providing breaks. In addition, the interventions and assessments are no more stressful than standard care limiting the risk.

- For the parent/legal guardian participants the risks are minimal and include the possibility of feeling stressed about completing the interventions or assessment visits or parent could become emotionally distressed by talking about their NICCU experiences or current emotional status as it relates to providing the interventions. The risks are similar for all infants.
  - To mitigate the risk of parent stress, parent/legal guardian participants will be asked to do the best they can to complete the intervention, but they will not be pressured or made to feel bad if they did not complete as much intervention as was requested.
  - To mitigate the risk of parents becoming emotionally distressed, the assessment and intervention team will be provided with a

resource manual including signs of depression and anxiety. Study staff will refer any parent who has signs of mental health conditions to their primary care physician or if emergent care is needed to the Emergency Department. In the 2 previous studies using this protocol no parent has needed to be referred to the emergency department.

- For both infants and parents there is a health risk from being in contact with people living outside the family home.
  - We thoroughly clean the toys, equipment, and surfaces infants and parents come into contact with before and after each visit.
  - If it is recommended by CHLA or USC to discontinue in-person visits due to COVID, we can provide assessment and intervention via telehealth.

- For both infants and parents there is the risk of loss of confidentiality and privacy as a part of being in this study.
  - To minimize loss of confidentiality and privacy, all electronic video data is stored on the USC OneDrive with a secure server. Medical records, scorable assessments, demographics, and visit records will be entered into a REDCap Database on HIPAA Compliant servers housed at USC with hard copies used during visits stored in lock cabinets in a locked office accessible by trained study staff. All assessment sessions and intervention sessions are completed in the NICCU, family home, at CHLA, or in the USC research lab with a locking door. All videos and forms used in the study will only be identified by the subject ID number and the date of the visit.

7.2 Known Potential Benefits

- It is possible that participating parents/legal guardians will report enjoyment or learning about their infant's development from participating in the assessment visits. In addition it is possible that infant participants will benefit from being in the SMI intervention group. However, this is the purpose of this study and therefore is not known at this time.
- Infants who will be included in this study are all eligible for early intervention developmental support services in California. However, there is little data to suggest what is best practice in the timing, dose, or type of intervention provided. This study will start to address this gap in the literature.
- Parents/legal guardians or infant participants will be given $20 per assessment visit (3 total) and a small toy to compensate them for their time and participation in the study. Compensation will be provided as cash or a gift card.
- If a family chooses for their study visits to be at CHLA or USC, the family will be provided with a parking voucher.

7.1 Specification of Safety Parameters

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Adverse events will be assessed and recorded at each assessment and intervention session.

7.3 Adverse Events and Serious Adverse Events

Adverse event (AE) is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include lacerations requiring medical care or a head injury due to a fall.

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning or require medical care.
- **Severe** – Events interrupt a participant's usual daily activity and may require hospitalization.

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Potentially Related** – There is some evidence to suggest a causal relationship. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Site medically responsible investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.4 Reporting Procedures

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

7.5 Follow-up for Adverse Events

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

The PI will be responsible for safety monitoring. All assessors and interventionists will ask the parent/legal guardian about adverse events at every study visit and the PI will report them to the IRB as stated above. The PI will regularly review the data collected, including adverse events, and will formally review the SMI intervention midway and at the end of enrollment of infants receiving the SMI intervention.

8 INTERVENTION DISCONTINUATION

Discontinuation from the SMI intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance (Losing touch with the family / missing more than 3 visits)
- Infants who become medically unstable or requires ventilator support prohibiting participation in more than 1 assessment or 10 days of intervention will be dropped from the study.
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive SMI therapist or parent delivered intervention for 10 consecutive days.

The reason for participant discontinuation or withdrawal from the study will be recorded in the participant tracking records. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutive assessment visits or 3 intervention visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within a week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a clinical trial (CT) to evaluate the feasibility and begin to evaluate the effect of early sensorimotor intervention (SMI) for infants with HIE.

Primary Endpoint:

- Assessment 3 when the infants are 6 months of age and infants have completed the intervention

Secondary Endpoints:

- Assessment 1 at NICCU discharge when infants have completed the NICCU intervention
- Assessment 2 when the infants are 3 months of age and have completed part of the intervention.

Refer to Study Objectives on page 3 for primary and secondary hypothesis.

Refer to Outcome Measures on pages 12-14 for alphabetical list of outcome measures with validity and reliability data.

9.2 Sample Size and Randomization

No power analysis is included as this is a pilot study.

Refer to Enrollment, Baseline, and/or Randomization on page11 for details on enrollment.

The assessors will not discuss intervention with the interventionist. Some assessments will be videotaped and scored via video by coders.

9.3 Interim analyses and Stopping Rules

The study will be stopped if there is a high number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings will be presented to the study statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician will report his findings to the Safety Officer and/or funding agency. The findings will be used to determine what steps will be taken.

9.4 Outcomes

Refer to Outcome Measures on pages 12-14 for alphabetical list of outcome measures with validity and reliability data.

9.5 Data Analyses

Descriptive statistics will be used to describe the study sample. All outcome measures will be reviewed for outliers and assessed for normality.

Given the small sample size, means and standard deviations (SD), frequency and proportions will be compared without statistical analysis depending on assessments of normality. Bayley-4 motor and cognitive composites will be quantified at 6 months for use in future clinical trial planning.

Primary Objective: Feasibility Aims

1. Is it feasible to complete 1 baseline survey, 1 assessment and 2 parent/therapist collaborative SMI intervention sessions with infants with moderate or severe HIE prior to NICCU discharge?
   H1: ≥80% of eligible infants will enroll and complete 1 baseline survey, 1 assessment and 2 intervention visits. - This will be assessed using frequency and proportions.

2. What proportion of parents complete ≥80% of the recommended SMI intervention?
   H2a: Parent/infant dyads will complete at least 8 of 10 recommended visits with the therapist. - This will be assessed using frequency and proportions.
   H2b: Parents will report daily completion of interventions on 80% of randomly sampled days. - This will be assessed using frequency and proportions.
3. What proportion of parents complete 100% of the baseline and 3 assessment visits?
   H3a: Parent/infant dyads will complete the baseline and 3 assessment visits.

Secondary Objectives:

4. Is it feasible to evaluate the impact of brain lesion location on response to intervention?
   H4: ≥50% of enrolled infants will have an MRI with tractography and cortical volume measurement post therapeutic hypothermia. - This will be assessed using frequency and proportions.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

All data collection will be completed directly into electronic data collection forms on USC REDCap or onto paper forms which are only labelled with the subject identification number.

A secure recruitment database in REDCap will be housed at USC and used to store all information on potentially eligible subjects identified by clinicians, parents, or medical record search. This secure database will only include the necessary information to determine eligibility and to document if the parent/guardian provided consent.

A second REDCap database housed at USC will be used to maintain all confidential data (except videos) on participants who enroll in the study. Only the study coordinator, PI, assessor and study intervention therapist will have access to both the subject name and PHI and identifying ID number. This information is needed to ensure the team can contact the family for visits and use the infants correct ID number only on all documentation. All written documentation and videos will only be identified by ID number. Videos will be stored on USC OneDrive for Research which includes safe storage of protected health information including video. This online storage system enables us to upload and encrypt

all study documents, datasheets, videos and other data files which are only labeled with participant IDs.

10.2 Data Management

10.3 Quality Assurance

10.3.1 Training

Interventionist Training and Fidelity: The PI will train therapists to complete this intervention using detailed manuals, videos, and practice sessions. Adherence measures will include a measure of the frequency with which the intervention therapist demonstrates and/or talks about the SMI key principles and strategies assessed through videotaped sessions. Adherence of the parent providing the SMI intervention will be assessed during videotaped sessions by documenting the frequency with which the parent uses the key strategies of the SMI intervention. To encourage the intervention therapists to self-reflect on their use of key principles and strategies of the intervention, therapists will complete an intervention fidelity checklist after each visit.

Assessor Training: The assessors will read the test manuals and watch the training videos for the standardized assessments that they will perform: TIMP, GMA, HINE, Bayley 4. In addition, the assessors who will score the GMA and HINE will be certified. To establish reliability for each standardized assessment, the assessors will perform 2 assessments of infants aged 0 to 6 months with an experienced examiner co-scoring. Reliability will be calculated for subscale and total scores. Criterion reliability of >90% agreement on subscale and total scores must be met. Remediation plan: Assessors will be able to complete additional assessments to meet the reliability criterion, however no study assessments can be completed until the reliability criterion has been met.

10.3.2 Quality Control Committee

NA

10.3.3 Metrics

NA

10.3.4 Protocol Deviations

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the

protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NICHD Program Official. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.3.5 Monitoring

The PI will be responsible for assuring protocol compliance, and data quality at the clinical sites, including review of records, consent forms, etc.).

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.

11.2 Informed Consent Forms

A signed consent form will be obtained from the parent/legal guardian of each infant-parent dyad that participates in the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each parent/legal guardian and this fact will be documented in REDCap..

11.3 Participant Confidentiality

All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored on the USC REDCap for internal use during the study. At least weekly, all collected data at each site is uploaded to the USC REDCap.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored using the USC REDCap. This will include the participant's contact or identifying information, but will only be accessible by the assessment and intervention team members who need this information for their specific study visits. For all other study team members, individual participants and their research data will be identified by a unique study identification number only. The USC REDCap is secured and password protected.

Identification/screening. Medical records will be reviewed on each admission to the CHLA NICCU. The names of all reviewed records will be entered into the secure USC REDCap database that is only available to the study team. Only data that is needed to determine eligibility will be entered into the database which will be destroyed at the end of the study. No one outside the study recruitment team and the PI will have access to this secure database.

Recruitment/consenting. All discussion about the study with potential participants will be completed in a private area or at the infants bedside in the NICCU if the parent prefers to stay in this location. Once a consent is signed, the infant-parent dyad will be assigned a study identification number so the names of the participants will only be on the consent forms.

Study Conduct. All study records will only be labelled with the study identification number for the dyad. The video recording will have the participants faces visible but no names will be used by the study team during videotaping and the video files will be stored only with identification numbers to protect privacy.

Data Dissemination. All data will be disseminated in aggregate form without identifying any individual. No names will be used to label any participant. Any photos or video included in the dissemination will have consent for use in education by the parent/legal guardian.

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the Sponsor, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the Sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

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

13 COMMITTEES

NA

14 PUBLICATION OF RESEARCH FINDINGS

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

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

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the PI.

All concepts being considered for publications and presentations will be reviewed by the study team for agreement that the paper will not violate any of the planned analysis or will represent the data inaccurately/incompletely. The PI will review any proposals for study staff and consider approving for publication.

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16 SUPPLEMENTS/APPENDICES